Technology Assessment Report commissioned by the NIHR Evidence Synthesis Programme on behalf of the National Institute for Health and Care Excellence

Title of Project: Clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack

Produced by: Bristol Technology Assessment Group

Authors: Joe Carroll, Senior Research Associate in Health Economic Modelling, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol *(Joint First Author)*

Catalina Lopez Manzano, Research Associate in Evidence Synthesis, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol *(Joint First Author)*

Eve Tomlinson, Research Associate in Evidence Synthesis, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Ayman Sadek, Research Associate in Health Economic Modelling, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Chris Cooper, Research Fellow in Health Technology Assessment and Information Science, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Hayley E. Jones, Associate Professor in Medical Statistics, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Lorraine Rowsell, Patient representative

John Knight, Patient representative

Andrew Mumford, Professor of Haematology, University of Bristol. Research Director SW NHS Genomic Medicine Service Alliance.

Rachel Palmer, Pharmacy Lead, South West NHS Genomic Medicine Service Alliance

William Hollingworth, Professor in Health Economics, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Nicky J. Welton, Professor in Statistical and Health Economic Modelling, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol *(Joint last author)*

Penny Whiting, Professor of Clinical Epidemiology, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol *(Joint last author)*

Corresponding Author

Professor Penny Whiting
Bristol TAG
Bristol Medical School
[redacted]
e-mail: [redacted]

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR135620.

Declared competing interests of the authors

None of the authors have any conflicts of interest.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Academic in confidence (AiC) data are redacted [redacted] throughout the report.

Keywords

Stroke
CYP2C19 testing
Antiplatelet therapy
Clopidogrel
Systematic review
Economic model

Abstract

Background

People who have a stroke or TIA are at increased risk of secondary vascular events. Antiplatelet medications, most commonly clopidogrel, are prescribed to reduce this risk. Some people are unable to metabolise clopidogrel due to genetic variants in the *CYP2C19* gene - known as "clopidogrel resistance". Relevant variants can be detected using laboratory-based tests or point of care tests (POCT) – Genomadix Cube and Genedrive; this could allow targeting of more suitable treatment.

Objective

To assess the clinical- and cost-effectiveness of genetic testing to identify clopidogrel resistance in people with ischaemic stroke or TIA.

Design

Systematic review and economic model.

Results

Two studies assessed the secondary vascular events in patients tested for LOF alleles and treated accordingly. They found a reduced risk, but confidence intervals were wide (HR 0.50, 95% CI 0.09, 2.74 and HR 0.53, 95% CI 0.24, 1.18).

Seven RCTs compared clopidogrel with alternative treatment in people with genetic variants. Ticagrelor was associated with a lower risk of secondary vascular events than clopidogrel (summary HR 0.76, 95% CI 0.65, 0.90; 2 studies). There was no evidence of differences between other antiplatelet treatment strategies.

Twenty-five studies compared outcomes in people with and without genetic variants treated with clopidogrel. People with genetic variants treated with clopidogrel were at increased risk of secondary vascular events (HR 1.72, 95% CI 1.43, 2.08; 18 studies). There was no difference in the risk of bleeding (HR 0.98, 95% CI 0.68, 1.40; 5 studies).

Eleven studies evaluated Genomadix Cube accuracy; no studies evaluated Genedrive. Summary sensitivity was 100% (95% CI 94, 100%) and summary specificity was 100% (95% CI 99, 100%). Seventeen studies evaluated technical performance of POCT. Test failure rate ranged from 0.4% to 19% for Genomadix Cube; time to results was 1 hour for Genomadix Cube and 40 mins for Genedrive.

Eight of 10 genomic laboratory hubs completed a survey on technical performance. Preferred technologies for *CYP2C19* testing included: next-generation sequencing, MassARRAY, LAMP, and PCR-based SNP genotyping assays. Costs per test ranged from £15 to £250. Most labs expected test failure rate to be <1%. Additional testing capacity and faster turnaround time would be possible with additional resources.

We found that laboratory and point of care *CYP2C19* testing strategies were cost-saving and increase quality adjusted life-years (QALYs) compared with no testing. All *CYP2C19* testing strategies gave similar costs, QALYs and expected net monetary benefit. Findings were robust to all sensitivity and scenario analyses explored. Results for Genedrive may change when diagnostic and performance data becomes available.

Conclusions

Our results suggest that *CYP2C19* testing followed by tailored treatment is likely to be effective and cost-effective in both populations modelled (non-minor ischaemic stroke and TIA/minor ischaemic stroke).

Word count: 443 words

Scientific Summary

Background

Stroke is a neurological condition that can cause lasting brain damage, disability, and death. Symptoms of stroke happen suddenly and include problems with movement, speech, vision, and the face drooping on one side. A TIA ("transient ischaemic attack") is a milder related condition. Each year, there are around 100 000 strokes and 60 000 TIAs in the UK.

People who have a stroke or TIA are at increased risk of another vascular occlusive event. To reduce this risk, doctors often prescribe antiplatelet medication, most commonly clopidogrel. Clopidogrel is a prodrug, which means it needs to be metabolised by an enzyme called P450 CYP to achieve its pharmacological effect; a substantial proportion of the population have a reduced ability to perform this conversion. This is known as "clopidogrel resistance", and can be caused by genetic variants, mainly in the *CYP2C19* gene, in addition to other clinical factors.

Relevant genetic variants can be detected using laboratory-based tests or point of care tests (POCT). Opportune detection of patients with genetic variants associated with "clopidogrel resistance" could help doctors to initiate a more suitable treatment, potentially preventing new occlusive vascular events in this population.

Objectives

The overall aim was to summarise the clinical- and cost-effectiveness of genetic testing to identify clopidogrel resistance in people with non-cardioembolic ischaemic stroke or TIA.

Objective 1: Do people who have genetic testing for clopidogrel resistance, and who are treated based on these results, have a reduced risk of secondary vascular occlusive events compared to those who are not tested and are treated with clopidogrel following standard guidelines?

Objective 2: Do people who have loss of function (LOF) alleles associated with clopidogrel resistance have a reduced risk of secondary vascular occlusive events if treated with alternative interventions compared to treatment with clopidogrel?

Objective 3: Do people who have *LOF* alleles associated with clopidogrel resistance have an increased risk of secondary vascular occlusive events when treated with clopidogrel compared to patients without LOF alleles who are treated with clopidogrel?

Objective 4: What is the accuracy of point of care genotype tests for detecting variants associated with clopidogrel resistance?

Objective 5: What is the technical performance (other than accuracy) and cost of the different *CYP2C19* genetic tests?

Objective 6: What is the cost-effectiveness of different POCT and laboratory based genetic tests for clopidogrel resistance compared with not testing for clopidogrel resistance?

Methods

Clinical effectiveness review

A systematic review was conducted. This was supplemented by a survey of genomic laboratory hubs on the technical performance of *CYPC19* genetic tests.

Eight databases and two trial registries were searched. We screened trial registries, reference lists of reviews and study reports, relevant websites and information submitted by test manufacturers.

Title and abstract screening were conducted by two reviewers independently. Inclusion assessment, data extraction, and risk of bias assessment were performed by one reviewer and checked by a second. Risk of bias was assessed using the RoB 2 (RCTs), ROBINS-E (observational studies), and modified QUADAS-2 (diagnostic accuracy studies) tools.

For each objective, we provided a narrative summary of study details, risk of bias, and results. Random and fixed effects meta-analysis was performed to generate summary effect estimates; heterogeneity was investigated using stratified analyses and meta-regression. Forest plots were produced to show individual and summary effect estimates with 95% confidence intervals (CIs).

Cost-effectiveness

We developed a decision analytic model to evaluate the cost-effectiveness of POCT and laboratory tests for *CYP2C19* LOF alleles, compared with no testing in two populations in England and Wales: (i) TIA / minor ischaemic stroke, and (ii) non-minor ischaemic stroke; and also present results for a mixed ischaemic stroke and TIA population. We modelled patients moving between 5 health states: no recurrent stroke, minor stroke, major bleed or intra-cranial haemorrhage, moderate stroke, and severe stroke, with mortality rate depending on health state. A decision tree was used to capture short-term (90 day) outcomes, and a Markov model with 1-year cycles captured longer-term outcomes over a life-time horizon. Costs and quality adjusted life years (QALYs) were estimated using a 3.5% discount rate for both.

Model inputs were derived from the clinical effectiveness review, reviews of previous cost-effectiveness models of *CYP2C19* testing and cost-effectiveness models of anti-platelets for stroke prevention, results from the survey of laboratories, information provided by Genedrive and Genomadix, and additional targeted searches. Uncertainty was explored using probabilistic sensitivity analysis, and a range of scenario analyses to test robustness of results to model assumptions.

Results

Objective 1

Two non-randomised studies evaluated the clinical impact of genetic testing plus personalised treatment. Both were at high risk of bias due to potential confounding. Both studies treated patients in the control group, who were either not tested or were not treated based on their *CYP2C19* status, with clopidogrel 75 mg/day. The intervention group were then treated based on the presence of LOF alleles. Both studies treated those with no LOF alleles in the same way as the control group (i.e., clopidogrel 75mg/day), one study gave high dose clopidogrel to those with one LOF allele and ticagrelor to those with two LOF alleles. In the other study, those with at least one LOF allele were given aspirin 100mg/day.

There was a suggestion that the risk of secondary vascular events was reduced in patients tested for LOF alleles and treated accordingly, but confidence intervals were wide and overlapped the null (composite outcome of secondary vascular events: HR 0.50, 95% CI 0.09, 2.74 and HR 0.53, 95% CI 0.24, 1.18).

Objective 2

Seven RCTs compared treatment with clopidogrel with alternative antiplatelet therapies compared in people with LOF alleles. Four were at low risk of bias, three had concerns regarding missing data and lack of information on allocation concealment. There was evidence that ticagrelor was associated with a lower risk of secondary vascular events than clopidogrel (summary HR 0.76, 95% CI 0.65, 0.90; 2 studies), including ischaemic stroke (HR 0.77, 95% CI 0.65, 0.93; 2 studies). One study suggested that ticagrelor was associated with an increased risk of bleeding (HR 2.18, 95% CI 1.66, 2.86); the other found no difference in the risk of bleeding with ticagrelor compared to clopidogrel (HR 1.01, 95% CI 0.60, 1.69). There was no statistical evidence for differences between antiplatelet treatment strategies for other comparisons or bleeding outcomes.

Objective 3

Twenty-five studies (20 cohort studies and 5 trials) compared people with and without LOF alleles, all of whom were treated with clopidogrel (alone or combined with aspirin or other antiplatelet drugs) to see whether the risk of secondary vascular occlusive events differed between groups. Six studies were judged at high risk of bias as we considered that loss to follow-up could potentially be related to incidence of vascular events. There was strong evidence that people with LOF alleles treated with clopidogrel (or clopidogrel plus short-term aspirin) have a greater incidence of secondary vascular events (HR 1.72, 95% CI 1.43, 2.08; 18 studies), stroke (HR 1.46, 95% CI 1.09, 1.95; 5 studies) and ischaemic stroke (HR 1.99, 95% CI 1.49, 2.64; 12 studies) than those without LOF alleles. Meta-regression analyses showed statistical evidence of a reduced effect of LOF alleles in patients given a loading dose of clopidogrel relative to those who were not (relative hazard ratio (RHR): 0.64, 95% CI 0.42, 0.97), and in patients taking clopidogrel plus long-term aspirin relative to those taking only clopidogrel or clopidogrel plus short-term aspirin (RHR: 0.45, 95% CI 0.22, 0.93). Meta-regression did not show evidence for a difference in LOF alleles effect on vascular

occlusive outcomes across different ethnicities (Asian or mixed relative to white), study location (China, Europe, Asia non-China, Turkey, and International) or follow-up time (follow-up of 6 months, 1 year, 1 to 3 years and 3 to 5 years relative to up to 3 months). There was no difference in the risk of bleeding between those with and without LOF alleles (HR 0.98, 95% CI 0.68, 1.40; 5 studies).

Objective 4

Eleven studies reported data on the accuracy of the POCT in scope. All evaluated Spartan versions of the Genomadix Cube test: Spartan Cube, Spartan RX or Spartan FRX, against a laboratory reference standard – there were no studies on the accuracy of Genedrive. All studies were judged at low risk of bias. None of the studies were conducted in a stroke population. The Genomadix (Spartan) *CYP2C19* tests were found to have very high accuracy for the detection of *2 and/or *3 LOF alleles. Summary sensitivity was 100% (95% CI 94, 100%) and summary specificity was also 100% (95% CI 99, 100%). There were very few disagreements between the Genomadix (Spartan) *CYP2C19* tests and laboratory-based reference standards – 8 of the 11 studies reported perfect agreement between the tests. There was no suggestion of a difference across the three different versions of the test evaluated.

Objective 5

Seventeen studies evaluated the technical performance of the POCT. One evaluated Genedrive; others evaluated Genomadix (Spartan) *CYP2C19* tests. Only one study was conducted in a stroke population. Test failure rate for Genomadix (Spartan) *CYP2C19* tests ranged from 0.4% to 19%. Most studies reported that time from buccal swab for to results for Genomadix (Spartan) *CYP2C19* tests was around 1 hour, although two studies reported higher estimates of 90 mins and 90-120 mins. One study of Genedrive reported that it gives results in around 40 mins. Studies suggested that Genomadix (Spartan) *CYP2C19* tests were simple, user-friendly, and can require minimal training. Limitations included storage conditions (analytes need to be frozen), only one sample can be genotyped at a time, and it only tests for *2, *3 and *17 alleles. The study that evaluated Genedrive, noted the test is simple, portable, rapid, does not require analytes to be frozen, and tests for *2, *3, *4, *8, and *17 alleles. Genedrive and Genomadix provided information on the platform cost, assay cost, and cost of external control kits, which were used in our economic model.

Eight of the 10 genomic laboratory hubs completed the survey. All but one had sequencing technologies, and all had targeted *CYP2C19* gene variant detection (e.g., TaqMan). Preferred technologies for performing *CYP2C19* testing included: next-generation sequencing (2 labs), MassARRAY(3 labs), LAMP (3 labs), PCR-based SNP genotyping assays (e.g., TaqMan) (1 lab). Resource requirements varied. Costs per test ranged from around £15 (MassARRAY, although another lab estimated this as £100) to £250 for Next-generation gene sequencing. Most labs reported that tests could be performed by existing staff members with standard training or that the test was fully automated, although one lab stated that their preferred test would be new to their lab and would require training. Most

labs expected test failure rate to be <1%. Testing capacity ranged from 0 to 200 tests per week, and turnaround time from 24-72 hours to 1-2 weeks. Most labs reported that additional testing capacity and faster turnaround time would be possible with additional resources (staff, lab space, automation, and equipment). Major barriers to implementing testing were the scale of activity and current capacity (4 labs); one highlighted that they do not currently perform any tests of this scale in the NHS.

Objective 6

In our base-case for all populations, we found that laboratory and point of care *CYP2C19* testing strategies generated more QALYs and lower costs compared with no testing (i.e., no testing was dominated by the *CYP2C19* testing strategies). All *CYP2C19* testing strategies gave similar QALYs, so we compare them using expected net monetary benefit at willingness-to-pay of £20,000 per QALY, where higher expected net benefit is preferred. In the non-minor ischaemic stroke population the expected net benefits were £6,230, £6,214, and £6,138 for Genedrive, the laboratory test, and the Genomadix Cube *CYP2C19* Test respectively. In the TIA / minor stroke population the expected net benefits were £2,932, £2,802, and £2,829 for Genedrive, the laboratory test, and the Genomadix Cube *CYP2C19* Test respectively. In both populations net monetary benefit is similar, suggesting little difference between the tests.

The model inputs that have the biggest impact on the cost-effectiveness results were the costs of the different stroke states, and the treatment effects for stroke in patients with *CYP2C19* LOF, and the hazard ratio for major bleed / ICH on aspirin relative to clopidogrel. However, varying these parameters did not change the overall finding that *CYP2C19* testing is cost-saving and generates more QALYs compared with no-testing. Cost-effectiveness acceptability curves show that there is a high probability that one of the testing strategies is the most cost-effective, with Genedrive having the highest probability of being cost-effective.

It should be noted that due to limited information on Genedrive, assumptions were based on data for the Genomadix Cube *CYP2C19* Test, with the exception of the costs. The results for Genedrive should therefore be considered exploratory only and the findings may change as further evidence for Genedrive becomes available.

The overall finding that *CYP2C19* testing is cost-saving and generates more QALYs compared with no-testing was robust in all the scenarios that we explored. The scenarios where *CYP2C19* testing was most cost-effective were when prevalence of *CYP2C19* LOF was high and for younger cohorts of patients. The scenarios where *CYP2C19* testing was least cost-effective were when we assumed that only 69.9% of LOF patients actually receive alternative treatment, and when the alternative treatment was ticagrelor. In these scenarios *CYP2C19* testing was still cost-saving but with a smaller increase in QALYs.

Conclusions

Our results suggest that *CYP2C19* testing followed by tailored treatment is likely to be effective and cost-effective in both populations modelled (non-minor ischaemic stroke and TIA/minor ischaemic stroke). Lab-tests and POCT tests generate similar cost-savings and QALY benefits. Implementation of *CYP2C19* testing would require sufficient capacity for lab-tests and freezers / storage for POCTs, and training and processes in place to encourage uptake of alternative treatment for patients with LOF variants.

There are four areas where further research is required:

- Accuracy and technical performance (e.g. test failure rate, cost, time to perform the test) of Genedrive
- Test failure rate of Genomadix Cube in an NHS setting
- Value of testing additional LOF alleles beyond *2 and *3
- Appropriateness of treatment dichotomy based on LOF alleles used in our appraisal compared to a more complex approach to tailored treatment

Study registration

The review was registered at PROSPERO (CRD42022357661).

Funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR135620.

Word count: 2364 words

Plain English Summary

What is the problem?

A stroke occurs when the supply of blood to the brain is cut off. Symptoms of stroke happen suddenly and vary depending on which part of the brain is affected. They usually include problems with movement, speech, vision, and the face drooping on one side. A TIA ("transient ischaemic attack") is a milder related condition. There are around 100 000 strokes and 60 000 TIAs every year in the UK.

People who have a stroke or TIA are at greater risk of having another stroke. To reduce the chances of this happening, doctors will often prescribe medication. The most common medication used is called "clopidogrel". However, clopidogrel does not work for everyone. One reason for this is having specific variations of a gene called the *CYP2C19* gene. Around one in three people in the UK have this variation.

What did we do?

We wanted to know whether introducing genetic testing to identify variations in the *CYP2C19* gene for people who have had a stroke or TIA can help doctors prescribe a treatment that will work for them, reducing the risk of having another stroke. We also wanted to know if doing this test would be a good use of NHS money.

What did we find?

Doing a genetic test to identify variations in the *CYP2C19* gene, and prescribing an alternative medication for people with these variations, reduces the chances of having a new stroke. It is likely that a genetic test for variations of the *CYP2C19* gene would represent value for money for the NHS.

Table of contents

Contents

List of Tables

List of Figures

Definition of Terms and List of Abbreviations

Term	Definition
ABCD^2	Risk of stroke scoring system after a suspected transient ischemic attack (TIA)
ACE	Angiotensin-converting enzyme
ACS	Acute Coronary Syndrome
Alt Tx	Alternative treatment
ATC	Anatomical Therapeutic Chemical code
ATO	Arterial thrombo-occlusive
AUC ROC	Area Under the Receiver Operating Characteristics Curve
BNF	British National Formulary
CAD	Coronary Artery Disease
CAP	College of American Pathologists
CAS	Chemical Abstracts Service
CEA	Cost-Effectiveness Analysis
CI	Confidence interval
CIHI	Canadian Institute for Health Information
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CPIC	Clinical Pharmacogenetics Implementation Consortium
CRD	Centre for Reviews and Dissemination
CT	Computerised Tomography
CYP	Cytochrome P450
DAC	Diagnostics Advisory Committee
DAPT	Dual Anti Platelet Therapy
DAR	Diagnostics Assessment Report
DNA	Deoxyribonucleic acid
DPYD	Dihydropyrimidine dehydrogenase
EAG	Evidence Assessment Group
ECH	Extracranial Haemorrhage
ECR	Electronic care record
EDI	Equality, Diversity And Inclusion Section
EM	Extensive Metabolisers
EMA	European Medicines Agency
EPR	Electronic patient records
EQ-5D	EuroQol 5 dimensions
EQA	External Quality Assessment
FN	False Negative
FP	False Positive
FU	Follow-up
GBP	Great Britain Pound
eGFR	Estimated glomerular filtration rate
GLH	Genomic laboratory hubs
GMSA	Genomic Medicine Service Alliance
GOF	Gain of Function

Term	Definition
GS	Gendrive System
HD	High dose
HFE	Hemochromatosis gene
HIS	Health Informatics service
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICAD	Intracranial atherosclerotic disease
ICER	Incremental Cost-Effectiveness Rario
ICH	Intracranial haemorrhage
ICVD	WHO International Clinical Trials Registry Platform
IM	Intermediate metaboliser
iMLDR	Improved Multiple Ligase Detection Reaction
iPLEX	Increased Plexing Efficiency and Flexibility
IQR	Interquartile range
IS	Ischaemic stroke
ITT	Intention to treat
LAMP	Loop-Mediated Isothermal Amplification
LCI	Lower Confidence Interval
LIMS	Laboratory Information Management System
LOF	Loss of Function
MALDI-TOF	Matrix-assisted laser desorption/ionization-time of flight
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NA	Not Applicable
NGS	Next-generation sequencing
NHS	National Health Service
NHS EED	NHS Economic Evaluations Database
NI	No information
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NIHSS	National Institutes of Health Stroke Scale
NoLOF	Loss of Function Non-carriers
NR	Not Reported
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NSRP	Nanjing Stroke Registry Program
ONS	Office for National Statistics
OSCARSS	Organising Support for Carers of Stroke Survivors
OXVASC	Oxford Vascular observational study
PCI	Percutaneous Coronary Intervention
PCR	Polymerase Chain Reaction
RFLP	Restriction fragment length polymorphism
PDF	Portable Document Format

Term	Definition
PHE	Public Health England
PM	Poor metaboliser
PN	Probably no
POC	Point of Care
POCT	Point of Care Test
PPI	Proton pumb inhibitor
PRESS	Peer Review of Electronic Search Strategies
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PY	Probably Yes
ppy	Per Person Year
QALY	Quality Adjusted Life Year
RCP	Royal College of Physicians
RCT	Randomized Controlled Trial
REML	Restricted Maximum Likelihood
SD	Standard deviation
SE	Standard error
SN	Strong No
SNP	Single-Nucleotide Polymorphisms
SLSR	South London Stroke Registry
SSNAP	Sentinel Stroke National Audit Programme
STEMI	ST-Segment Elevation Myocardial Infarction
SY	Strong Yes
TAT	Turnaround time
TIA	Transient Ischaemic Attack
TN	True Negative
TP	True Positive
UCI	Upper confidence interval
UK	United Kingdom
UKAS	United Kingdom Accreditation Service
US	United States
VISTA	Virtual International Stroke Trials Archive
WHO	World Health Organisation
WN	Weak no
WTE	Whole Time Equivalent
WY	Weak Yes

1 Background and Definition of Decision problem

1.1 Population

The population of interest for this appraisal is people who have had non-cardioembolic ischaemic stroke, minor stroke, or transient ischaemic attack (TIA), and for whom clopidogrel treatment is being considered. Approximately 100,000 strokes occur every year in the UK and between 46,000 and 65,000 people experience a TIA.[1] Around 85% of strokes are ischaemic, occurring when the supply of blood to a part of the brain is interrupted, usually by a blocked artery.[1] It has been suggested that a TIA is not a separate pathological entity, but exists on an ischaemic stroke spectrum, constituting the mildest form.[2] Symptoms of stroke often occur suddenly and vary depending on the part of the brain being compromised. Symptoms tend to include: issues with movement, speech, facial drooping, and vision.

The median age for stroke in the UK is 77 years and a quarter of strokes in the UK happen in people of working age.[3] Lifestyle factors associated with stroke and TIA include smoking, alcohol and drug abuse, physical inactivity, and poor diet. The presence of cardiovascular diseases, and medical conditions including diabetes mellitus, atrial fibrillation, chronic kidney disease and migraine, are also risk factors for stroke.[1] Other risk factors include previous stroke/TIA, family history of stroke, lower education, and genetic or hereditary factors. Strokes are more common in people with African-Caribbean or South Asian background (Stroke Association; Kings Fund).[4, 5]

People who have experienced a stroke or TIA are at an increased risk of further occlusive vascular events (e.g., ischaemic stroke, transient ischaemic attack, and myocardial infarction).[6] TIA precedes stroke in 15% of cases, providing a crucial opportunity to prevent more severe stroke.[7] Risk of stroke after TIA has been found to be approximately 8% at seven days, 11.5% at one month, and 17.3% at three months. Risk of recurrent stroke after minor stroke has been suggested to be 11.5%, 15% and 18.5%, respectively.[8] NICE TA210 recommends the use of antiplatelet medications as a preventative treatment for people who have had an ischaemic stroke or TIA.[9] This includes clopidogrel treatment and is discussed further in section 2.4.

1.2 Target condition: Clopidogrel resistance

Clopidogrel is an irreversible adenosine diphosphate (ADP)-receptor antagonist with antiplatelet properties. It is available as branded and generic preparations and has marketing authorisation for patients who have recently had an ischaemic stroke or TIA.[10]

Clopidogrel is a prodrug, which needs to be converted (metabolised) into an active form by P450 CYP enzymes.[11] A substantial proportion of the population are less able to metabolise clopidogrel to its active form and so clopidogrel does not achieve its pharmacological effect, usually the result of genetic variants, mainly in the *CYP2C19* gene. This is known as "clopidogrel resistance". As well as the *CYP2C19* gene, other factors that may cause or

exacerbate clopidogrel resistance include taking drugs such as omeprazole, which compete for metabolism by the CYP450 system [12], and factors such as obesity, diabetes, and hypertension.[13] There is also a potential role of other rare genetic changes. Thus, both genetic and clinical factors need to be considered when determining whether an individual will respond to clopidogrel treatment.

1.2.1 Genetic basis of clopidogrel resistance

Cytochrome P450 2C19 is one of the main enzymes that metabolises clopidogrel to its active form. This enzyme is encoded by the *CYP2C19* gene. *CYP2C19* is one of many genes associated with clopidogrel response but it is widely recognised as being the most validated genetic determinant.[14] The *CYP2C19* gene has multiple variant forms (alleles) which produce *CYP2C19* enzymes. These alleles are given a star (*) number for identification. The Pharmacogene Variation Consortium (PharmVar) has outlined more than 35 star (*) allele haplotypes.[15] The Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for *CYP2C19* genotype and clopidogrel therapy notes that *CYP2C19* allele *1 pertains to normal function, and that *2 and *3 are the most common alleles associated with loss of function (LOF). A systematic review found that people who carried one or two of these alleles had an increased risk of stroke and composite vascular events in contrast to noncarriers among patients with ischaemic stroke or TIA treated with clopidogrel.[16] Some alleles, in particular allele *17, are associated with increased function.[14]

A person's genotype is their unique sequence of DNA, whilst their phenotype is the observable expression of this genotype. A person's phenotype (in this case, how they will respond to (metabolise) clopidogrel) can be predicted based on their allele function combinations. Generally, people with the genotype of two normal function alleles (e.g., *CYP2C19**1/*1) have the phenotype of normal metabolisers. Intermediate metabolisers have one normal function allele and one LOF allele (e.g., *CYP2C19**1/*2). Poor metabolisers have two LOF alleles (e.g., *CYP2C19**2/*3). Rapid metabolisers have one normal and one increased function allele (e.g., *CYP2C19**1/*17) and those with two increased function alleles (e.g., *CYP2C19* *17/*17) are ultra-rapid metabolisers.[14]

There are significant ethnic variations in the incidence of the different *CYP2C19* alleles. Table 1**Error! Reference source not found.** provides an overview of some of the main *CYP2C19* alleles, their impact on clopidogrel metabolism, and their prevalence in different populations.

Table 1 Overview of the main *CYP2C19* alleles, their impact on clopidogrel metabolism and prevalence in different populations

Allele	Impact on clopidogrel metabolism	Prevalence							
		Global	European	African	Asian	South Asian	East Asian	Latin-American	UK
*2	LOF	16.02	14.72	17.50	29.19	36.70	28.01	16.16	15.08
*3	LOF	0.26	0.58	0.05	0.80	0.33	0.78	0.07	0.05

*4	LOF	0.32	0.33	0.07	0.10	0.04	0.06	0.35	0.16
*17	Increased function	19.60	23.13	22.64	1.80	7.00	1.00	16.4	20.89

Data from National Institute for Health and PharmVar.[17, 18]

1.3 Diagnostic Test

This review focuses on two categories of *CYP2C19* genetic testing: point-of-care tests (POCT) and laboratory-based tests. POCT include any analytical test carried out by a healthcare professional outside of the laboratory, although it is also possible to install near patient testing equipment in local laboratories, which may overcome challenges associated with storage of reagents.[19] These tests have the potential to deliver results more quickly than standard laboratory-based tests. The two POCT in scope are the Genomadix Cube *CYP2C19* System and the Genedrive *CYP2C19* ID Kit. The Genomadix Cube test was previously known as the "Spartan Cube", which is a successor to the "Spartan RX CYP2C 19 System". The two Spartan tests are very similar but there are some differences: the 3 reaction tubes have been integrated into a single test cartridge, the swabs and test cartridges are packaged separately, and the DNA analyser device is smaller.[20] There are also differences in the mechanisms used to heat and cool the samples; the storage, use, and stability of the specimens on the swab; the optical system; and the test workflow.[21]

Laboratory-based tests are conducted by technicians in the laboratory. In the National Health Service (NHS), genomic testing is generally delivered by a network of 7 Genomic Laboratory Hubs. Testing for *CYP2C19* is not currently included in the National Genomic Test Directory of tests commissioned by the NHS in England. Table 2 provides an overview of some of the available *CYP2C19* genetic tests. The POCTs only target specific LOF alleles. Laboratory based tests have the potential to target all LOF alleles, however commercial kits are likely to only test for the most common variants or those with established clinical utility. However, lab-based testing would have greater flexibility to alter variants screened for as new evidence emerges.

Table 2 Characteristics of *CYP2C19* point of care and laboratory tests

Name of test	Type of test	General information	*CYP2C19* alleles targeted	Time to run test
Genomadix Cube *CYP2C19* system	Point of care	Intended to be used in conjunction with clinical judgement and routine monitoring to determine therapeutic strategy for drugs metabolized by the *CYP2C19* enzyme. Test kit cartridges must be stored between −15°C and −80°C	*2, *3, *17	The test takes 1 hour to run for each cartridge.

Name of test	Type of test	General information	*CYP2C19* alleles targeted	Time to run test
		and used within 15 minutes of removal from the freezer. Results are stored locally on a laptop connected to the device and can be exported as a PDF.		
Genedrive *CYP2C19* ID Kit	Point of care	Used for qualitative in vitro molecular diagnostic tests. Test for *CYP2C19* under development and likely to be available to NHS in early 2023. Results will be able to be transferred electronically to patient records by internet or through third-party middleware, or printed with an optional label printer.	*2, *3, *4, *8, *17, *35	Less than 1 hour to run for each cartridge.
Sanger *CYP2C19* sequencing	Laboratory	Routine genomic testing approach used in all NHS genomic laboratory hubs. This test sequences a single DNA fragment at a time.	All alleles	Depends on sample numbers and number of alleles being tested for – more will mean longer turnaround times
Next-generation *CYP2C19* gene sequencing	Laboratory	Sequences millions of short DNA sequences in parallel.	All alleles	Quicker turnaround for large sample numbers compared to Sanger sequencing.

Name of test	Type of test	General information	*CYP2C19* alleles targeted	Time to run test
Targeted *CYP2C19* gene variant	Laboratory	Targeted genotyping assay amplifies and detects specific variants in target genomic DNA. Examples include: • Polymerase chain reaction (PCR)-based SNP genotyping assays using fluorescent reporter systems, such as TaqMan (ThermoFisher) • Other PCR-based genotyping panels that use proprietary detection methods, such as the xTAG *CYP2C19* Kit v3 (Luminex) • Variant detection using mass spectrometry, such as MassARRAY (Agena Bioscience) • Loop-mediated isothermal amplification (LAMP), such as the LAMP human *CYP2C19* mutation KIT (LaCAR MDx Technologies)	Potential to target all alleles but usually target specific alleles.	The methods of detection, equipment requirements and throughput capability vary between systems.

1.4 Place of the technology in the treatment pathway

Guidelines on appropriate antiplatelet therapy for the secondary prevention of stroke vary. The two main guidance documents of relevance are NICE guidance NG128 on stroke and TIA[3] and guidance from the Royal College of Physicians (RCP) on therapy for secondary prevention for people with stroke.[22] The treatment pathway is shown in

Figure 1 for (i) adults with non-minor ischaemic stroke and (ii) adults with minor stroke or TIA. Pathways are different in children and for patients with atrial fibrillation. In children, aspirin rather than clopidogrel is currently recommended to prevent recurrence. Other antiplatelets, including clopidogrel, should only be considered when there are other risk factors for cerebrovascular disease.[23] People who have disabling ischaemic stroke, and who are in atrial fibrillation, should be treated with aspirin for 2 weeks after which anticoagulation treatment should be considered.[3]

Everyone with a suspected stroke should be admitted to a specialist acute stroke unit following assessment by first responders. NICE guidance NG128 states that within 24 hours of ischaemic stroke onset, daily aspirin 300mg should be offered unless the individual is

intolerant to aspirin.[3] Aspirin should be continued until 2 weeks after stroke symptoms begin or until discharged.

For people with high-risk TIA (often defined as patients with an ABCD2 score of ≥ 4)[24] or minor stroke, dual anti-platelet therapy of aspirin and clopidogrel is often used in line with guidance from the European Stroke Organisation, beginning with 2 weeks acute dual therapy. [25] After 2 weeks of acute treatment, NICE guidance recommends long-term antiplatelet treatment with clopidogrel monotherapy.[3] However, in practice patients are often given dual treatment with aspirin and clopidogrel before moving to longer term clopidogrel monotherapy. The recommended duration of dual therapy varies according to guidance from up to 21 days,[8] 21 to 90 days,[26] or up to 90 days.[27] This is consistent with the NICE clinical knowledge summary on secondary prevention following stroke and TIA, updated in 2022, which states that "dual therapy with aspirin plus clopidogrel (for up to 90 days) or aspirin plus ticagrelor (for 30 days) may be initiated in secondary care for some people (for example people at high risk of TIA, or those with intracranial stenosis) followed by antiplatelet monotherapy."[27] In those who are intolerant of aspirin, the RCP guidelines suggest clopidogrel could be considered as initial treatment.[22]

For patients with TIA that is not high-risk (ABCD2 score of < 4), NICE guidance (TA210) recommends urgent treatment with modified-release dipyridamole in combination with aspirin in the first instance.[9] However, the NICE clinical knowledge summary advises clopidogrel monotherapy following acute 2-week treatment with aspirin,[27] and the Royal College of Physicians Guidelines recommend clopidogrel regardless of stroke risk score for TIA patients. [22]

Currently, genetic testing for clopidogrel resistance is not routinely performed in the NHS before using clopidogrel in ischaemic stroke or TIA patients. If genetic testing to inform preventative treatment is introduced in the NHS in people with stroke, it could take place in hospital before long-term anti-platelet treatment is started 2 weeks post-ischaemic stroke, or sooner in the case of TIA. People with an allele suggesting poor or intermediate metabolism of clopidogrel could be treated with an alternative to clopidogrel, while those without these alleles would receive standard clopidogrel treatment. Alternative treatments could include the following:

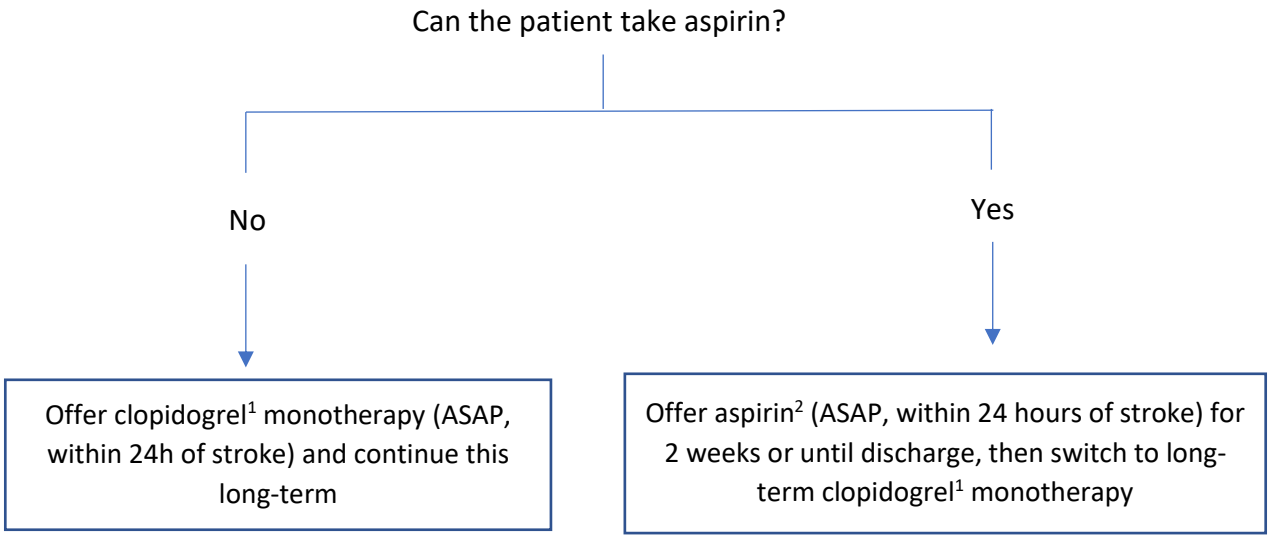
- Aspirin
- Aspirin combined with dipyridamole
- Clopidogrel dose escalation *(Unlicensed)*
- Ticagrelor *(Unlicensed)*

We heard from our clinical advisors that of these the most likely to be used in NHS practise would be aspirin combined with dipyridamole, with a potential treatment pathway shown in Figure 2 for people with (i) non-minor ischaemic stroke and (ii) minor stroke or TIA. Ticagrelor does not have marketing authorisation in the UK for secondary prevention after ischaemic stroke or TIA. However, we have heard from clinicians that it is sometimes used

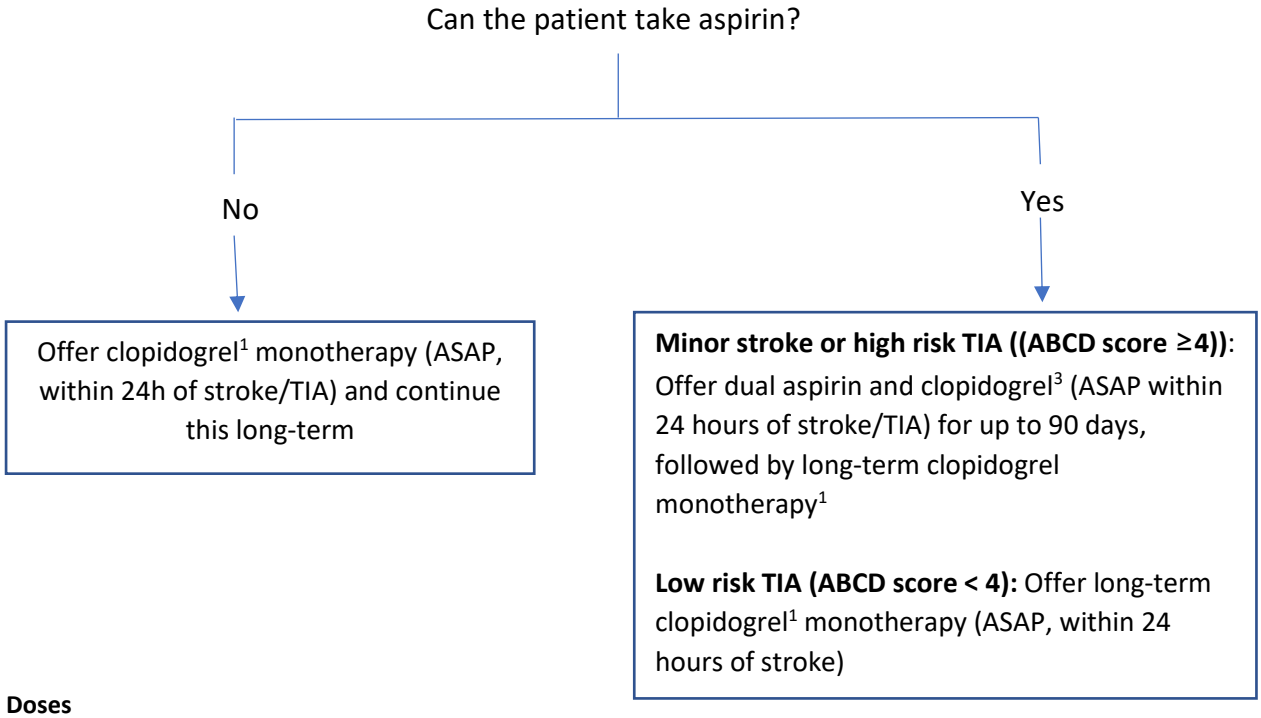
in high-risk patients, although it is not considered in those at high-risk of bleeding due to an elevated bleeding risk. There is a suspended NICE technology appraisal on ticagrelor for preventing stroke after previous ischaemic stroke or high-risk TIA.[28] This was suspended by the company on 11 May 2021, who also withdrew their application for marketing authorisation for stroke to the European Medicines Agency (EMA) in December 2021.[28] Ticagrelor in combination with aspirin for up to 30 days is however included as a potential treatment for secondary prevention for some people (for example people at high risk of TIA, or those with intracranial stenosis) in the 2022 NICE clinical knowledge summary on secondary prevention following stroke and TIA.[27]

Figure 1 Treatment pathway for current NHS practice: (i) Non minor ischaemic stroke, (ii) Minor ischaemic stroke (with NIHSS <3) or TIA

(i) Non-minor ischaemic stroke



(ii) Minor stroke (with NIHSS < 3) or TIA

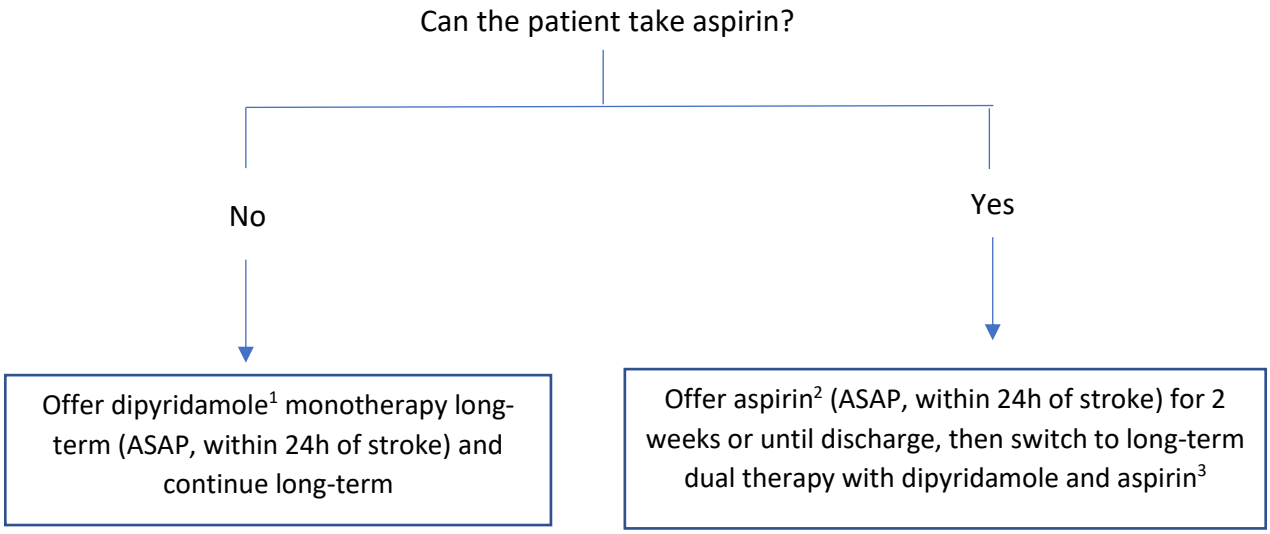


Doses

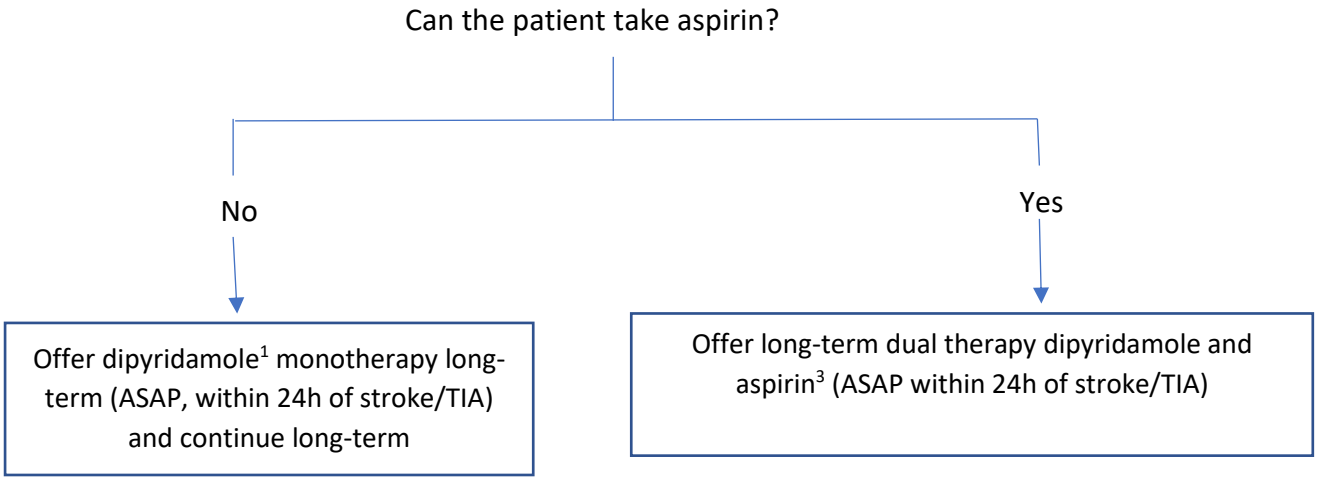
1. clopidogrel 75mg daily (after loading dose of 300mg)
2. aspirin 300mg daily
3. aspirin 75mg daily plus clopidogrel 75mg daily (after loading dose of 300mg)

Figure 2 Potential treatment pathway for people with *CYP2C19* Loss of Function (LOF) alleles: (i) Non minor ischaemic stroke, (ii) Minor stroke (with NIHSS <3) or TIA

(i) Non-minor ischaemic stroke



(ii) Minor stroke (with NIHSS < 3) or TIA



Doses

1. modified-release dipyridamole 200mg twice daily
2. aspirin 300mg daily
3. aspirin 75mg daily plus modified-release dipyridamole 200mg twice daily

2 Objectives

The overall aim of this project is to summarise the evidence on the clinical- and cost-effectiveness of genetic testing to identify clopidogrel resistance in people with non-cardioembolic ischaemic stroke or TIA. We defined the following objectives to address the overall aim:

Objective 1: Do people who have genetic testing for clopidogrel resistance, and who are treated based on these results, have a reduced risk of secondary vascular occlusive events compared to those who are not tested and are treated with clopidogrel following standard guidelines?

Objective 2: Do people who have loss of function alleles associated with clopidogrel resistance have a reduced risk of secondary vascular occlusive events if treated with alternative interventions compared to treatment with clopidogrel?

Objective 3: Do people who have loss of function alleles associated with clopidogrel resistance have an increased risk of secondary vascular occlusive events when treated with clopidogrel compared to patients without loss of function alleles who are treated with clopidogrel?

Objective 4: What is the accuracy of point of care genotype tests for detecting variants associated with clopidogrel resistance?

Objective 5: What is the technical performance (other than accuracy) and cost of the different *CYP2C19* genetic tests?

Objective 6: What is the cost-effectiveness of different POCT and laboratory based genetic tests for clopidogrel resistance compared with not testing for clopidogrel resistance?

Objective 1 to 3 focus on assessing whether people with LOF alleles have better outcomes if treated with alternative anti-platelet drugs. Objectives 4 and 5 evaluate the accuracy and technical performance of *CYP2C19* genetic tests.

3 Assessment of clinical effectiveness

A systematic review was conducted to summarise the evidence on the clinical effectiveness of clopidogrel genotype testing after ischaemic stroke, including minor stroke and TIA. The systematic review followed the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care, [29] the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy[30], and the NICE Health Technology Evaluations Manual.[31] The protocol was registered on the PROSPERO database (CRD42022357661) and the systematic review is reported according to PRISMA-2020 and PRISMA-DTA guidelines.[32, 33] The systematic review was supplemented by a survey of manufacturers of POCT tests and genomic laboratory hubs to collect information on the technical performance of the different CYPC19 genetic tests (Objective 5; Section 3.5).

3.1 Inclusion and exclusion criteria

3.1.1 Objectives 1, 2 and 3

Inclusion criteria for objectives 1, 2 and 3 are summarised in Table 3. Studies that met these criteria were eligible for inclusion:

Table 3 Inclusion Criteria for Objectives 1, 2 and 3

	Objective 1	**Objective 2**	**Objective 3**
Participants	Adults or children who have experienced an Ischaemic Stroke or TIA	Adults or children who have experienced an Ischaemic Stroke or TIA and who have one or two *CYP2C19* LOF alleles associated with under metabolism of clopidogrel (e.g. *2 or *3)	Adults or children who have had an ischaemic stroke or TIA who are treated with clopidogrel alone or in combination with a second antiplatelet drug.
Intervention/ exposure	Any *CYP2C19* genotype test followed by any alternative antiplatelet drug(s).	Any alternative antiplatelet drug(s).	Presence of one or two *CYP2C19* LOF alleles for metabolism of clopidogrel (e.g. *2 or *3)
Comparators	No testing; all patients treated with clopidogrel alone or in combination with a second antiplatelet drug	Clopidogrel alone or in combination with a second antiplatelet drug	No LOF alleles
Outcomes	Incidence of secondary vascular occlusive events Adverse events (e.g. bleeding or headache) Mortality Time to starting antiplatelet treatment, or to change of antiplatelet treatment Impact of test result on decisions about care Health care resource use (e.g. Length of hospital stay) Quality of life Healthcare costs		

	Objective 1	Objective 2	Objective 3
Study design	Randomised controlled trials (RCT) or cohort studies	RCT or cohort studies	Cohort studies

3.1.2 Objectives 4 and 5

Inclusion criteria for objectives 4 and 5 are summarised in Table 4. Additional data for objective 5, in particular for standard laboratory-based tests, were identified through the survey of laboratories (section 3.5). Studies that fulfilled the following criteria were eligible for inclusion:

Table 4 Inclusion criteria for objectives 4 and 5

Participants	Adults or children who have experienced an Ischaemic Stroke or TIA. If insufficient studies are found in these populations then we will include studies in other populations; we do not anticipate that test accuracy is likely to differ substantially based on population.
Index test	Either of the following POCT: Genomadix or Spartan cube *CYP2C19* system *(referred to as "Genomadix Cube").* Studies of the previous version of this test, the Spartan RX *CYP2C19* System and Spartan FRX *CYP2C19* were also eligible. Genedrive system *CYP2C19* test *(referred to as "Genedrive test" from here)*
Target condition	Presence of at least one *CYP2C19* LOF allele
Reference standard	Any reported laboratory-based reference standard for *CYP2C19*
Outcomes	Data on sensitivity and specificity or sufficient data to construct a 2x2 table of test accuracy. Test failure rate; number of people with variant forms of *CYP2C19* (and incidence of particular alleles); time to results; ease of use of test; cost of testing
Setting	Any setting
Study design	Any primary study

3.2 Study identification

Studies were identified using bibliographic and non-bibliographic search methods following the guidance in the NICE handbook.[31] We carried out two searches:

Search 1, undertaken on August 10 2022, aimed to address objectives 1, 2 and 3, taking the following form: ((search terms for Clopidogrel) AND (search terms for *CYP2C19*))

Search 2, undertaken on August 11 2022, aimed to address objectives 4 and 5, taking the following form: ((terms for point of care tests OR Genomadix OR Genedrive) AND (terms for *CYP2C19* OR terms for Clopidogrel))

The search strategies are reported in *Appendix 1*: Literature search strategies, using a search narrative.[34] They were developed by one researcher (CC) and checked by another (ET) using the Peer Review of Electronic Search Strategies (PRESS) checklist.[35].

3.2.1 Bibliographic searching

We searched the following databases from inception:

- MEDLINE (MEDALL) via Ovid
- Embase via Ovid
- The Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley
- The Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO Host
- ECONLit via EBSCO Host
- Health Technology Assessment (HTA) Library via the York CRD interface
- NHS EEDs Via the York CRD interface
- Tufts CEA Register via the Tufts Medical Centre website.

3.2.2 Non-bibliographic search methods

We also searched the following trials registry resources:

- ClinicalTrials.gov via https://www.clinicaltrials.gov/
- World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) via https://www.who.int/clinical-trials-registry-platform

We screened the manufacturer submissions and their respective websites to identify additional relevant studies.

For all objectives, the reference lists of studies included at full-text screening were checked through manual review. Reference lists of any reviews (systematic or non-systematic) identified by our searches were also screened. For objectives 4 and 5 (the accuracy review), studies fulfilling eligibility criteria at full-text were forward citation searched using the Science Citations Index (Clarivate).

3.2.3 Managing the searches

Data were exported to EndNote X9 for deduplication using the default deduplication settings.

3.3 Review strategy

Two reviewers independently screened titles and abstracts identified by the searches. Full copies of all reports considered potentially relevant were obtained and two reviewers independently assessed these for inclusion. Any disagreements were resolved by consensus or discussion with a third reviewer.

Data were extracted using standardised data extraction forms developed in Microsoft Access. Data extraction forms were piloted on a small sample of papers and adapted as necessary. Data were extracted by one reviewer and checked in detail by a second reviewer. Any disagreements were resolved by consensus or discussion with a third reviewer.

3.3.1 Objectives 1, 2 and 3

Data were extracted on the following: study name, study design (RCT or cohort study), objective that study addresses, funding sources (public, industry, mixed), study location, participants (type of stroke, age, sex, ethnicity), inclusion criteria, omeprazole use, number of eligible patients, number of patients recruited, *CYP2C19* test details (test used, alleles tested for and definition of poor metaboliser), interventions (e.g. clopidogrel, alternative anti-platelet drug), and incidence of secondary vascular occlusive events (number in intervention/exposed group and number in control group). Data were also extracted on the following secondary outcomes, where reported: adverse events (e.g. bleeding or headache), mortality, time to starting antiplatelet treatment, or to change of antiplatelet treatment, impact of test result on decisions about care, health care resource use (e.g. Length of hospital stay), quality of life and healthcare costs.

Dichotomous data were extracted as number of patients with events and/or number of events and total number of patients in each treatment arm. Data on follow-up time was also extracted. Where available, summary effect estimates together with 95% CIs and p-values for comparisons between groups together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic were also extracted. None of the studies reported continuous or categorical outcome data. Where studies reported results stratified by ethnicity, these were extracted separately.

3.3.2 Objectives 4 and 5

Data were extracted on the following: funding (industry, non-industry, mixed), study location, start date, study design, inclusion criteria, exclusion criteria, participants (condition, age, sex, ethnicity), POCT genetic test (Genomadix cube or Genedrive test) and reference standard test details (name, number tested, alleles tested for, who administered test, threshold for positive result), and accuracy data. Where reported, we also extracted data on the following secondary outcomes: test failure rate; number of people with variant forms of *CYP2C19* (and incidence of particular alleles); time to results; ease of use of test; cost of testing.

Accuracy data were extracted as 2x2 tables comparing the POCT with a laboratory reference standard. Where 2x2 data were not available, data were extracted on any reported estimates of accuracy (e.g., sensitivity, specificity, area under the receiver operating characteristic curve (AUC ROC)). Authors of studies were also contacted to request data to allow construction of 2x2 tables.

Each individual will have two alleles – one or both of these may be associated with LOF. As described in Section 1.2.1, some alleles are associated with over-metabolism rather than poor metabolism (e.g., *17). As no difference in treatment is recommended in people who are over-metabolisers, these alleles were grouped with those that are associated with normal function. This gave three potential categories for each individual:

- Two LOF alleles (e.g. *2/*2 or *3/*3 or *3/*2)
- One LOF allele (e.g. *2/*1, *3/*1, *3/17, or *2/*17)
- Normal function (e.g. *1/*1 or *1/*17)

These categories were dichotomised into alleles that encode for normal function and those that are non-functional. A "positive" test result (non-functional) was defined as the presence of at least one LOF allele. A positive reference standard was as reported in the study - either detection of any loss of allele function, or detection of those alleles that are detectable by the POCT evaluated. If data were reported for both possible reference standards then data were extracted for both of these. The reference standard was also dichotomised so that a "poor metaboliser" was defined as having at least one LOF allele.

Where multiple sets of 2x2 data were reported in a single study, for example for different tests, thresholds, or alleles, all data were extracted.

3.4 Risk of Bias assessment

The risk of bias in included RCTs and controlled clinical trials (CCTs) was assessed using the ROB 2 tool.[36] Observational studies of exposure were assessed using the ROBINS-E tool.[37] Diagnostic accuracy studies were assessed using a modified version of QUADAS-2.[38] We omitted two signalling questions – "If a threshold was used, was it pre-specified" in the Index Test domain, and "Was there an appropriate interval between index test and reference standard" in the Flow and Timing domain. Genetic tests do not have a threshold in the standard test accuracy sense – they identify the presence or absence of certain alleles and so we considered that this question did not apply to this review. Similarly, the question on timing is not relevant for genetic tests as the allele would either be present or not and this would not change over time: therefore the time interval between tests does not matter. We did not formally assess applicability as our research question was broad and all studies were applicable; instead, we extracted data on potential sources of variation such as population and considered these in our synthesis. Details of the tools are provided in *Appendix 4*: Data extraction tables. Quality assessment was undertaken by one reviewer and checked by a second reviewer. Disagreements were resolved by consensus or discussion with a third reviewer.

3.5 Survey of laboratories

We conducted a web-based survey to gather data on the technical performance characteristics of *CYP2C19* genetic tests (objective 5). The survey was sent to 7 genomic laboratory hubs who are responsible for delivering genomic testing in the NHS in England

and to genomic laboratory hubs in Wales, Northern Ireland and Scotland. The survey collected information on:

- Platforms capable of performing *CYP2C19* testing available in the lab
- Preferred test platform for running *CYP2C19*
- Reason for preference
- For each platform or genetic test we ask for information on:
    - Alleles that would be tested for
    - Impact of having to test for additional alleles
    - Time to results
    - Resources for running tests:
        - Staff time
        - Staff grade
        - Cost per test to run
        - Maintenance of machines/quality assurance
        - Additional administrative resources
    - Ease of use
    - Test failure rate
    - Current testing capacity
    - Whether faster turnaround would be possible with additional resources and what these would be
    - Whether additional testing capacity would be possible with additional resources and what these would be
    - Could test be performed in local testing laboratories
- Facilitators and barriers to implementing testing, and what platform would be most likely to be implemented
- How feasible would it be to install POCT tests in local laboratories and extra resources required

3.6 Synthesis methods

For each objective, a narrative summary of all the included studies is presented. This includes a summary of the study characteristics and study quality.

3.6.1 Objectives 1, 2 and 3

We extracted and used hazard ratios (HR) presented by the studies where available. For observational (cohort) studies, estimates that had been adjusted for potential confounders were used if reported, otherwise unadjusted estimates were used. When HRs were not provided in the study publication, they were estimated with a hazard rate analysis of event frequencies in relation to time at risk (when follow-up time was available), or from 2x2 tables of event numbers using complementary log-log (cloglog) transformations, assuming proportional hazards.[15] For studies with a zero-cell, we applied a "continuity correction", adding 0.5 to every cell.

Objective 1

We did not identify sufficient data on similar intervention comparisons to carry out a meta-analysis for any outcomes for objective 1. We provide a narrative summary of results from these studies, presented together with a forest plot showing hazard ratios estimates comparing secondary occlusive vascular events between patients who received a genetic test and were treated accordingly, against patients with standard treatment with clopidogrel.

Objective 2

Where at least two studies evaluated the same outcome, meta-analysis was used to generate summary effect estimates for each objective. We had intended to perform random effects meta-analyses, but insufficient data were available for this. Therefore fixed effect meta-analyses were performed. Forest plots were produced for each outcome showing individual and summary HRs with 95% confidence intervals (CIs), stratified by interventions evaluated. To inform decisions on whether to conduct network meta-analyses, we drew network plots of treatment comparisons for each outcome, to assess whether networks were connected and whether loops of evidence existed. [39] Network meta-analysis was not subsequently performed for any outcome.

Objective 3

We used random effects meta-analysis to estimate summary HRs, 95% CIs, and 95% prediction intervals, for each outcome evaluated by the included studies, when at least three studies were available. Heterogeneity and inconsistency across studies were quantified using the tau and I^2 statistics. A restricted maximum likelihood (REML) approach was used to estimate tau.[40] Fixed effect meta-analyses were performed as sensitivity analyses, or as the sole analyses if only two studies were available. Funnel plots were produced for each outcome, to assess the presence of small study effects.[41, 42]

We used subgroup analysis and meta-regression to investigate potential heterogeneity in the HR for risk of secondary vascular occlusive events. In investigating heterogeneity, we included different vascular event outcomes (composite outcome, stroke, ischaemic stroke) in the same analyses. This allowed us to include more studies in these analyses, increasing power to detect differences in HR across variables. This was a post hoc decision based on observing that estimates of HR were very similar for these outcomes within studies that reported on two or more. For these analyses, we selected one outcome per study related to a secondary vascular event based on the following hierarchy: composite outcome, any stroke, ischaemic stroke.

We conducted subgroup analysis and univariable meta-regression to explore whether the HR for risk of secondary vascular occlusive events in those with LOF compared to those with LOF alleles varied with any of the following covariates:

- Ethnicity: Asian, White, mixed, Hispanic, black or not reported (pre-specified)
- Primary event: stroke, stroke or TIA, TIA (pre-specified)

- Risk of bias: high vs low (pre-specified)
- Clopidogrel regimen: clopidogrel alone (which includes clopidogrel plus initial aspirin), clopidogrel plus long-term aspirin, clopidogrel plus optional aspirin (which also includes other antiplatelets or anticoagulants) *(post-hoc exploratory)*
- Proton-pump inhibitor use: <10%, 10-20%, 20-30%, 40-50%, >50% or not reported *(post-hoc exploratory)*
- Duration of follow-up: 3 months, 6 months, 1 year, 1-3 years, 3-5 years or not reported (post-hoc exploratory)
- Loading dose (whether a higher initial dose of clopidogrel was administered): yes, no not reported

Where a study reported multiple categories (e.g., estimates stratified by ethnicity), these separate estimates were used in the relevant subgroup analyses.

3.6.2 Objective 4

Estimates of sensitivity and specificity of the POCTs were calculated from each set of 2 x 2 data, under the assumption that the laboratory reference standards have correctly categorised all study participants. Analyses were stratified according to POCT. Summary estimates of sensitivity and specificity together with 95% confidence intervals (CIs) were calculated using bivariate random effects meta-analysis of sensitivity and specificity, using binomial likelihoods.[43, 44] Coupled forest plots of sensitivity and specificity were used to display results from individual studies and summary estimates, to allow visual assessment of heterogeneity. Due to homogeneity of estimates across studies, heterogeneity was not formally investigated.

3.6.3 Objective 5

We did not identify sufficient data to carry out a meta-analysis for the secondary outcomes that address objective 5. We provide a narrative summary of results from these studies, presented together with a summary of the results of the web-based survey (section 4.6.2).

4 Results of clinical effectiveness review

4.1 Results of the searches

The process of study identification and selection is summarised in Figure 3 (Objectives 1-3) and Figure 4 (Objectives 4-5). Studies included , stratified by objective, and studies excluded at full-text are reported in *Appendix 2*: Tables of included, on-going, or excluded studies .

4.1.1 Search 1: objectives 1-3

The searches of bibliographic databases and trials registries identified 4338 references. After initial screening of titles and abstracts, 131 references were considered to be potentially relevant and ordered for full paper screening; of these, 29 studies reported in 50 reports were included in the review: two studies for objective 1; seven studies for objective 2; and 25 studies for objective 3. Five studies were included for objectives and 3. We identified three on-going studies, one for objective 1, and two for objective 3 (*Appendix 2*: Tables of included, on-going, or excluded studies).

4.1.2 Search 2: objectives 4-5

The searches of bibliographic databases and trials registries identified 555 references. After initial screening of titles and abstracts, 35 references were considered to be potentially relevant and ordered for full paper screening; of these, 21 studies reported in 25 publications were included in the review. Nine studies for objective 4 (three of these reported a pre-trial and a main-trial) and 17 studies for objective 5. Some studies were eligible for both objectives. All 21 references included in the manufacturer's submissions were identified by our searches; four were included in the review and 17 references did not meet inclusion criteria (*Studies included in manufacturers' submissions*).

Figure 3 Prisma flow chart: objectives 1-3

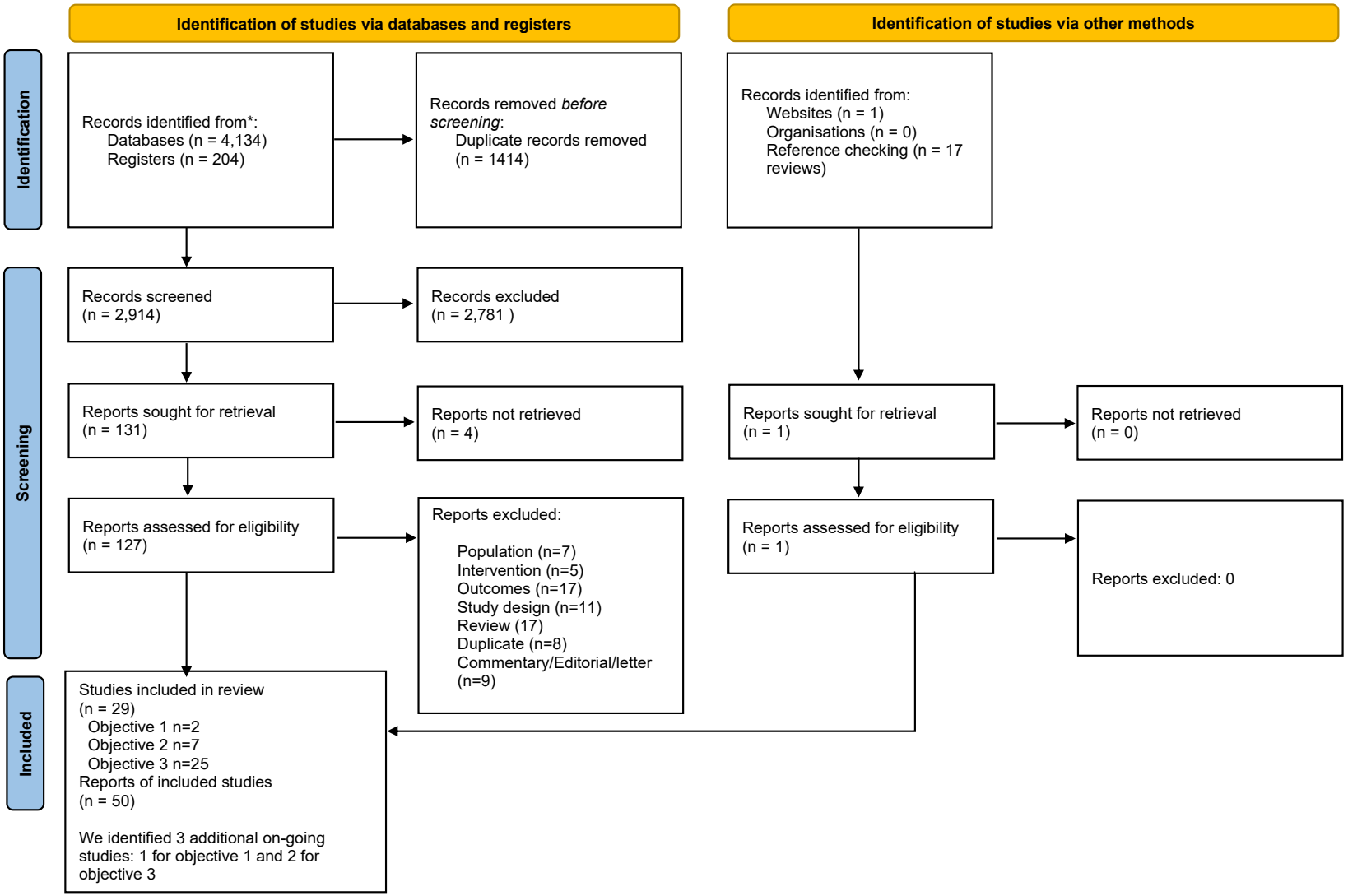
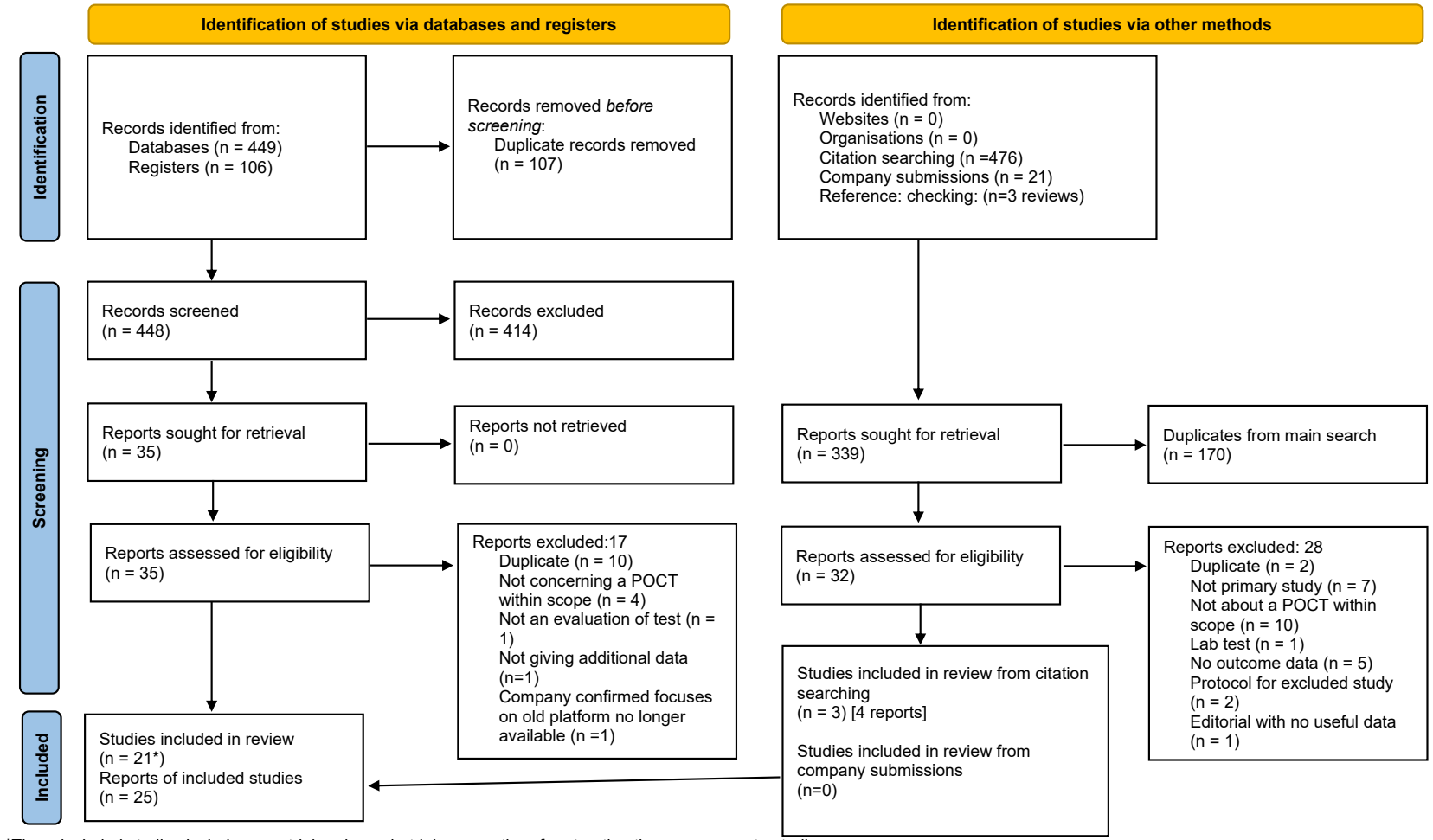


Figure 4 PRISMA flow chart: objectives 4-5



*Three included studies include a pre-trial and a main-trial, we are therefore treating these as separate studies

4.2 Objective 1

Two controlled trials from China were included for objective 1.[45, 46] Full details on these studies are reported in *Appendix 4*: Data extraction tables. Both studies were small (80 and 190 patients) and did not provide sample size or power calculations. Duration of follow-up was 90 days in one study and 1 year in the other. One of these studies was reported in Chinese and was extracted with help from a native Chinese speaker and using Google Translate.[45] Both studies used laboratory based testing to determine the presence of LOF alleles.

Xia et al.[45] allocated 80 patients to two groups:

- Group A: All received clopidogrel 75 mg/day
- Group B: genotyped for the *1, *2, *3 and *17 alleles
    - No LOF alleles: clopidogrel 75 mg/day (same as control)
    - One LOF allele: clopidogrel 150 mg
    - Two LOF alleles: ticagrelor *(this was recorded as "tigrillo" in the English abstract but translation of the Chinese term suggested that this was ticagrelor)*

Lan et al.[46] genotyped all participants for the *1, *2, *3, and *17 alleles. Participants were then divided into 2 groups (group A and B with 90 patients in each) so that equal numbers with each potential genotype were included in each group. All patients were initially treated with clopidogrel (300 mg loading dose followed by 75 mg/day) and aspirin 100 mg day for 21 days. Treatment after this varied by intervention group and presence of LOF alleles:

- Group A: clopidogrel 75 mg/day
- Group B:
    - normal metaboliser (no LOF alleles) and extensive metaboliser (1 or 2 *17 alleles): clopidogrel 75 mg/day
    - poor metaboliser (1 or 2 LOF alleles): aspirin 100 mg/day

This study did not technically meet inclusion criteria for objective 1, as all patients were tested, however, as half of the tested patients were treated as if they had not been tested (i.e., standard treatment), we considered it appropriate to include this study for this objective.

Both studies enrolled patients with a stroke as a primary event. Mean age was 69 years and percentage of female participants was 38% in both studies. One study was funded by non-industry[46] and the other did not report funding sources[45].

4.2.1 Risk of Bias

Both studies[45, 46] were judged at high risk of bias for all outcomes extracted (Table 5). There was no clear information on the allocation process, and they were not randomised – the Lan study[46] allocated patients so that equal numbers of each genotype were included in each

group, but it was unclear how this was done. There was no evidence of a pre-registered protocol for either study. Full details on risk of bias assessment are presented in *Appendix 4*: Data extraction tables

Table 5 Risk of bias assessment for CTs evaluating Objective 1

Study Details	Domain						Rationale
	1	2	3	4	5	Overall	
Lan et al (2019)[46]	☹	☹	☹	☺	😐	☹	Not randomised. Patients and carers were likely aware of the allocation, and there is no information on potential deviations, which could have affected the outcome. High proportion of loss to follow-up. No evidence of a pre-registered protocol.
Xia et al (2021)[45]	☹	☹	☺	☺	😐	☹	Not randomised. Patients and carers were likely aware of the allocation, and there is no information on potential deviations from the intervention, which could have affected the outcome. No evidence of a pre-registered protocol.

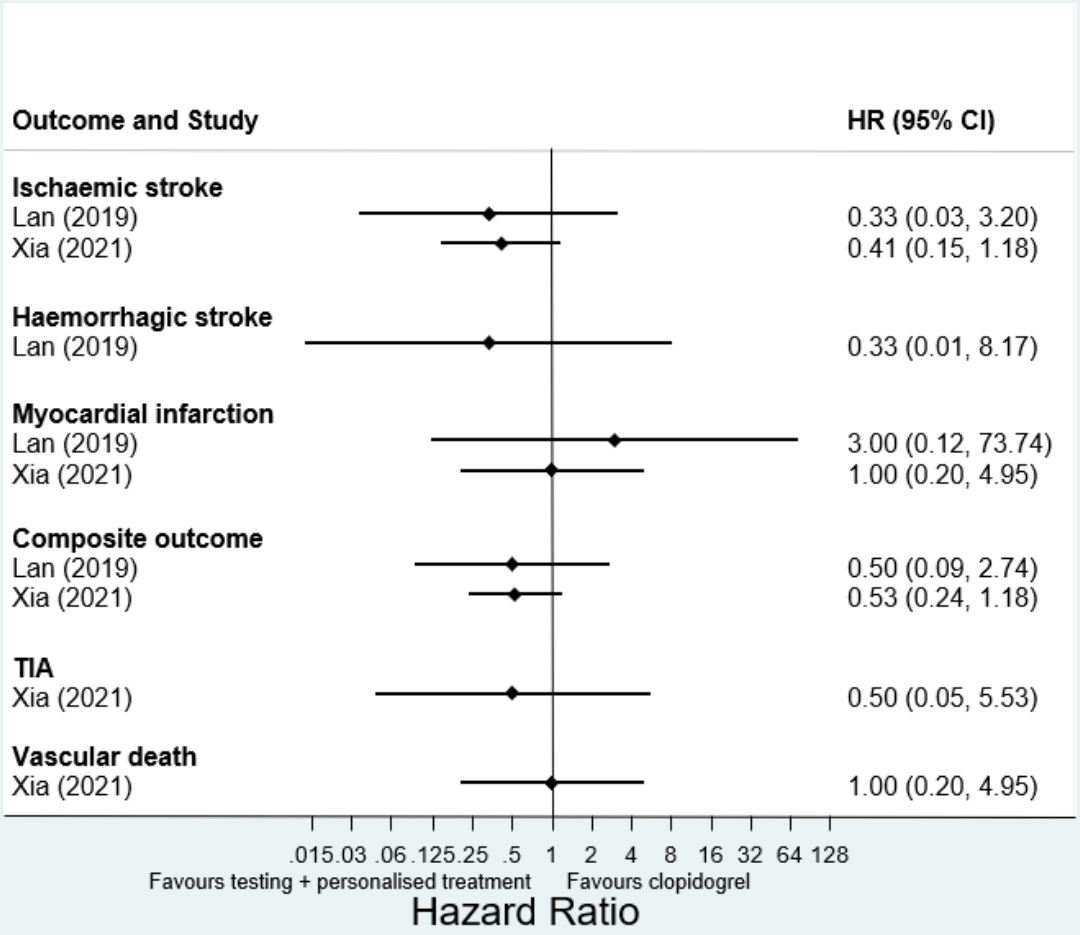
1: Randomisation process; 2: deviation from intended intervention; 3: missing outcome data; 4: measurement of selective outcome reporting outcome

4.2.2 Results

Incidence of secondary vascular events

Both studies [45, 46] presented data on incidence of secondary ischaemic stroke and myocardial infarction. Xia et al.[45] reported the incidence of TIA, vascular death and a composite outcome (including stroke, TIA, myocardial infarction and death). Lan et al.[46] reported data on haemorrhagic stroke. We additionally calculated a composite outcome for Lan et al, adding events for all outcomes reported. Figure 5 provides an overview of results for incidence of secondary vascular events in these studies. We did not meta-analyse results from these two studies due to the differences in interventions. In general, hazard ratios suggested a reduction in composite outcomes, secondary ischaemic stroke, haemorrhagic stroke, and TIA in patients tested for LOF alleles and treated accordingly, but confidence intervals were wide and included the null (HR = 1) in all cases. There was no evidence of benefit in either group for vascular death or myocardial infarction, although incidence of these outcomes was low (<5%). Full details on results are presented in *Appendix 4*: Data extraction tables

Figure 5 Forest plot showing Hazard Ratios (HR) (95%CI) for secondary vascular events in patients treated with clopidogrel compared with patients tested for loss of function alleles and offered personalized treatment.



4.3 Objective 2

Seven trials, reported in 23 full report publications, were included for objective 2.[47-53] All studies were published in English. Two trials were restricted to patients with LOF alleles who were then randomised to different antiplatelet therapies. The other five studies were not restricted based on LOF alleles – patients were randomised to different antiplatelet strategies, a subgroup analysis was then performed restricted to those with LOF alleles. Table 6 shows an overview of the studies included for objective 2. Full details on the studies are reported in *Appendix 4*: Data extraction tables .

Three studies included patients who presented with stroke as their primary event, and four included patients with either stroke or TIA. Five studies took place in China and recruited patients predominantly of Chinese origin, one was done in South Korea including mostly patients of South Korean heritage, and one took place in an international setting, with a majority white (67%) ethnicity. Mean age ranged from 60.8 (standard deviation (SD) 8.7) to

64.8 (SD not reported). The percentage of females ranged from 24% to 45%. Sample size ranged between 154 to 6412.

Three studies compared clopidogrel plus aspirin with aspirin alone. In the clopidogrel arm, one of these studies gave a one-off 300 mg loading dose of clopidogrel and aspirin only for an initial 21-day period, the second did not offer a loading dose of clopidogrel and stopped aspirin after 30 days, and the third gave a 600 mg loading dose of clopidogrel and continued the aspirin in combination with clopidogrel longer term. Two studies compared clopidogrel with ticagrelor – both studies included a 300 mg clopidogrel loading dose and an initial 21-day period when aspirin was given in addition to the clopidogrel or ticagrelor. One study compared clopidogrel with triflusal, without a loading dose in either arm. The final study compared a standard dose of clopidogrel (75 mg) with a higher dose of clopidogrel (150 mg). In this study all patients received a 300 mg loading dose of clopidogrel and 150 mg aspirin for the first 21 days; after this clopidogrel was stopped and patients continued treatment with 150 mg aspirin alone. One study was funded by industry organisations (drug manufacturer), one was funded by non-industry but drugs and genetic tests were supplied by industry, and five were funded by non-industry organisations.

Four studies used laboratory based genotyping tests (Seeplex *CYP2C19* ACE genotyping system and Real-Q *CYP2C19* genotyping kit, Drug Metabolism Enzyme TaqMan Allelic Discrimination Assay, and Sequenom MassARRAY iPLEX platform (Sequenom)), one used a point of care test (GMEX point-of-care genotyping system), and two did not report the type of test that was used. Six studies investigated the two main LOF alleles (*2 and *3) and one study only genotyped one LOF allele (*2).

Duration of follow-up ranged across studies: five studies had a follow-up time of 90 days, 1 followed patients up between 2 and 3 years, and 1 between 4 and 5 years.

Table 6 Characteristics of studies that evaluated Objective 2

Feature	Category	Number of studies
Population	Stroke	3
	Stroke and TIA	4
Comparisons	(Clopidogrel 75 mg/day + aspirin 50-325 mg/day) vs aspirin 50-325 mg/day	1
	(Clopidogrel 75 mg/day + aspirin 75-200 mg/day for first 21/30 days) vs Aspirin	2
	Clopidogrel 75 mg/day vs triflusal 300 mg twice daily	1
	Clopidogrel 75 mg/day (+aspirin 75-300 mg/day for 21 days) vs ticagrelor 90 mg(+aspirin 75-300 mg/day for 21 days)	2
	Clopidogrel 75 mg/day (+aspirin) vs high dose (HD) clopidogrel 150 mg/day (+ aspirin) for 21 days followed by aspirin alone	1
Clopidogrel Loading dose	600 mg	1
	300 mg	4

Feature	Category	Number of studies
	No loading dose	2
Design	RCT	7
Country	South Korea	1
	USA	1
	China	5
Funding	Non-industry	5
	Drugs & tests provided by industry	1
	Industry - other	1
***CYP2C19* test**	Seeplex *CYP2C19* ACE genotyping system and Real-Q *CYP2C19* genotyping kit	1
	Drug Metabolism Enzyme TaqMan Allelic Discrimination Assay	1
	GMEX point-of-care genotyping system	1
	Sequenom MassARRAY iPLEX platform	2
	NR	2
LOF alleles	*CYP2C19* *2 and *3	6
	CYP2C19 *2 only	1
Follow-up time	90 days	5
	2 to 3 years (731 to 1095 days)	1
	4 to 5 years (1461 to 1825 days)	1

Abbreviations: RCT: randomized controlled trial.

4.3.1 Risk of bias

All outcomes assessed for every study were judged at the same level of risk of bias. Four of the seven studies were judged at low risk of bias.[47, 49, 51, 52] One study was judged at some concerns due to lack of information on allocation concealment. Two studies were judged at high concerns, one due to lack of information on loss to follow-up, and the other due to lack of information on the randomisation process and potential deviations from the intended intervention. Table 7 provides a summary of the risk of bias assessment for each study; full details are provided in *Appendix 4*: Data extraction tables.

Table 7 Risk of bias assessment for RCTs evaluating Objective 2

Study Details	Domain						Rationale
	1	2	3	4	5	Overall	
Chen et al (2019)[52]	☺	☺	☺	☺	☺	☺	No concerns
Han et al (2017)[47]	☺	☺	☺	☺	☺	☺	No concerns
Meschia et al (2020)[48]	☺	☺	☹	☺	☺	☹	No clear data on loss to follow up, and it could potentially be related to the outcomes
Wang et al (2016a)[51]	☺	☺	☺	☺	☺	☺	No concerns
Wang et al (2021)[49]	☺	☺	☺	☺	☺	☺	No concerns
Wu et al. (2020)[50]	😐	☺	☺	☺	☺	😐	No information on allocation concealment, baseline differences don't suggest a problem with the randomisation process.
Yi et al (2018)[53]	😐	☹	☺	☺	☺	☹	No information on allocation concealment, no data on blinding and potential deviations from the intended interventions. No information on statistical analysis

1: Randomisation process; 2: deviation from intended intervention; 3: missing outcome data; 4: measurement of selective outcome reporting outcome

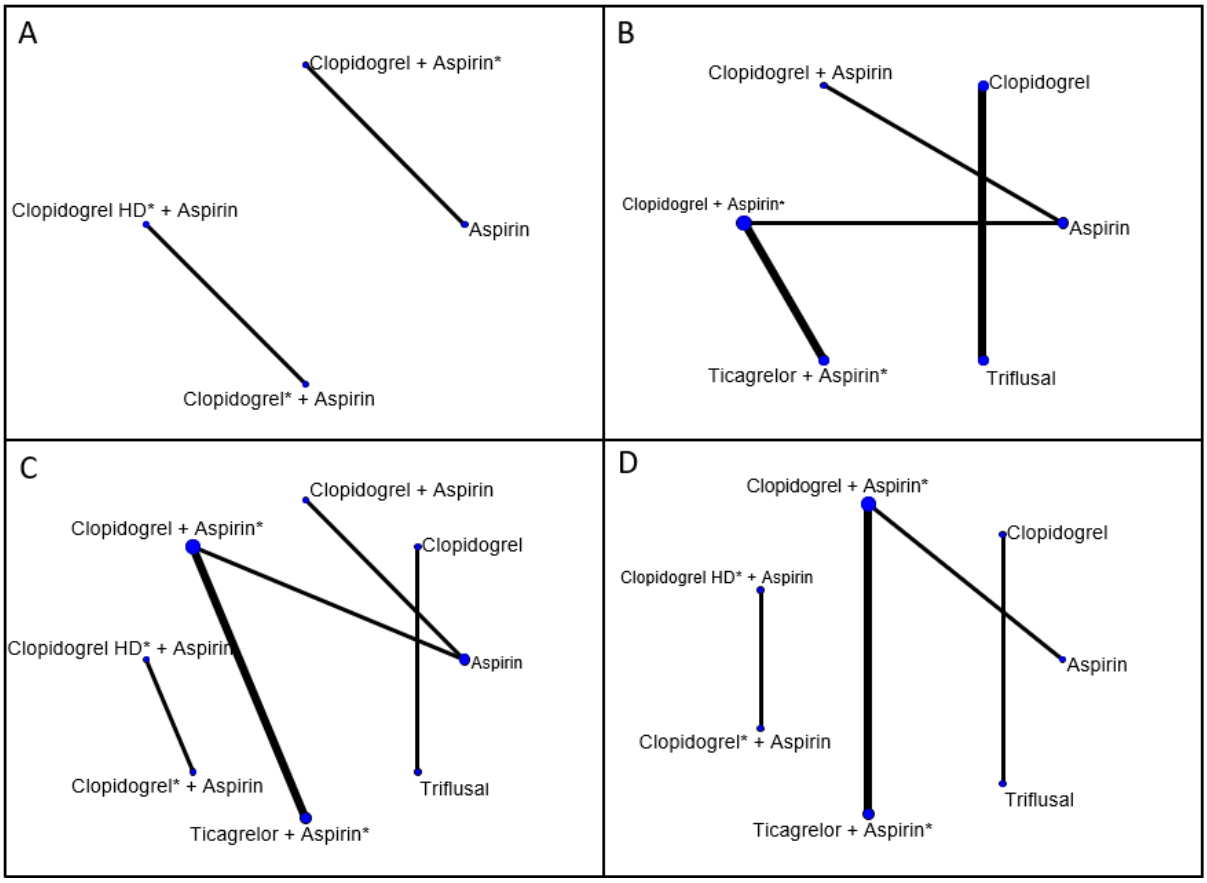
4.3.2 Results

Included studies presented data on incidence of secondary vascular occlusive events, adverse events, and mortality, in people who had LOF alleles associated with clopidogrel resistance, and where treated with alternative interventions compared to standard treatment with clopidogrel. There were no studies reporting data on other outcomes of interest for objective 2.

Secondary vascular occlusive events

Six studies reported data on the incidence of a composite outcome of secondary vascular occlusive events (including stroke, TIA, myocardial infarction, and vascular death), five studies on incidence of secondary stroke, six studies on incidence of secondary ischaemic stroke, one on incidence of secondary TIA, two on secondary myocardial infarction, two on secondary vascular death, and two studies presented data on mortality of any cause. Figure 6 shows the network of intervention comparisons for each outcome. These are all seen to be disconnected, with no loops of evidence, so network meta-analysis was performed. As there were a maximum of 2 studies making any one comparison between treatments, only fixed effect meta-analyses were performed.

Figure 6 Network plots showing drug comparisons for main outcomes in Objective 2



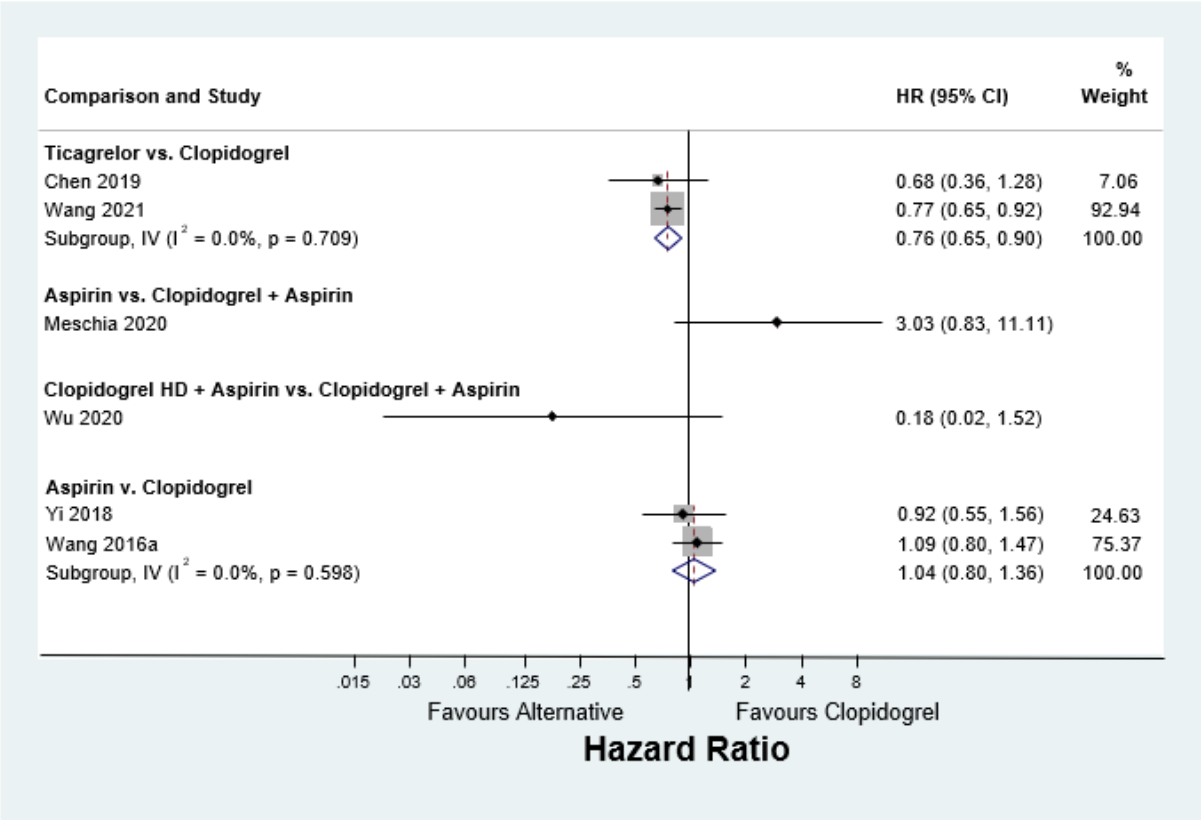
A. Composite outcome, B. Any stroke, C. Ischaemic stroke, D. Any bleeding

* Drug given on a temporary basis (21 – 31 days)

Composite outcome of secondary vascular occlusive events

There was some evidence that treatment with alternatives to clopidogrel reduced the risk of secondary vascular events in those with LOF alleles (Figure 7). Ticagrelor was associated with a reduced incidence of secondary vascular events compared to clopidogrel (summary Hazard Ratio (HR) 0.76, 95% CI 0.65, 0.90; 2 studies). There was a suggestion that high dose clopidogrel plus aspirin was associated with a reduced incidence of secondary vascular occlusive events compared to standard dose clopidogrel plus aspirin, but CIs were wide (HR 0.18, 95% CI 0.02, 1.52; 1 study). There was no difference in the incidence of vascular events amongst those taking clopidogrel alone compared to aspirin, although one other study suggested that the risk of secondary vascular events was higher for those taking aspirin alone compared to clopidogrel plus aspirin. However, this was a small study with very few events (all corresponding to ischaemic strokes), and confidence intervals were wide (HR 3.03, 95% CI 0.83, 11.11). All summary estimates are from fixed effects meta-analysis.

Figure 7 Forest plot showing hazard ratios (HR) (95% CI) for incidence of a composite of secondary vascular events in carriers of loss of function alleles receiving standard therapy with clopidogrel (or clopidogrel + aspirin) compared with an alternative antiplatelet



Stroke

The risk of stroke and ischaemic stroke was also reduced in those with LOF alleles taking ticagrelor compared to those taking clopidogrel (HR 0.76, 95% CI 0.63, 0.92 for any stroke; HR 0.77, 95% CI 0.65, 0.93 for ischaemic stroke; 2 studies; Figure 8 and Figure 9). There was no evidence of a difference in stroke risk between clopidogrel and triflusal, or between clopidogrel alone and aspirin. As with the composite clinical outcome, the study that compared clopidogrel plus aspirin (vs. aspirin alone) for the duration of the study suggested that the risk of stroke was higher for aspirin alone compared to clopidogrel plus aspirin (HR 3.03, 95% CI 0.83, 11.11).

Figure 8 Forest plot showing hazard ratios (HR) (95% CI) for incidence of any stroke in carriers of loss of function alleles receiving standard therapy with Clopidogrel (or Clopidogrel + Aspirin) compared with an alternative antiplatelet

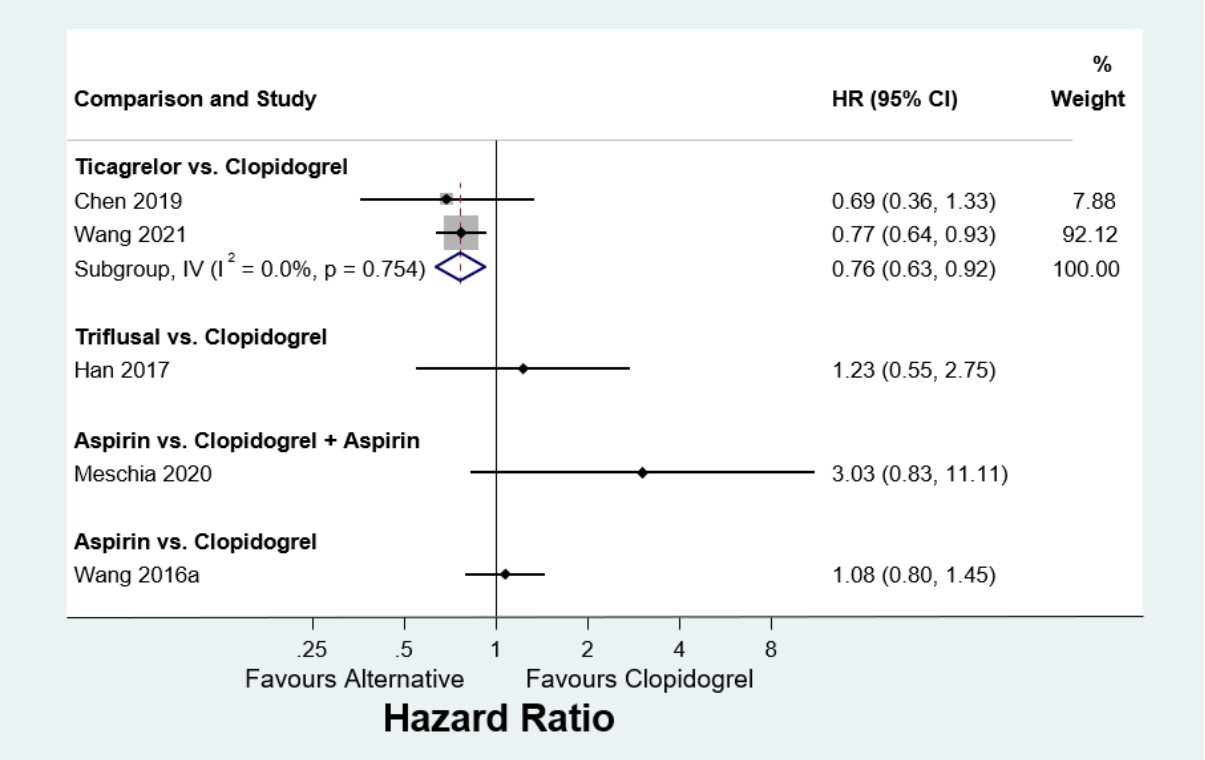
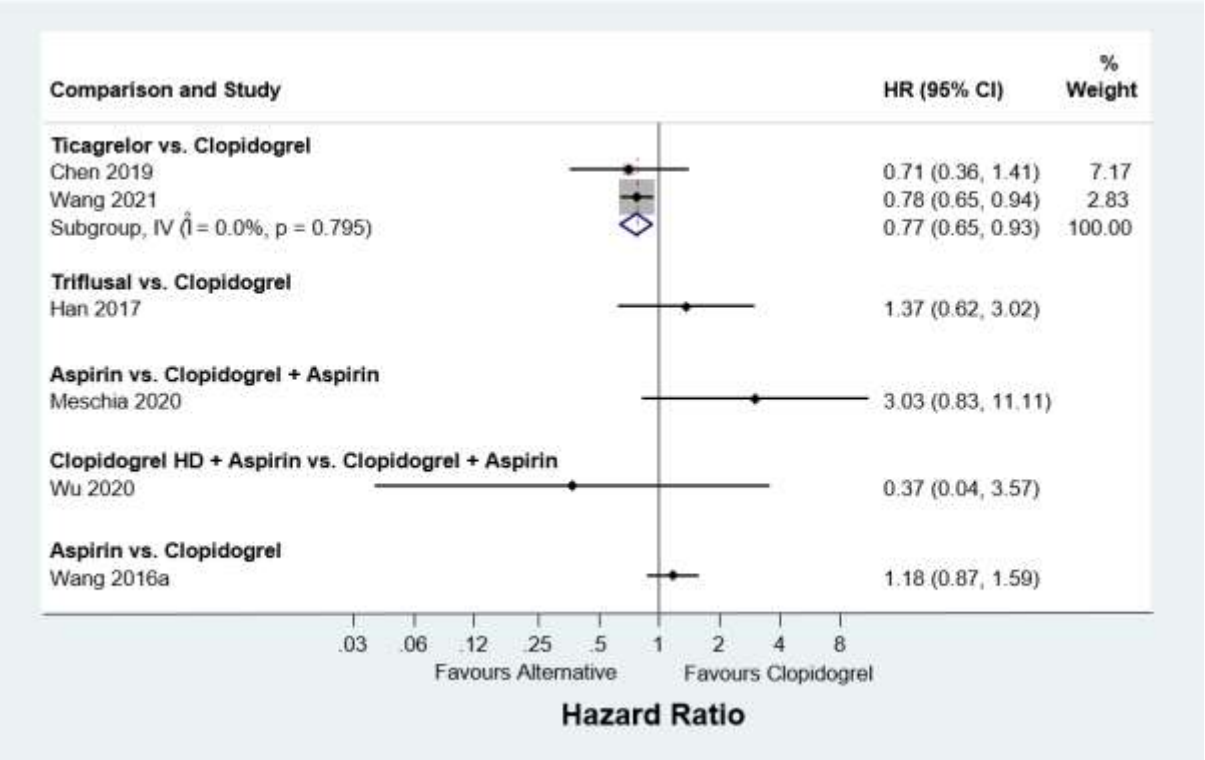


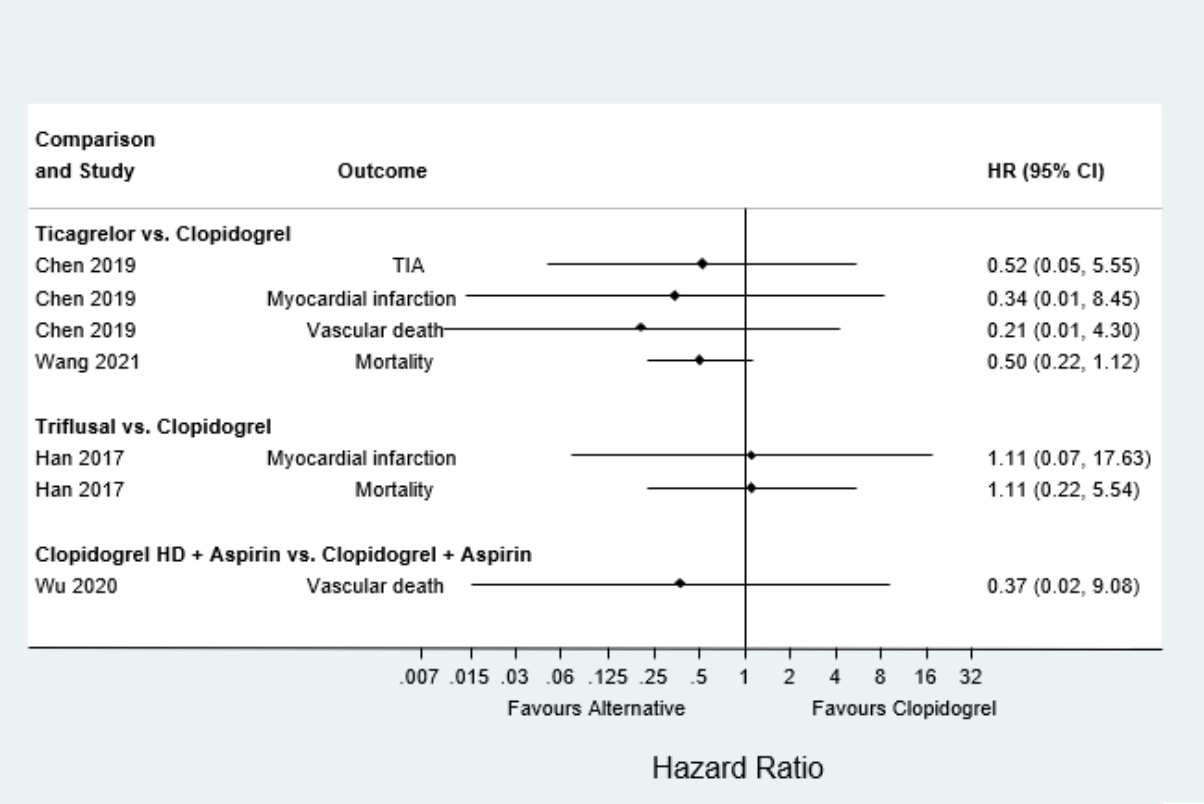
Figure 9 Forest plot showing hazard ratios (HR) (95% CI) for incidence of ischaemic stroke in carriers of loss of function alleles receiving standard therapy with Clopidogrel (or Clopidogrel + Aspirin) compared with an alternative antiplatelet



Other secondary efficacy outcomes

Other secondary outcomes evaluated included TIA, myocardial infarction (MI), vascular death, and mortality. There were very few events for these outcomes and no statistical evidence of a difference between any of the antiplatelet strategies evaluated (Figure 10).

Figure 10 Forest plot showing hazard ratios (HR) (95% CI) for incidence of other secondary vascular event outcomes in carriers of loss of function alleles receiving standard therapy with Clopidogrel (or Clopidogrel + Aspirin) compared with an alternative antiplatelet



Adverse events

Seven studies reported data on incidence of bleeding events in those with LOF alleles treated with different antiplatelet therapies. One study reported an increased risk of bleeding with ticagrelor compared to clopidogrel, while the other study that compared ticagrelor with clopidogrel found no difference in the risk of bleeding. There was no statistical evidence for differences between antiplatelet treatment strategies for any of the other comparisons or bleeding outcomes (Figure 11 and Figure 12).

Figure 11 Forest plot showing hazard ratios (HR) (95% CI) for incidence of any bleeding events in carriers of loss of function alleles receiving standard therapy with Clopidogrel (or Clopidogrel + Aspirin) compared with an alternative antiplatelet

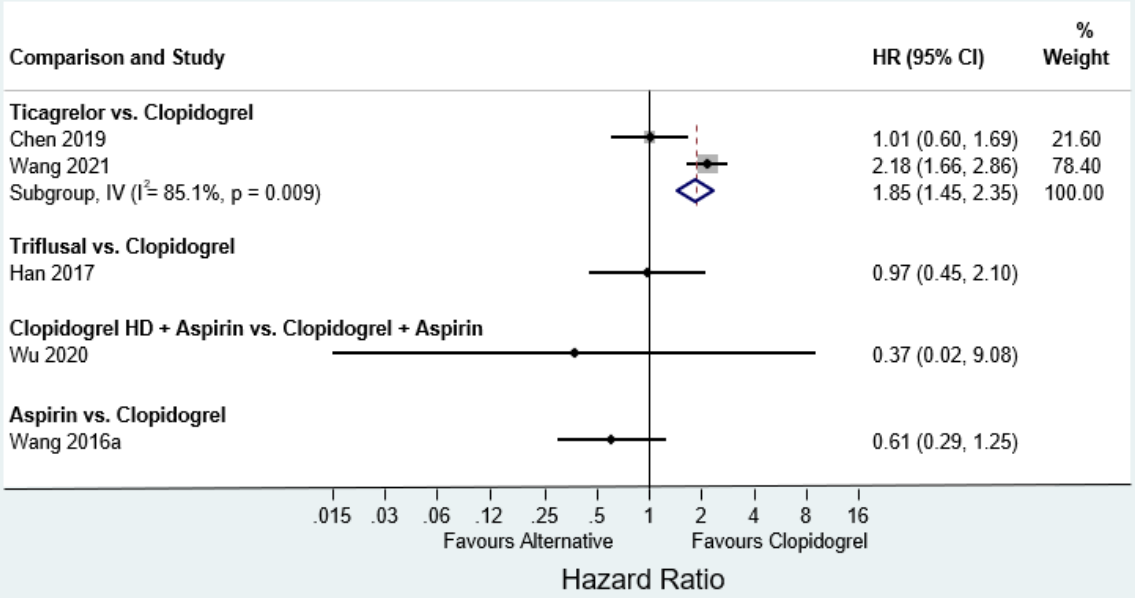
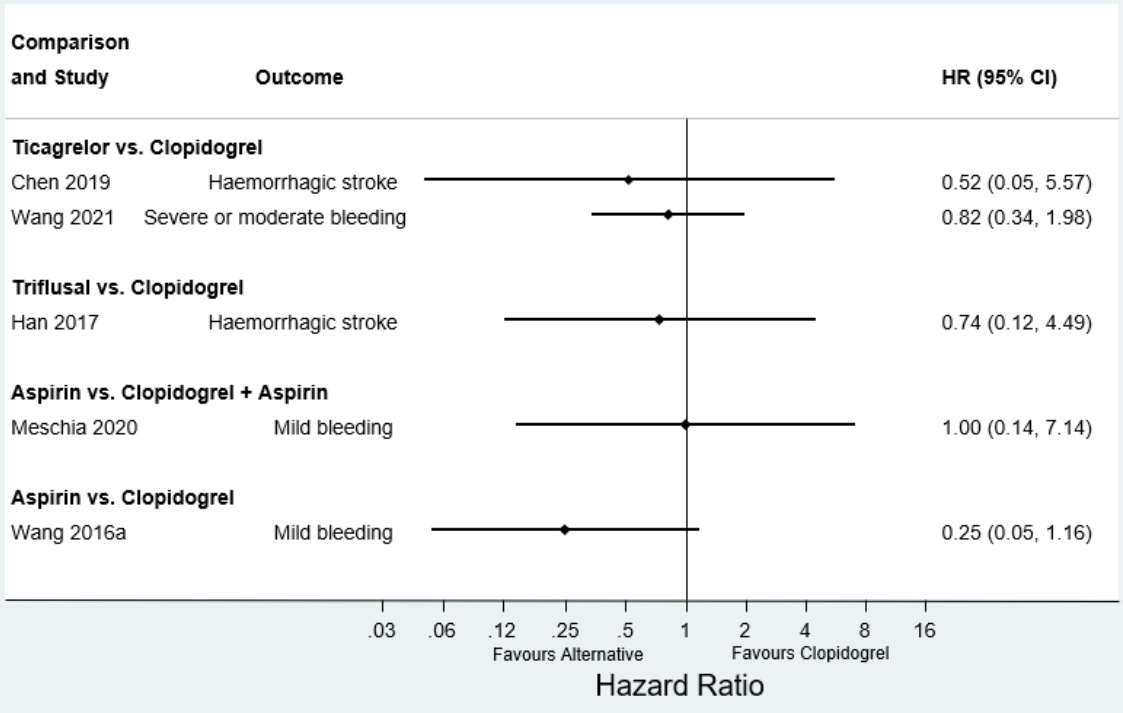


Figure 12 Forest plot showing hazard ratios (HR) (95% CI) for incidence of other secondary adverse events in carriers of loss of function alleles receiving standard therapy with Clopidogrel (or Clopidogrel + Aspirin) compared with an alternative antiplatelet



4.4 Objective 3

25 studies reported in 45 publications were included for objective 3.[47, 48, 51-73] All studies were published in English. Five of the studies included for objective 2 also provided data for objective 3.[47, 48, 51-53]

Table 8 provides an overview of the studies included for objective 3. Full details on the studies are reported in *Appendix 4*: Data extraction tables.

Twenty studies used a cohort design – 13 enrolled participants prospectively and seven used a retrospective design. The five RCTs also included for objective 2 compared standard clopidogrel therapy against an alternative and provided data for participants with and without LOF alleles. Data were extracted from these studies for the clopidogrel treatment arm only, effectively giving a cohort of patients treated with clopidogrel in whom results could be compared between those with and without LOF alleles. All studies administered clopidogrel to all patients, and outcomes were compared between those with and without LOF alleles. In 15 studies, patients received clopidogrel alone, 7 studies gave clopidogrel plus transitory aspirin (14-30 days), 3 studies administered both clopidogrel and aspirin for the duration of the study, and the other two included patients taking clopidogrel, with or without other antiplatelets. In four studies, an initial loading dose of clopidogrel was given to all participants, in two studies some patients had been given an initial loading dose, and 21 studies did not give a loading dose.

Four studies had a follow-up time of 90 days, 5 followed up patients for 180 days, 2 for 365 days, four studies from one to two years, one study from two to three years, one study from three to four years, and two from four to 5 years. Eight studies did not report follow-up time.

Most studies enrolled patients who had experienced a stroke as their primary event (14 studies), one study only enrolled patients who had experienced a TIA and ten studies enrolled patients who had experienced a stroke or TIA. Most studies were conducted in Asia (13 in China, 2 in Japan and 1 in Korea), four studies were conducted in the USA with single studies from other countries. One study had drugs and tests provided by industry, one was sponsored by a commercial company, other studies either did not report on funding source or were funded by non-commercial organisations. A variety of different laboratory tests were used to determine *CYP2C19* status – none of the studies used POCT. The majority of studies tested for both *2 and *3 LOF alleles, five studies only tested for *2 and two did not report on which LOF alleles were tested for. Two studies tested for additional alleles as well as *2 and *3 – 8* in one study and *5, *6, *7 and *8 in the other.

Table 8 Characteristics of studies that evaluated Objective 3

Feature	Category	Number of studies
Population	Stroke	14
	TIA	1
	Both	10
Drug(s)	Clopidogrel	15
	Clopidogrel + Aspirin	3
	Clopidogrel + Aspirin (for 14-30 days)	5
	Clopidogrel (Any additional antiplatelets allowed)	2
Clopidogrel loading dose	Yes	4
	Optional	2
	No	19
Clopidogrel dose	75 mg	18
	NR	7
Aspirin dose	50-325 mg	8
Design	RCT sub-analysis	5
	Prospective cohort	13
	Retrospective cohort	7
Country	South Korea	1
	USA	4
	China	13
	International	1
	Czech Republic	1
	Scotland	1
	Japan	2
	Spain	1
	Turkey	1
Funding	Non-industry	16
	Drugs & tests provided by industry	1
	Industry - other	1
	Not stated	7
***CYP2C19* test**	Seeplex *CYP2C19* ACE genotyping system and Real-Q *CYP2C19* genotyping kit	1
	Drug Metabolism Enzyme TaqMan Allelic Discrimination Assay	6
	Sequenom MassARRAY iPLEX platform	4
	Sequenom MassARRAY iPLEX platform and Drug Metabolism Enzyme TaqMan Allelic Discrimination Assay	2
	PCR-RFLP	1
	Improved Multiple Ligase Detection Reaction (iMLDR)	3
	Cwbiotech	1
	Lightmix	1
	NR	4
	Perkin Elmer Gene Amp PCR Systems 9600	1

Feature	Category	Number of studies
	LightScanner system	1
Loss of function alleles	*CYP2C19* *2 and *3	16
	CYP2C19 *2	5
	NR	2
	CYP2C19 *2 ,*3 and *8	1
	CYP2C19 *2 ,*3, *4, *5, *6, *7 and *8	1
Follow-up time	90 days	4
	180 days	5
	365 days	2
	1 to 2 years (366 to 730 days)	4
	2 to 3 years (731 to 1095 days)	1
	3 to 4 years (1096 to 1460 days)	1
	4 to 5 years (1461 to 1825 days)	2
	NR	8

*Studies that enrolled participants who received clopidogrel with or without additional antiplatelet or anticoagulant drugs after having a stroke.

4.4.1 Risk of bias

Nineteen studies were judged to be at low concern regarding risk of bias; seven studies had high concerns (Table 9). Studies judged at high risk of bias were due to potential loss to follow-up and the potential for this to be related to the outcome (3 studies), likelihood of ethnically diverse population that was not described in detail or considered in the synthesis (2 studies), and selection of participants dependant on clopidogrel prescription redemption (retrospective study) which might be associated with the outcome (1 study). All outcomes evaluated for each study were judged to have the same risk of bias.

Table 9 Results of the ROBINS-E assessment for studies evaluating Objective 3

Study Details	Domain								Rationale
	1	2	3	4	5	6	7	Overall	
Chen et al (2019)[52]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Diaz-Villamarin et al. (2018)[54]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Fu et al. (2020)[55]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Fukuma et al. (2022)[56]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Han et al (2017)[47]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Hoh et al. (2016)[57]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Lin et al. (2014)[58]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Liu et al. (2020)[59]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Lv et al. (2022)[60]	☺	☺	☺	☺	☹	☺	☺	☹	High percentage of loss to follow-up, likely related to the outcome
McDonough et al. (2015)[61]	☺	☺	☺	☺	☹	☺	☺	☹	No data on loss to follow-up, potential missing data likely related to outcome.

Study Details	Domain								Rationale
	1	2	3	4	5	6	7	Overall	
Meschia et al (2020)[48]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Ni et al.(2017)[62]	☺	☺	☺	☺	☹	☺	☺	☹	No data on loss to follow up. Potential missing data likely to be related with the outcome
Patel et al. (2021) [63]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Qiu et al. (2015)[64]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Sen et al. (2014)[65]	☹	☺	☺	☺	☺	☺	☺	☹	Population likely not ethnically homogeneous, no info on ethnicity, not adjusted.
Spokoyny et al. (2014) [66]	☹	☺	☺	☺	☺	☺	☺	☹	Ethnicity is a common cause of CYP219 variations and recurrent events - mixed population, results probably not adjusted by ethnicity
Sun et al. (2015)[67]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Tanaka et al. (2019)[68]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Tomak et al (2018)[69]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Tornio et al. (2018)[70]	☺	☺	☹	☺	☺	☺	☺	☹	Retrospective study - Inclusion of participants dependant on redemption of clopidogrel prescription which is associated with the outcome.
Wang et al (2016a)[51]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Wang et al. (2016b)[71]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Yi et al (2018)[53]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Yi et al. (2017)[72]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns
Zhang et al. (2017)[73]	☺	☺	☺	☺	☺	☺	☺	☺	No concerns

4.4.2 Results

Secondary Occlusive Events

There was strong evidence that people with LOF alleles treated with clopidogrel (or clopidogrel plus aspirin) have a greater incidence of secondary vascular events (HR 1.72, 95% CI 1.43, 2.08; 18 studies;

Figure 13), stroke (HR 1.46, 95% CI 1.09, 1.95; 5 studies, Figure 14) and ischaemic stroke (HR 1.99, 95% CI 1.49, 2.64; 12 studies; Figure 15) than those without LOF alleles (estimates from random effects meta-analysis). There was some evidence of heterogeneity for the composite outcome of secondary vascular events (I^2=33%; Tau^2 =0.027); there was little or no evidence of heterogeneity for other outcomes. Fixed effect meta-analysis estimates were very similar to pooled results from random effects analyses.

Figure 13 Forest plot showing hazard ratios (HR) (95% CI) for incidence of a composite outcome of secondary vascular events in carriers of LOF alleles compared with non-carriers of LOF alleles receiving standard therapy with clopidogrel (or clopidogrel + aspirin)

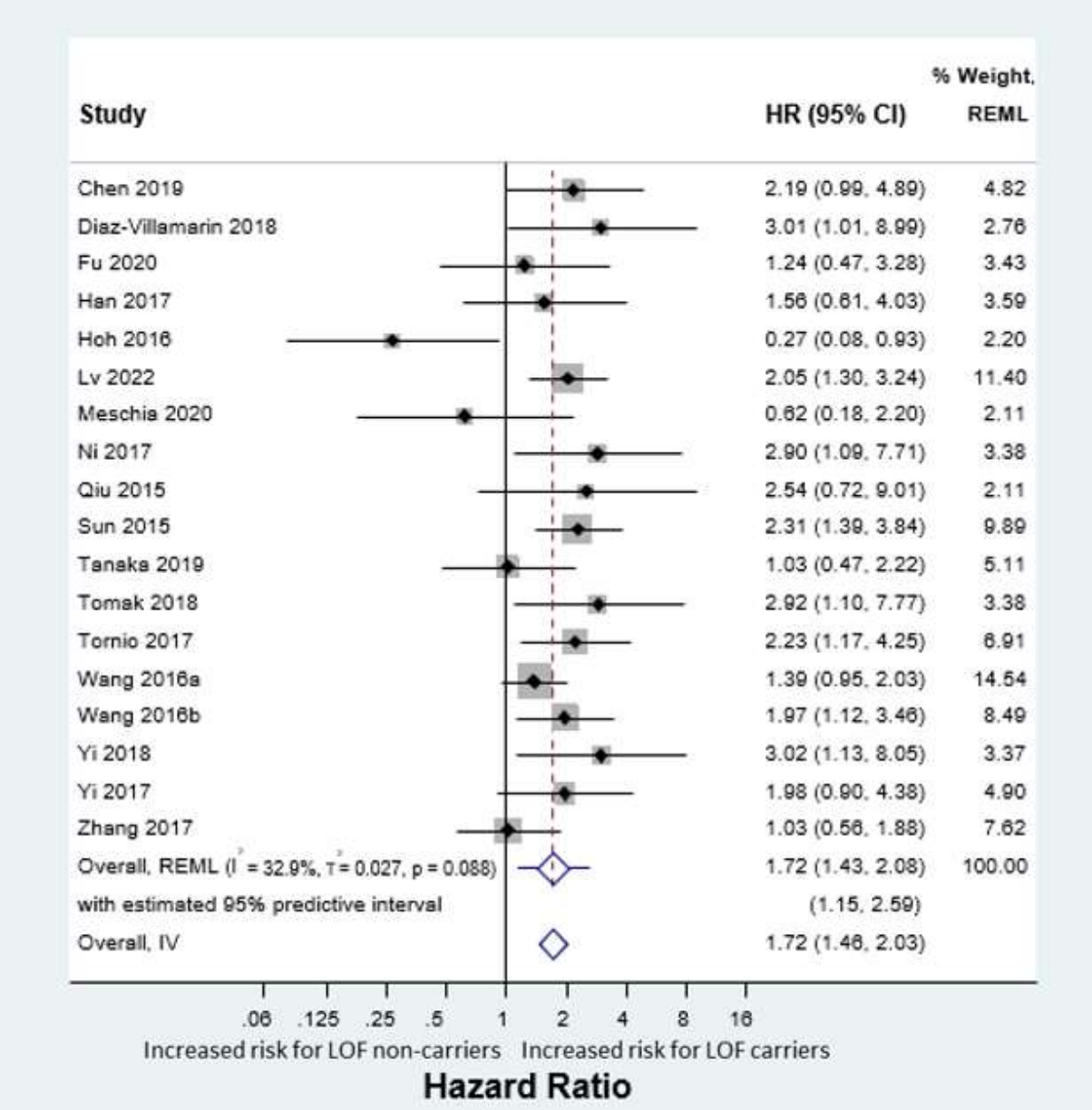


Figure 14 Forest plot showing hazard ratios (HR) (95% CI) for incidence of incidence of any stroke in carriers of LOF alleles compared with non-carriers of LOF alleles receiving standard therapy with clopidogrel (or clopidogrel + aspirin)

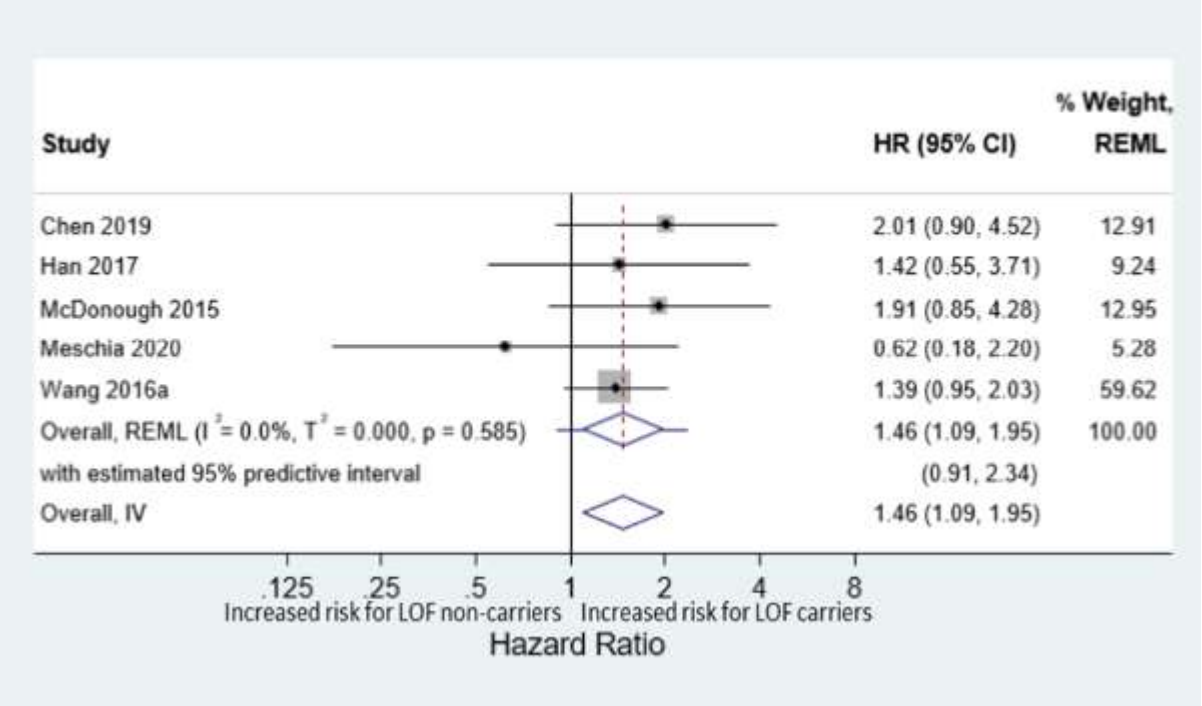
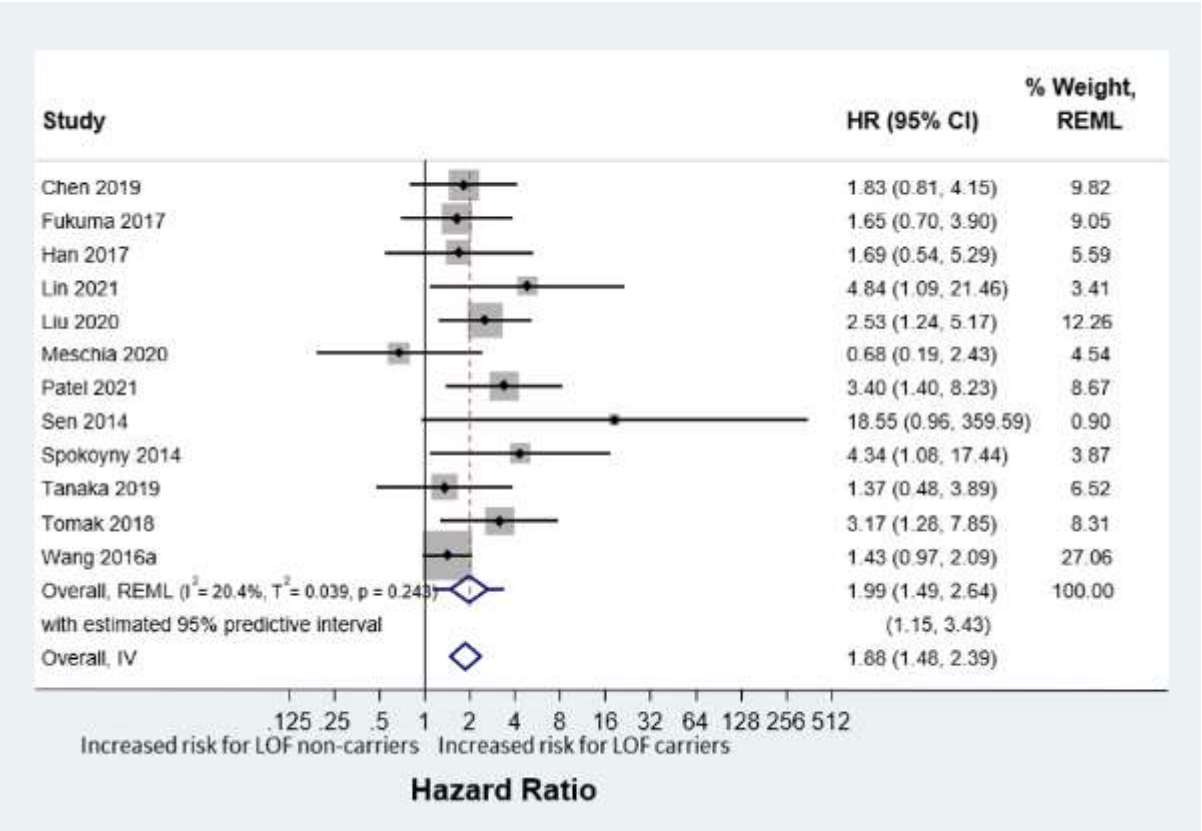


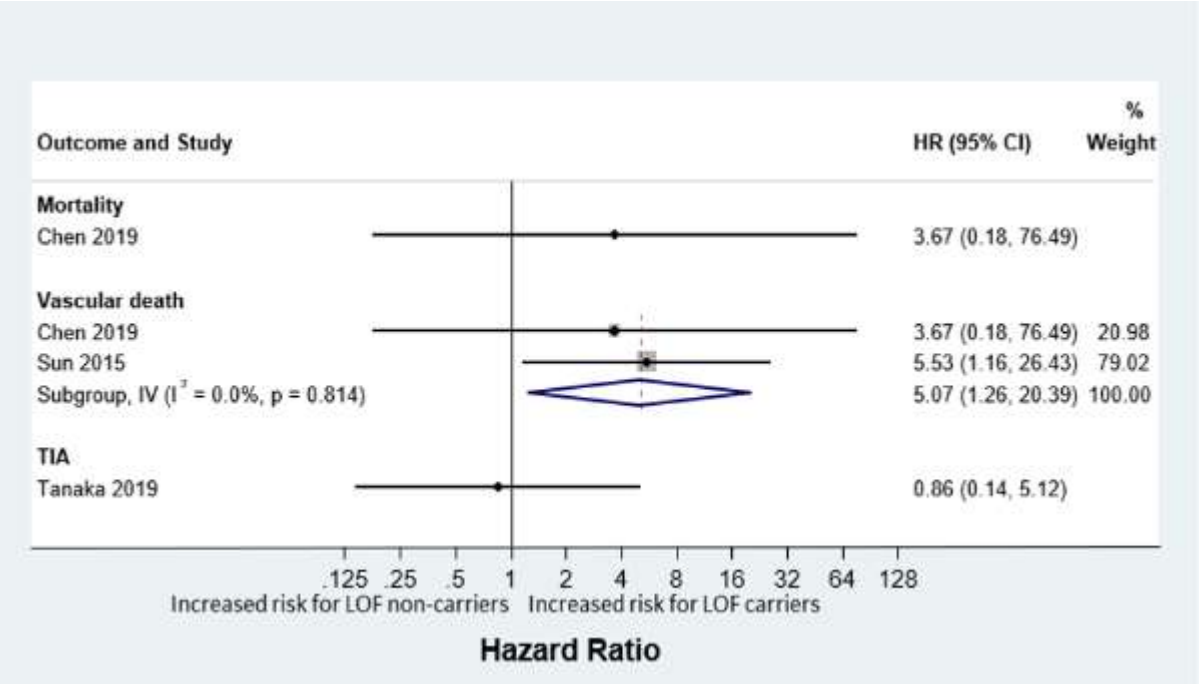
Figure 15 Forest plot showing hazard ratios (HR) (95% CI) for incidence of ischaemic stroke in carriers of LOF alleles compared with non-carriers of LOF alleles receiving standard therapy with clopidogrel (or clopidogrel + aspirin)



Secondary efficacy outcomes

There was little evidence to suggest any association between LOF alleles and secondary outcomes of mortality and TIA (Figure 16). However, these were evaluated in very few studies and there were very few events. There was evidence that the risk of vascular death is increased in patients with LOF alleles treated with clopidogrel compared to those without LOF alleles (HR 5.07, 95% CI 1.26, 20.39).

Figure 16 Forest plot showing hazard ratios (HR) (95% CI) for incidence of secondary vascular occlusive outcomes in carriers of loss of function alleles compared with non-carriers of loss of function alleles receiving standard therapy with Clopidogrel (or Clopidogrel + Aspirin)



Investigation of heterogeneity

Within studies that evaluated multiple vascular occlusive event outcomes, estimates of HR were very similar for composite outcome, stroke and ischaemic stroke (ischaemic stroke accounted for most of the secondary vascular outcomes reported in all studies). As described in the Methods, a post hoc decision was therefore made to combine data across different types of vascular event when exploring heterogeneity. Forest plots stratified for each of these variables are provided in *Appendix 5*: Additional Analyses for Objective 3. Results of univariable meta-regressions are show in

Table 10.

Table 10 Meta-regression analyses showing ratios of HRs for incidence of secondary vascular occlusive events in LOF carriers compared with non-carriers, stratified by key covariates

Covariate	Group	RHR	95% CI	p-value	Tau^2	I^2	R^2
Ethnicity	White	1	Reference		0.03	26.82%	24.99%
	Asian	0.71	0.39, 1.27	0.24			
	Mixed	0.56	0.23, 1.34	0.18			
	Black	0.52	0.13, 2.13	0.35			
	Hispanic	0.18	0.02, 1.40	0.09			
	NR	7.24	1.49, 4.39	0.25			
Regimen	Clopidogrel	1	Reference		0.04	23.79%	58.11%
	Clopidogrel + optional aspirin	0.82	0.29, 2.34	0.71			
	Clopidogrel + aspirin	0.45	0.22, 0.93	0.03			
Loading dose	No loading dose	1	Reference		0	1870%	100%
	Loading dose	0.64	0.43, 0.96	0.03			
	Loading dose optional	1.01	0.64, 1.61	0.95			
Risk of bias	Low risk	1	Reference		0.02	27.45%	14.17%
	High risk	1.33	0.84, 2.12	0.21			
Primary event	Stroke	1	Reference		0	3.45%	100%
	Stroke or TIA	0.62	0.44, 0.86	0.006			
	TIA	1.53	0.57, 4.05	0.38			
PPI use	0-10%	1	Reference		0.03	20.17	12.74%
	10-20%	0.97	0.56, 1.66	0.91			
	2 0-30%	1.29	0.61, 2.7	0.48			
	40-50%	1.34	0.31, 5.8	0.68			
	50-60%	0.14	0.03, 0.59	0.01			
	NR	0.99	0.63, 2.49	0.99			
Follow-up time	3 months	1	Reference		0.12	23.62%	48.78%
	6 months	1.11	0.61, 2.02	0.711			
	1 year	0.61	0.18, 2.05	0.401			
	1-3 years	1.34	0.76, 2.36	0.291			
	3-5 years	1.52	0.77, 2.99	0.207			
	NR	1.74	0.97, 2.18	0.062			
Study location	Europe	1	Reference		0.38	31.91%	57.21%
	China	0.75	0.38, 1.48	0.38			
	Asia	0.53	0.21, 1.29	0.152			
	US	0.56	0.21, 1.45	0.216			
	International	0.75	0.22, 2.55	0.625			
	Turkey	7.26	0.38, 1.48	0.259			

RHR: ratio of hazard ratios; NR: not reported; TIA: transient ischaemic attack; Tau^2= estimates of between-study variance; I^2= proportion of variability in the meta-analysis that is explained by other differences between the included studies rather than by sampling error or the included covariate (i.e. residual heterogeneity); R^2= estimated proportion of heterogeneity that is explained by the covariate

There was evidence of a reduced effect of LOF alleles in patients given a loading dose of clopidogrel relative to those who were not (RHR: 0.64, 95% CI 0.42, 0.97), in patients taking clopidogrel plus long-term aspirin relative to those taking only clopidogrel or clopidogrel plus short-term aspirin (RHR: 0.45, 95% CI 0.22, 0.93), and in studies that included patients with stroke and TIA as primary events compared with only patients with stroke (RHR: 0.62, 95% CI 0.44, 0.86). The stratified analysis based on clopidogrel regimen suggested that there was no evidence of a difference in the risk of secondary vascular events between those taking clopidogrel plus aspirin (HR 0.92; 95% CI 0.50, 1.74). There was no evidence of a difference between studies which included patients with TIA as primary event and those including patients with stroke, but only one study investigated TIA patients exclusively.

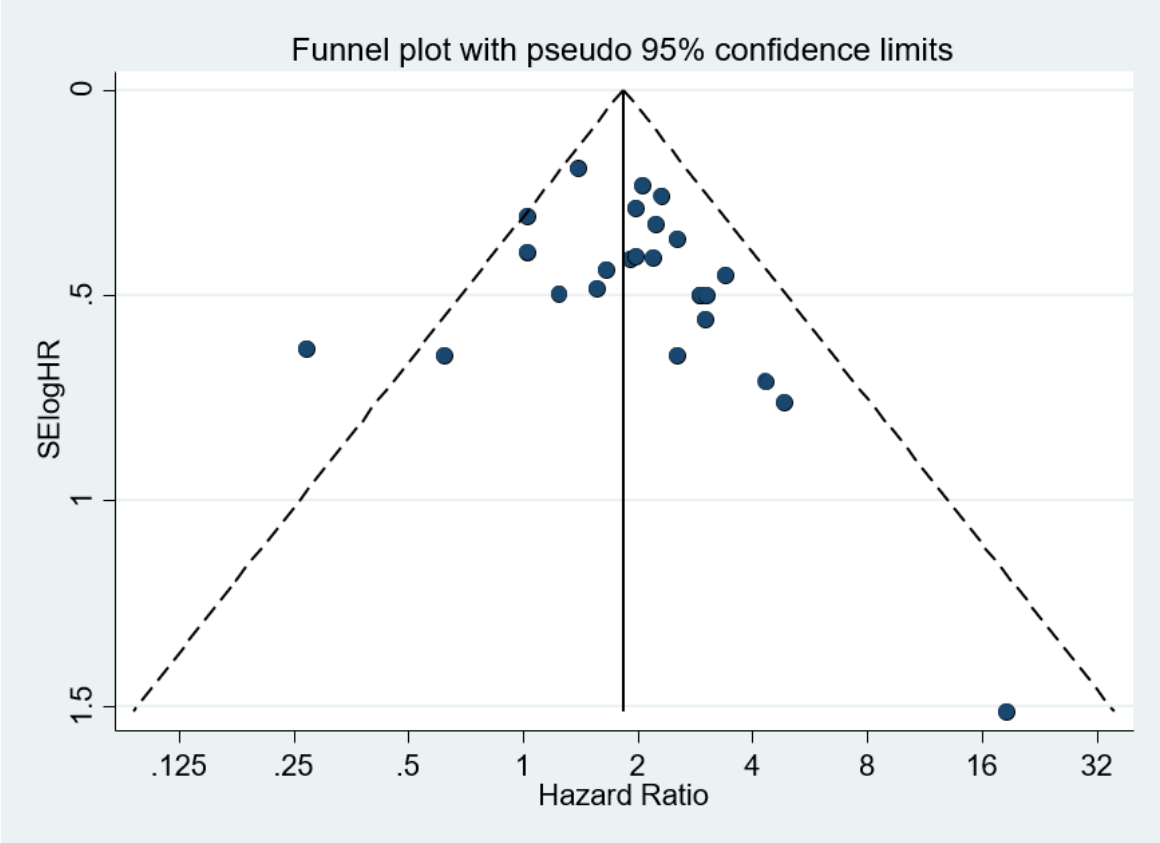
There was some suggestion from subgroup analyses that effects of LOF alleles may vary by ethnicity, with a possibly reduced effect in studies in mixed and Hispanic populations compared with white. However, there was considerable uncertainty in these stratified estimates, resulting in no statistical evidence for differences between LOF effect by ethnicity in the meta-regression.

There was no evidence for a difference in LOF alleles effect on secondary vascular occlusive outcomes based on risk of bias, PPI use, study location, or duration of follow-up.

Investigation of small study effects

The funnel plot showing hazard ratios for incidence of secondary vascular occlusive outcomes in carriers of LOF alleles compared with non-carriers of LOF alleles appears symmetrical (Figure 17). This suggests that there is no evidence of small study effects.

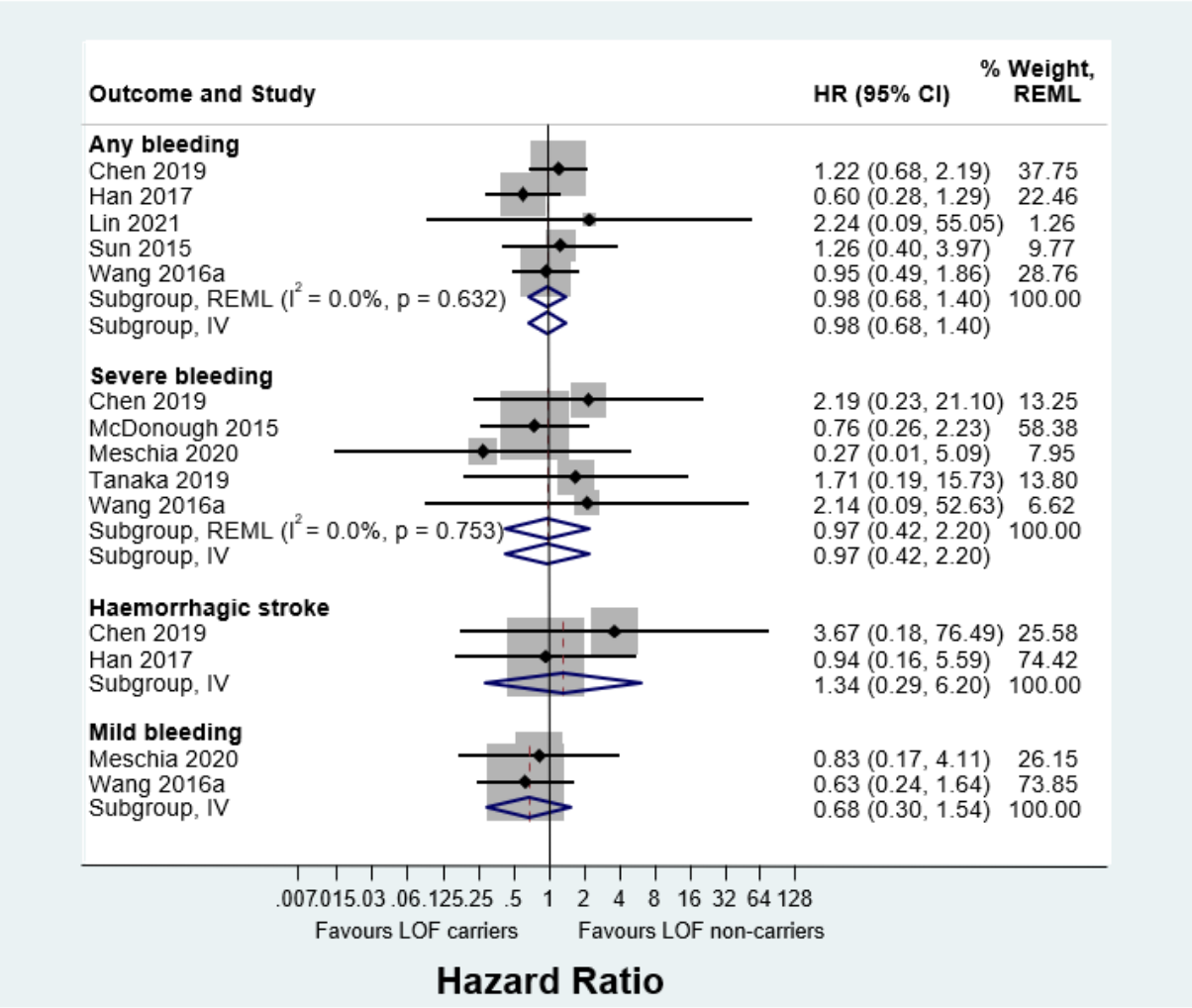
Figure 17 Funnel plot of hazard ratios for incidence of secondary vascular occlusive outcomes in carriers of loss of function alleles compared with non-carriers of loss of function alleles



Adverse events

There was no evidence of a difference in the risk of bleeding among those with and without LOF alleles (Figure 18) for each category of bleeding assessed: any bleeding (HR 0.98, 95% CI 0.68, 1.40; 5 studies), severe bleeding (HR 0.97, 95% CI 0.42, 2.20; 5 studies), haemorrhagic stroke (HR 1.34, 95% CI 0.29, 6.20; 2 studies) or mild bleeding (HR 0.68, 95% CI 0.30, 1.54; 2 studies). There was no evidence of heterogeneity for any of these outcomes (I^2=0). For this reason, subgroup analyses and meta-regression was not performed. Fixed effect meta-analysis estimates were identical to pooled results from random effects analyses.

Figure 18 Forest plot showing HRs (95% CI) for incidence of secondary adverse effect outcomes in carriers of loss of function alleles compared with non-carriers of loss of function alleles receiving standard therapy with Clopidogrel (or Clopidogrel + Aspirin)



4.5 Objective 4

Nine studies, reported in 12 publications, reported data on test accuracy of the POCT in scope. Two studies reported separate accuracy data for a pre-trial and the main trial – these are treated as separate studies giving a total of 11 studies.[74, 75] Three studies were only available as clinical trial registrations, all others were published as full reports. All studies available only as clinical trial registrations were conducted by Spartan (Genomadix), who provided additional information when requested for two of the studies.[76, 77] All studies were reported in English.

All studies evaluated Spartan versions of the test. Two evaluated Spartan Cube,[76, 77] eight evaluated Spartan RX,[74, 75, 78-81] and one evaluated Spartan FRX.[82] These tests are considered broadly equivalent to the Genomadix Cube and so were evaluated as a single group referred to from here as "Genomadix (Spartan) *CYP2C19* tests", unless referring to specific tests. There were no studies on the accuracy of Genedrive.

Table 11 provides an overview of the studies included for objective 4. Full details of the studies are reported in *Appendix 4*: Data extraction tables. Five studies were funded by the test manufacturer. One study was funded by other industry organisations and one by both industry and non-industry.

Six studies recruited patients undergoing percutaneous coronary intervention (PCI). The two pre-trials included healthy volunteers as they were pre-trial validations of the test. Three studies did not report details on the population studied – all were only available as clinical trial registrations. None of the studies were conducted in our population of interest – stroke patients.

The number of participants ranged from 8[77] to 2587[74]. Three studies tested samples from individuals multiple times. One conducted 267 tests in 37 participants,[75] [redacted]

Two studies took place in Europe, six studies in Canada, one in South Korea, and two studies (reported in the same publication) were multi-national conducted in USA/ Canada/ South Korea/ Mexico.

Studies targeted different combinations of the three alleles that can be detected using Genomadix (Spartan) *CYP2C19* tests (*2, *3, *17). Seven studies targeted all three LOF alleles, one targeted 2* and 17*, and the remainder targeted only 2*. We dichotomised results into presence of LOF alleles or no LOF alleles so that those with at least one 2* or 3* LOF allele were considered to have LOF alleles; we categorised 17* as normal function, as described in the methods. The reference standard (standard laboratory test) was bidirectional sequencing in 3 studies, direct DNA sequencing in two studies, and Sanger sequencing in 1 study (all these methods can detect the presence of any LOF allele). The remaining four studies used Taqman, which can be set up with different probes to detect different LOF alleles. One of the studies used Sanger sequencing as an additional reference standard where there were discrepancies between the Genomadix Cube and Taqman results. In all studies, even those that used a reference standard that could detect any LOF alleles, the laboratory tests only targeted the same alleles as were targeted by the Genomadix Cube. Estimates of accuracy from these studies therefore show the accuracy in detecting only those variants that Genomadix (Spartan) *CYP2C19* tests can detect (and in four studies only the 2* LOF allele), rather than the accuracy for the detection of any variant associated with LOF.

Table 11 Characteristics of studies that evaluated the accuracy of Genomadix Cube (Spartan)

Feature	Category	Number of studies
POCT	Spartan (Genomadix) Cube	2
	Spartan (Genomadix) RX	8
	Spartan (Genomadix) FRX	1

Feature	Category	Number of studies
Population	Not reported	3
	Healthy volunteers	2
	PCI	6
Country	Canada	6
	South Korea	1
	Malta	1
	Czech Republic	1
	Multi-country International (US/ Canada/ South Korea/ Mexico)	2
Funding	Industry - test manufacturer	5
	Industry – other	1
	Non-industry	4
	Mixed (industry and non-industry)	1
Alleles targeted	2*, 3* and 17*	7
	2*, 17*	1
	2* only	3
Reference standard (laboratory test)	Bidirectional sequencing	3
	Direct DNA sequencing	2
	Sanger Sequencing	1
	Taqman	3
	Taqman plus Sanger sequencing where POCT and Taqman discordant	1

Abbreviations: PCI: percutaneous coronary intervention, STEMI: ST-segment elevation myocardial infarction, DAPT: dual antiplatelet therapy, ACS: acute coronary syndrome, CAD: coronary artery disease

4.5.1 Risk of bias

All studies were considered at low risk of bias. An overview of risk of bias in the studies is provided in Table 12. Although a variety of different populations were enrolled, and enrolment was not always consecutive, we considered that how patients were enrolled was unlikely to affect estimates of test performance. Information on whether the person interpreting the Genomadix (Spartan) *CYP2C19* test was blinded to the laboratory test was not reported, although some studies did suggest that this was conducted and interpreted before the laboratory test. However, as the Genomadix (Spartan) *CYP2C19* tests are objective in interpretation, blinding was considered unlikely to have influenced test interpretation. All studies used a laboratory-based reference standard – this was considered appropriate. Most of these are also objective in their interpretation and so we considered it unlikely that knowledge of the Genomadix (Spartan) *CYP2C19* test results could have biased interpretation of the reference standard. There were very few patients who did not receive both index test and reference standard and so there were no concerns regarding patient flow.

Table 12 Overview of risk of bias in studies that evaluated the accuracy of POCT tests

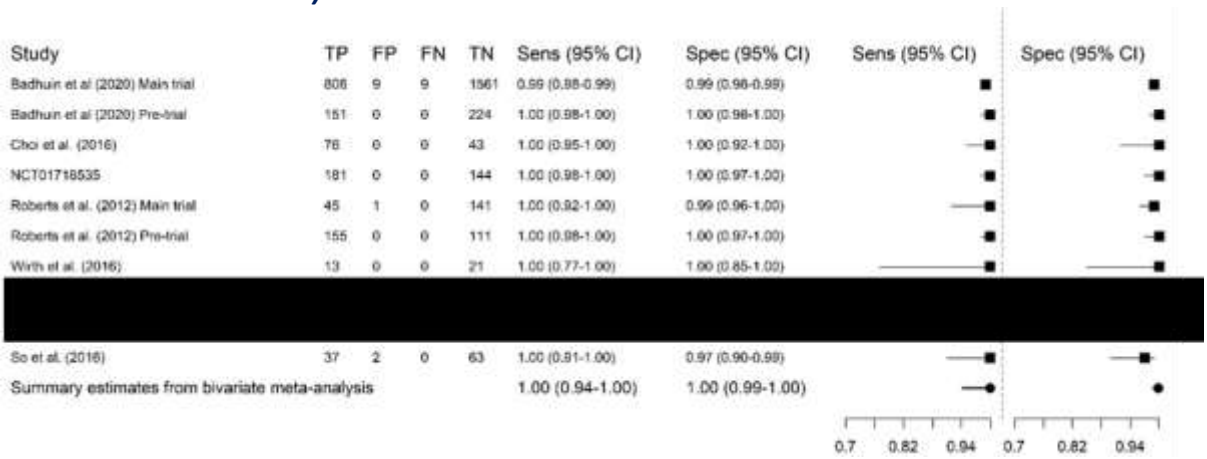
Study Details	Patient Selection	Index test	Reference standard	Flow & Timing	Overall	Rationale for Judgement
Baudhuin et al (2022)[74] – pre-trial	☺	☺	☺	☺	☺	No concerns

Study Details	Patient Selection	Index test	Reference standard	Flow & Timing	Overall	Rationale for Judgement
Baudhuin et al (2022)[74] – main trial	☺	☺	☺	☺	☺	No concerns
Choi et al. (2016)[78]	☺	☺	☺	☺	☺	No concerns
NCT01718535[82]	☺	☺	☺	☺	☺	No concerns
NCT04473573[77]	☺	☺	☺	☺	☺	No concerns
NCT04473586[76]	☺	☺	☺	☺	☺	No concerns
Petrek et al. 2016 [79, 83]	☺	☺	☺	☺	☺	No concerns
Roberts et al. (2012)[75] – pre-trial	☺	☺	☺	☺	☺	No concerns
Roberts et al. (2012)[75] – main-trial	☺	☺	☺	☺	☺	No concerns
So et al. (2016)[80]	☺	☺	☺	☺	☺	No concerns
Wirth et al. (2016)[81]	☺	☺	☺	☺	☺	No concerns

4.5.2 Results

Estimates of the accuracy of Genomadix (Spartan) *CYP2C19* tests were very high – 8 of the 11 studies reported 100% sensitivity and specificity. It was possible to extract 2x2 data for 9 of the 11 studies. We contacted the authors of the other two studies but did not receive a response.[74, 83] For one of these studies, we were able to estimate 2x2 data based on data reported in the paper.[74] Data were reported on sensitivity, specificity and the total number of people tested using Spartan (Genomadix) RX (255/2641 did not have a Genomadix Cube result). Data were not reported on the number tested who did and did not have LOF alleles based on the reference standard. However, information was available on the numbers with and without LOF in the total sample, we assumed that the proportion with LOF alleles would be similar in the tested subset and overall cohort and used this to estimate numbers with and without LOF in the tested sample and then applied sensitivity and specificity to the numbers to estimate 2 x2 data. Figure 19 shows paired estimates of sensitivity and specificity together with 95% confidence intervals for each study. Summary sensitivity was 100% (95% CI 94, 100%) and summary specificity was also 100% (95% CI 99, 100%).

Figure 19 Forest plot showing estimates of sensitivity and specificity for each included study and overall summary estimates of sensitivity and specificity for studies that evaluated the accuracy of Genomadix (Spartan) *CYP2C19* tests (*yellow box indicates AiC data).*



The proportion of discordant results ranged from 0 to 2.7% and was <1% in nine studies. Seven studies reported discordant results between Genomadix (Spartan) *CYP2C19* tests and the laboratory reference standard, but these only impacted estimates of accuracy in two studies as in other studies they did not affect the classification of the individual as a poor or normal metaboliser. An overview of discordant results is provided in Table 13.

Table 13 Overview of discordant results between Genomadix (Spartan) *CYP2C19* tests and laboratory reference standard tests

Study	Genomadix Test	Proportion discordant	Overview of discordant results	Impact on accuracy
Badhuin et al (2022)[74] – pre-trial	Spartan (Genomadix) RX	2/373 (0.5%)	2 discordant initially due to pre-analytical sample mix-up at testing centre. Samples re-collected and re-tested, then concordant.	None
Badhuin et al (2022)[74] – main-trial	Spartan (Genomadix) RX	21/2384 (0.9%)	21 discordant: • 9 non-carrier by Spartan, but had *2 or *3 by TaqMan • 11 heterozygous *2 or *3 by Spartan, but non-carrier by TaqMan • 1 sample heterozygous *2 by Spartan, but homozygous *2 by TaqMan	9 FN and 11 FP
Choi et al. (2016)[78]	Spartan (Genomadix) RX	2/119 (1.7%)	2 discordant: *3/*17 on Spartan and *1/*3 on SNP *1/*17 on Spartan and *1/*1 on SNP	None
NCT01718535[82]	Spartan (Genomadix) FRX	0/325 (0%)	None	None
NCT04473586[76]	Spartan (Genomadix) Cube	[redacted]	[redacted] * [redacted]	[redacted]

Study	Genomadix Test	Proportion discordant	Overview of discordant results	Impact on accuracy
			[redacted]	
NCT04473573 [77]	Spartan (Genomadix) Cube	[redacted]	[redacted]	[redacted]
Petrek et al. 2016 [79, 83]	Spartan (Genomadix) RX	0/53 (0%)	None	None
Roberts et al. (2012)[75] pre-trial	Spartan (Genomadix) RX	0/37(0%)	NA	None
Roberts et al. (2012)[75] main trial	Spartan (Genomadix) RX	1/187 (0.5%)	One incorrectly classified as *2 carrier on Spartan	1 FP
So et al. (2016)[80]	Spartan (Genomadix) RX	2/102 (2%)	No details	2 FP
Wirth et al. (2016)[81]	Spartan (Genomadix) RX	1/35 (2.9%)	One incorrectly classified as *2/*2 on Spartan vs one 2* on Taqman and on GenID	None

FP: Fales positive; FN: false negative

4.6 Objective 5

4.6.1 Technical performance of POCT

Seventeen studies, reported in 24 publications, reported on the technical performance of POCT.[74, 84 75T, 76-81, 85-92] Three studies reported data for both a pre-study and main study, these are included as separate studies giving a total of 20 included studies. All but one[82] of the studies included for objective 4 also provided data on test performance and so were also included for objective 5. Two studies were available as trial registry entries only (with additional information provided by Genomadix),[76, 77] two were conference abstracts (with a full conference poster shared for one of these),[89, 92] and all others were reported as full journal articles. All studies were reported in English. Table 14 provides an overview of the studies included for objective 5. Full details of the studies are reported in the baseline data tables and results tables presented in *Appendix 4*: Data extraction tables.

One study evaluated Genedrive,[92] detailing the development of an earlier version of the test. All other studies evaluated Spartan versions of the Genomadix Cube test. Two evaluated Spartan Cube,[76, 77] others evaluated Spartan RX.

Five of the studies reporting on technical performance were funded by the test manufacturer.[75-77, 82] One study was funded by other industry organisations and one by both industry and non-industry. Study populations and locations varied between studies. Conditions studied included stroke, coronary artery disease, healthy volunteers (in test pre-validation studies) and patients undergoing PCI. Five studies took place in Europe, 11 studies in North America,[75-77, 80, 86-89, 91] one in South Korea, one in Saudi Arabia, and two studies

(reported in the same publication) were international in USA/ Canada/ South Korea/ Mexico.

Table 14 Characteristics of 20 studies reporting on the technical performance of POCT

Feature	Category	Number of studies
Tests	Spartan (Genomadix) Cube	2
	Spartan (Genomadix) RX	17
	Genedrive	1
Population	PCI	9
	Not reported	5
	Healthy people	2
	Stroke	1
	STEMI	1
	Stable coronary artery disease	1
	Diagnostic coronary angiography	1
Outcomes	Test failure rate	10
	Number of people with variant forms of *CYP2C19* (%)	16
	Time to results	13
	Ease of use of test	8
	Cost of testing	2
Country	USA	6
	Saudi Arabia	1
	UK	1
	Poland	1
	Canada	5
	South Korea	1
	Malta	1
	Czech Republic	1
	Multi-country in Europe (Netherlands/ Italy/ Belgium)	1
	Multi-country International (US/ Canada/ South Korea/ Mexico)	2
Funding	Industry - test manufacturer	5
	Non-industry but kits provided by manufacturer	3
	Industry – other	1
	Non-industry	10
	Mixed (industry and non-industry)	1
	Not reported/ unclear	2

Abbreviations: PCI: percutaneous coronary intervention, STEMI: ST-segment elevation myocardial infarction, DAPT: dual antiplatelet therapy, ACS: acute coronary syndrome, CAD: coronary artery disease

Test failure rate

Ten studies, all of which evaluated Genomadix (Spartan) *CYP2C19* tests, reported test failure rate (Table 15)[74-77, 79, 81, 85, 86, 90, 91] There was substantial variation in test failure rate across studies, from a minimum of 0.4% of tests (1/267) to a maximum of 18.9% (10/53 patients) for the initial run. In some studies, samples that failed initially were retested and a subset produced results on retesting. Terminology to describe test failures also varied across studies. Though often described as "inconclusive results", studies also highlight device errors, failure during the amplification process and not identifying a genotype. Of studies

that reported what they did post-test failure, most said they repeated the genotype test and highlight the need to consider this when assessing the cost of genotyping.

Table 15 Overview of studies that reported on test failure rate (all GenoMadix Cube)

Study details	Number patients with unavailable test result	Details of missing results	Action taken post-test failure
Badhuin et al (2022)[74 93]	172/2642 (7%)	Main trial: In 54/2642 (2%) had no Spartan result available (no definition of what this means); 118 (4%) had inconclusive results.	NR
Bergmeijer et al. (2014) [85, 94]	39 (8%)	Inconclusive results	Sample shipped to central lab for Taqman genotyping (30 patients), repeated Spartan testing (2 patients), no further genotyping (7 patients).
Cavallari et al. (2018)[86]	129/931 (14%)	56 inconclusive results, 73 device errors	One additional sample collected (113 patients), two additional samples collected (10 patients), refused sample recollection (6 patients). 9/ 123 patients with additional sample collection had multiple inconclusive results.
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Petrek et al. 2016 [79, 83]	10/53 (18.9%)	Failure during amplification process (n=4), inconclusive result (n=3), only two of three alleles tested for gave results (n=3)	NR
	7/53 (13.2%)	Failure during amplification process (n=4), inconclusive result (n=3) – results not included where only 2/3 alleles gave a result	NR
Roberts et al. (2012)[75]	1/267 tests (0.4%)	Pre trial: Test did not identify a genotype. This is 1 test, not necessarily one patient (multiple tests done on each patient)	NR

Study details	Number patients with unavailable test result	Details of missing results	Action taken post-test failure
Tomaniak et al. (2017)[90 95, 96]	4/34 (11.8%)	Inconclusive results	Genotyping repeated. No further information given.
Wirth et al. (2016)[81 97]	5/35 (14.3%)	4 tests resulted in error (11.4% - no further details); 1 test inconclusive	The 4 tests resulting in error were repeated with a new test as per manufacturer's instructions. The inconclusive test was not repeated as the patient had been discharged home. No further information given.
Zhou et al. (2017)[91 98]	25/342 (7.3%)	Main trial: 14 inconclusive results (4%), 10 failed controls (3%), 1 instrument failure (0.3%) (no further information given).	12 patients resulted after re-testing; one patient refused to recollect sample and 1 had 2 consecutive inconclusive results. No further information given.

Studies funded by the test manufacturer are shaded grey

Number of people with variant forms of *CYP2C19* (%)

Thirteen studies reported the number of people with variant forms of *CYP2C19*.[7478, 80, 81, 84, 86, 88-91] We defined variant forms of *CYP2C19* as people with one LOF allele (intermediate metaboliser e.g. *2/*1) or two LOF alleles (poor metaboliser e.g. *2/*2). Table 16 provides an overview of the number of participants with each allele combination in the studies that reported this information.

Overall, intermediate metabolisers were more commonly found than poor metabolisers. The allele combination *2/*1 was most frequently reported and the *3 allele was reported less frequently than the *2 allele. The proportion of participants with variant forms varied from 15% to 64%. We would expect to see an association with ethnicity and *CYP2C19* variants, however, most studies did not provide information on ethnicity and so it was not possible to investigate this association. The UK population in the 2021 census was 81% white, 9.6% Asian, 4.2 % Black, 3% mixed ethnic groups and other (2.2%).[99] The five studies that reported on ethnicity had majority white ethnicity (68% to 100%), these reported that the proportion of people that were poor or intermediate metabolisers ranged from 29% to 38%. The study with the highest proportion of people with variant forms (64%) did not report on ethnicity but was conducted in South Korea and so is likely to have included a mainly Asian population.

Table 16 Number of people with variant forms of *CYP2C19*

Study details	Country	Ethnicity	Number of people with variant forms of *CYP2C19*										
			*2/*2	*3/*3	*3/*2	*2/*1	*3/*1	*3/17	*2/*17	Poor metaboliser*	Intermediate metaboliser*	Total no. with variant forms (%)	Comments
Al-Rubaish et al. (2021)[84]	Saudi Arabia	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	54 (21.1%)	Either *1/*2 or *2/*2
Badhuin et al (2022)[74, 93]	US, Canada, South Korea, Mexico	NR	19	1	5	96	7	0	23	25	126	151/373 (40%)	Pre-trial
	US, Canada, South Korea, Mexico	68% white, 23% east Asian	NR	NR	NR	NR	NR	NR	NR	NR	NR	837/2587 (32%)	Main-trial
Cavallari et al. (2018)[86]	USA	White 74.5%, black 23.7%, Asian 0.8%, other or not reported 1%.	7	NR	NR	NR	NR	NR	NR	7	106	113/392 (29%)	
Choi et al. (2016)[78]	South Korea	NR	11	1	10	40	13	1	0	22	54	76 (63.9%)	
Franchi et al. (2020)[88]	USA	NR	20	0	0	189	1	0	32	20	222	242/781 (28.5%)	
Gurbel et al. (2018)[89]	USA	NR	NR	NR	NR	NR	NR	NR	NR	11	157	168/578 (29%)	
Roberts et al. (2012)[75]	Canada	95% white ethnic origin	7	NR	NR	NR	NR	NR	NR	7	39	46/187 (25%)	Main trial
So et al. (2016)[80]	Canada	91% Caucasian	4	0	0	33	0	0	0	4	33	37 (36%)	

Study details	Country	Ethnicity	Number of people with variant forms of *CYP2C19*										
			***2/*2**	***3/*3**	***3/*2**	***2/*1**	***3/*1**	***3/17**	***2/*17**	**Poor metaboliser***	**Intermediate metaboliser***	**Total no. with variant forms (%)**	**Comments**
Tomaniak et al. (2017)[90, 95, 96]	Poland	NR	NR	NR	NR	NR	NR	NR	NR	2	12	14 (14.83%)	
Wirth et al. (2016)[81, 97]	Malta	100% Caucasian	1	NR	NR	NR	NR	NR	NR	1	12	13/34 (38%)	The 12 intermediate metabolisers had one copy of the *2 allele
Zhou et al. (2017)[91, 98]	USA	NR	0	0	2	4	0	0	1	2	5	7/12 (58%)	Pre-trial
	USA	NR	10	0	1	61	0	0	27	11	88	99 (37%)	Main trial

Time to results

Thirteen studies provided information on time to results (Table 17). Ten of these studies reported data on time to results based on experience from their study: all evaluated Spartan (Genomadix) RX.[75, 79-81, 84-86, 88-90]. Seven studies reported that the turnaround time from buccal swab to result took approximately 1 hour. Two studies reported that this took 90mins and one reported that it took 90-120min.

Three studies reported information about time to results, but this was reported as a description of a feature of the test, rather than being a clear finding from the study itself. [78, 91, 92] Two of the studies evaluated the Genomadix cube and stated that this takes one hour from sample to result. In addition, information reported by Genomadix, the test manufacturer, to the External Assessment Group (EAG), stated that the time to result for the test was 64 minutes. The study that evaluated Genedrive reported that it is 'rapid', taking around 40mins (no further information was reported).[92]

Table 17 Overview of studies that reported data on time to results for the POCT tests

Study details	Time to results
Al-Rubaish et al. (2021)[84]	First 50 patients: 90-120min to complete the results
Bergmeijer et al. (2014) [85, 94]	Result available within 1hr after collection of buccal swab.
Cavallari et al. (2018)[86]	For all patients genotyped: Median genotype test turnaround time was 96min (interquartile range of 78-144)
Choi et al. (2016)[78]	**Description of feature of the test:** time from sample to result ~60min
Franchi et al. (2020)[88]	Allele status within 1hr - readily available when the decision on choice of oral P2Y12-inhibiting therapy most commonly occurs.
Gurbel et al. (2018)[89]	Results available in all patients within 90min
Petrek et al. 2016 [79, 83]	Turnaround time (from buccal swab sampling to result print-out) was 60 min
Roberts et al. (2012)[75]	Main trial: Within 60min from test activation
So et al. (2016)[80]	Within 55min of test carrier status for all alleles was available
Genomadix (test manufacturer) response to request for information	**Description of feature of the test:** Time to result is 64 minutes.
Tomaniak et al. (2017)[90, 95, 96]	Mean (SD): 56min (11), from material collection to the testing results
Wirth et al. (2016)[81, 97]	Collection of sample to genotyping result within 1 hour
Zhou et al. (2017)[91, 98]	**Description of feature of the test (pre trial and main trial):** results are returned in one hour turnaround time
McDermott et al. (2020)[92] - Gendrive	**Description of feature of the test:** ~40min

Studies funded by the test manufacturer are shaded grey

Ease of use of test

Eight studies reported data on the ease of use of the test (Table 18). Five studies, all of which evaluated Spartan (Genomadix) RX, reported data on the ease of use of the POCT based on experience from their study.[74, 75, 79, 81, 86] Overall, these studies suggested that the process of using the Spartan POCT was simple, user-friendly, and that it can be conducted by staff who have received minimal training. Limitations highlighted include storage conditions of the POCT[81], and that only one sample can be genotyped at a time.[86]

Three studies reported further information on ease of use of POCT, however these were reported as descriptions of features of the test rather than direct findings from the study.[85, 87, 92] Regarding Genomadix Cube, these corroborate the findings outlined previously but add further limitations that the test is restricted to *2/*3/*17[85] and that there can be issues with sample collection, including sample recollection due to interference.[87] The study that evaluated Genedrive, noted that the test is simple, portable, rapid and does not require analytes to be frozen.[92]

Table 18 Overview of studies that provided information on ease of use of POCT tests

Study details	Ease of use of test*
Badhuin et al (2022)[74, 93]	Non laboratory trained personnel can successfully perform rapid genotyping in a POC setting
Bergmeijer et al. (2014)[85, 94]	**Description of feature of the test:** Buccal swab more patient friendly than venapuncture for blood sample, but test is limited to testing *2, *3, *17 for one patient at a time per genotyping device.
Cavallari et al. (2018)[86]	Could not be used as POCT due to absence of licensed molecular medical technologist so must be sent to central laboratory (the case for all of USA), and only a single sample genotyped at a time limiting number of patients that can be offered genotyping.
Davis et al. (2020)[87]	**Description of features of the test**: Barriers to implementation: time constraints, personnel requirements and coordination, storage and sample stability, samples unable to be collected by bedside nurses, patients unable to provide samples, sample recollection due to interference or improper techniques
Petrek et al. 2016 [79, 83]	Simple and non-invasive
Roberts et al. (2012)[75]	Main trial: Nurses with no previous laboratory training implemented test after 30min training session.
Wirth et al. (2016)[81, 97]	Simple procedure, portable, convenient, no laborious preparation, minimal training required to conduct test. User-friendly interpretation with no training required. Storage conditions limit ease of use.
McDermott et al. (2020)[92] - Genedrive	**Description of features of the test**: Portable, rapid (~40mins), no cold chain, simple read out for non-specialist users.

*Table reports findings from studies, unless flagged as "description of feature of the test" (these are not findings of the specific studies)

Studies funded by the test manufacturer are shaded grey

Cost of testing

Two studies provide information about POCT costs – one evaluated Spartan (Genomadix) RX[81], and the other evaluated Genedrive.[92] Additional information on the cost of Genomadix Cube was provided by the manufacturer (Table 19). Wirth et al (2016) estimate the cost per patient of Genomadix Cube POCT at 225 euros, compared to 13 euros for the Taqman laboratory assay and 23 euros for the GenID laboratory assay. The authors do not state how they calculated this costing. The manufacturers of the two tests shared information on costs.

Table 19 Overview of studies that provided information on cost of POCT tests

Study details	Test name	Cost of testing
Genomadix (test manufacturer) response to request for information	Genomadix Cube (Spartan)	**Description of feature of the test:** a) Platform cost: £3,500 per testing platform, b) Testing assay cost: £175 per test kit, c) external control kits: £50 GBP per external control kit
Genedrive (test manufacturer) response to request for information	Genedrive System	**Description of feature of the test:** a) Platform cost: 4,995 GBP per testing platform, b) Testing assay cost: £100 per test kit, c) external control kits: £100 per external control kit
Wirth et al. (2016)[81, 97]	Genomadix Cube (Spartan)	Estimated cost per patient test: 225 euros (Taqman estimated at 13 euros and GenID at 23 euros). No indication of how this was calculated.

Studies funded by the test manufacturer are shaded grey

4.6.2 Survey

The survey was sent to 10 laboratories (labs) for completion – the seven genomic laboratory hubs in England, All Wales Medical Genomics Services, Northern Ireland Regional Genetics Service and the Scottish Strategic Network for Genomic Medicine. Responses were received from 8 labs - 5 regional genomic laboratory hubs (Central and South; East; North West; South East; and North East and Yorkshire) and from the Scottish (NHS North Tayside), Welsh and Irish services. Full survey results are reported in *Appendix 6*: Survey Results.

Testing Platform

Table 20 provides an overview of the test platforms that each lab reported currently having in place that would be capable of performing *CYP2C19* genotyping, and the platforms identified as preferred platforms by each lab. Seven of the eight labs reported having Sanger sequencing, 6 also had next-generation gene sequencing; one did not report having any sequencing technology. All had at least one form of targeted *CYP2C19* gene variant detection, most commonly PCR-based SNP genotyping assays using fluorescent reporter systems, such as TaqMan (ThermoFisher) – this was also one of the most commonly reported reference standard in the DTA studies included for objective 4. Preferred technologies included next-generation sequencing (2 labs), MassARRAY(3 labs), LAMP (3

labs), PCR-based SNP genotyping assays using fluorescent reporter systems, such as TaqMan (ThermoFisher) and QuantStudio 12K Flex Real-Time PCR System or X9 Real-Time PCR System (1 lab). Note that two labs highlighted two different technologies as their preferred technology – one selected both MassARRAY and LAMP, the other selected next generation sequencing and LAMP. When asked about whether there are other platforms available that they may consider for *CYP2C19* testing, one lab reported that they were currently looking at NGS Genexus due to speed and capacity. Another stated that they would use Sanger sequencing as a back-up test for when LAMP produced indiscriminate results.

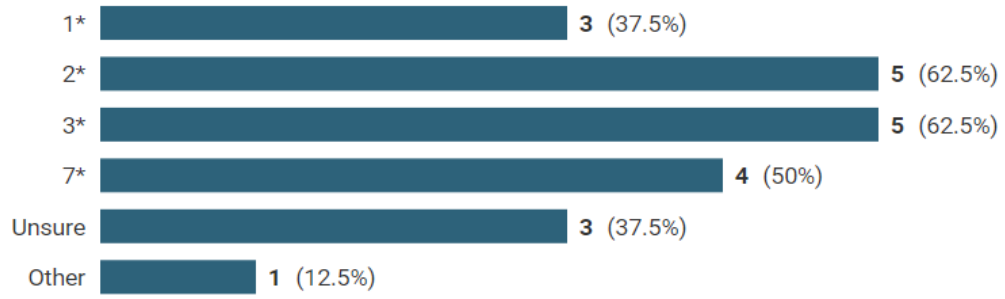
Table 20 Available and preferred *CYP2C19* testing technologies, with reasons for preferences

Technology	Technology Available	Preferred Technology	Reasons for preference
Sequencing technology			
Sanger *CYP2C19* sequencing	7	0	
Next-generation *CYP2C19* gene sequencing	6	2	• High through-put and massively parallel. Automated bioinformatics analysis. Pre-existing workflows established. • High throughput
Targeted *CYP2C19* gene variant detection			
PCR-based SNP genotyping assays using fluorescent reporter systems, such as TaqMan (ThermoFisher)	6	1	• Cost effective, Time efficient, Minimal staff time, Two-step process, High throughput, Robust technology, Simple analysis and reporting
Other PCR-based genotyping panels that use proprietary detection methods, such as the xTAG *CYP2C19* Kit v3 (Luminex)	1	0	
Variant detection using mass spectrometry, such as MassARRAY (Agena Bioscience)	4	3	• Ability to target multiple variants in a single assay applying automated PCR prep and automated genotype calling (validated within our lab for HFE and DPYD testing on this platform), reduced TAT and reduces the necessary staff resources. • Ability to PCR direct from blood is also feasible for this technology (in validation for HFE and DPYD within this lab). • Efficiency, cost and TAT • Commercial kits are available for *CYP2C19* testing - MassArray offers *2-*8 and *17. Also possible to design bespoke assays. If the *CYP2C19* assay was combined with other testing the MassArray is probably better suited for covering increased numbers of variants.
Loop-mediated isothermal amplification (LAMP), such as the LAMP human *CYP2C19* mutation KIT (LaCAR MDx Technologies)	4	3	• Can be done directly from blood and does not require extraction. easy method to set up and automate. • Commercial kits available for *CYP2C19* testing - current LaCAR test covers *2,*3 and *17 • Speed and lack of need for a DNA extraction.
Other: QuantStudio 12K Flex Real-Time PCR System or X9 Real-Time PCR System	1	1	• Higher throughput and can have automated loading. e.g.X9 can test 96 samples for 96 different SNPs in a 2 hour run.

Alleles targeted

Figure 20 provides an overview of the alleles that would be targeted in a request for *CYP2C19*. The one lab that responded as "other" stated that an NGS assay would be able to detect all sequence variants. *Note that there was an error in this question on the survey so that we asked about *7 rather than *17.*

Figure 20 Alleles targeted in request for *CYP2C19*



Four labs stated that the test would be affected by testing for all LOF alleles compared to only testing for *2 or *3 alleles, although two highlighted that this would depend on the technology. Potential impacts included increased cost and increased turnaround time.

Resources required

Two labs were not able to provide any information on resources required and one lab was only able to provide an estimate of the cost of the test.

Staff time

Three labs provided an estimate of staff time to run the selected test. One, that had selected LAMP as the preferred test, estimated 1-2 days in total: 1 -2 hours set up, 2 hours analysis, and 2 hours checking and reporting. The second, that selected QuantStudio 12K Flex Real-Time PCR System or X9 Real-Time PCR System, estimated 0.5 working time equivalent (WTE) for performing test 0.5 WTE for DNA extraction 0.2 WTE for admin. The third lab selected PCR-based SNP genotyping assays using fluorescent reporter systems as their performed test and are currently performing this test estimate staff time at 22mins/sample.

Staff grade

Estimates of staffing grade varied in the five labs that reported on this:

- Band 5 set up, Band 6 analysis & reporting, Band 7 checking and authorisation of reports
- Band 3 up to Band 8a
- Band 3, band 5, band 7
- Band 3, band 4, band 5
- Band 2, 3, 4 for laboratory work; band 7 for authorising reports

Cost

There was also variation in estimates of cost for test. Estimated costs are summarised in Table 21, which also shows the preferred technology that the estimate relates to.

Table 21 Estimates of costs per test and maintenance costs

Preferred Platform	Cost per test	Maintenance costs
MassARRAY (Agena Bioscience)	~ £15 per test	£15k maintenance plus EQA
LAMP	£40 per test (reagent cost only)	NR
MassARRAY or LAMP	~£100	NR
Next-generation gene sequencing or LAMP	£100-£250	NR
QuantStudio 12K Flex Real-Time PCR System or X9 Real-Time PCR System	~£200 per sample. Additional costs in data analysis either by scientists or using automated calling and reporting system = £5-10 per sample	£5000 pa for qPCR machine BUT for 10,000 sample pa we would need to increase our existing DNA extraction capacity, which may mean another automated DNA extraction system = £150k capital investment
PCR-based SNP genotyping assays using fluorescent reporter systems, e.g. TaqMan	£25.09 inc VAT – include reagents/consumables, staff time & overheads	NR

Additional administrative resources

Three labs highlighted additional administrative resources that would be required and one stated that they would be required but did not provide further details. One lab stated that these would not be required. Additional administrative resources required were:

- one band 4 admin
- LIMs upload to electronic care record where link does not exist - admin support to send results and upload to ECR.
- Preferable electronic test ordering but may require admin support for dealing with enquiries

Ease of use

Six labs reported that their preferred test could be performed by existing staff members who have received standard training, one lab reported that the test was fully automated (LAMP) and the other that additional training would be required – this lab had selected QuantStudio 12K Flex Real-Time PCR System or X9 Real-Time PCR System has their preferred test, which would be a new test for their lab and was the reason training would be required.

Test validity

Most labs reported that it was difficult to estimate the proportion of samples that would not return a valid result, most of those that responded stated that they expected this to be <1%. One lab did report ~90% for this question; it appears likely that they have misinterpreted the question. One lab, that are currently performing PCR-based SNP genotyping assays using fluorescent reporter systems reported that 5% of samples would not return a valid result.

Testing capacity and turnaround time

In the introduction to the survey we estimated that the NHS would need to perform approximately:

- 150 000 *CYP2C19* tests in the first year (assuming annual stroke incidence of 100 000 and TIA incidence of 50 000).
- 100 000 *CYP2C19* tests annually after this (57 000 first strokes, 46 000 first TIAs assuming ~10-15% of those with first stroke would previously have had a TIA and already been tested).

Two laboratories reported that there current testing capacity was 0, two were unable to answer this question and another said that they would not be able to process any samples without additional staff and equipment. One laboratory reported that there were currently delivering 110 tests per week, one that they were delivering 200 tests/week, and another that they could do 92 tests per run with up 2 runs per week (total 184 tests per week).

Estimated turnaround time from receiving a sample to returning a test result varied considerably across laboratories ranging from 24-72 hours (1 laboratory) to >4 weeks (1 laboratory). The most common estimate (5 laboratories) was 72 hours to 1 week; 1 laboratory estimates that results would be returned in 1-2 weeks.

Most laboratories reported that additional testing capacity and faster turnaround time would be possible with additional resources – one lab reported that faster turnaround time would not be possible (this lab had estimated turnaround time at 72 hours-1 week). Additional requirements included: additional staffing (6 labs); increased laboratory space (2 labs), increased automation (2 labs),and additional equipment (4 labs). One laboratory specified that staffing would need to be at all grades, another that more technical and IT staff would be needed, the others did not specify further.

Seven labs confirmed that the test could be performed in local laboratories but most said this would require additional staff training and/or equipment- one stated this could be done using existing staff and equipment. The laboratory that stated that the test could not be performed in local laboratories had selected a Real-Time PCR System as its preferred test.

Barriers to implementing *CYP2C19* testing

The major barriers to implementing *CYP2C19* testing were the scale of the predicted activity and current capacity (4 labs), with one highlighting that they do not currently perform any tests of this scale in the NHS and so do not have the infrastructure for this. Staffing was also seen as a major barrier – this was highlighted by 5 labs. Two labs highlighted the

importance of having automated/electronic laboratory systems in place. One lab, despite highlighting several barriers to implementing *CYP2C19* testing, did state that it is "entirely possible" to overcome these barriers. Another lab also highlighted facilitators to implementing testing including previous knowledge of pharmacogenomics testing in lab and the availability of appropriate equipment available within the department. The Scottish Tayside lab, which is currently piloting *CYP2C19* testing highlighted the following as barriers to implementing testing:

- Fixed budget for pilot so had to confine requests to Stroke Unit and Cardiology
- Unable to accept requests from GPs
- Difficulty for some medical disciplines to understand output of genetic results
- Separate requesting and reporting systems for acute and primary care

They also stated that strong support from stroke clinicians, specialist pharmacists and senior managers were facilitators for testing.

Implementation of rapid point of care tests in laboratory workflow

Six labs stated that it should be possible to implement a POCT test within the laboratory workflow. One highlighted that this would not be the most efficient process for the number of samples that would need to be tested, and another that there is no precedent for this in their lab. Additional resources needed included more additional staffing (3 labs) and additional freezers (one lab). Two labs stated that they would not be able to implement POCT. One explained that this would require staff to be able to drop all other duties to perform this test which would not be feasible. One of the labs that stated that it would be possible highlighted that delivering POCT would require different testing technology and cost would increase, another lab highlighted that the time for sample to be receiving in the laboratory might be an issue.

5 Assessment of cost effectiveness

5.1 Review of economic evaluations of *CYP2C19* genetic tests for clopidogrel resistance in non-cardioembolic ischaemic stroke and TIA patients

5.1.1 Review methods

We conducted a systematic review to identify previous studies on the cost-effectiveness of *CYP2C19* genetic tests for guiding treatment in non-cardioembolic ischaemic stroke and TIA patients. We searched the following databases:

- MEDLINE (MEDALL) via Ovid: 1946 to present;
- Embase via Ovid: 1974 to 2022 August 09 (Search 1) and 1974 to 2022 August 10 (Search 2);
- The Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley: Issue 7 of 12, July 2022; and
- The Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO Host: 1981 to present;
- ECONLit via EBSCO Host: 1986 to present;
- HTA Library via the York CRD interface;
- NHS Economic Evaluation Database (EED) via the York CRD interface; and
- Tufts CEA Register via the Tufts Medical Centre website.

We also included any relevant papers on cost-effectiveness identified in the clinical effectiveness reviews, searched citations in relevant publications that we identified, and asked experts in the field. We supplemented the searches with a targeted search for economic models of treatment for secondary prevention following non-cardioembolic ischaemic stroke or TIA. This search was undertaken in MEDLINE, Embase and EconLit. The search strategy for this search is reported in *Appendix 1*: Literature search strategies.

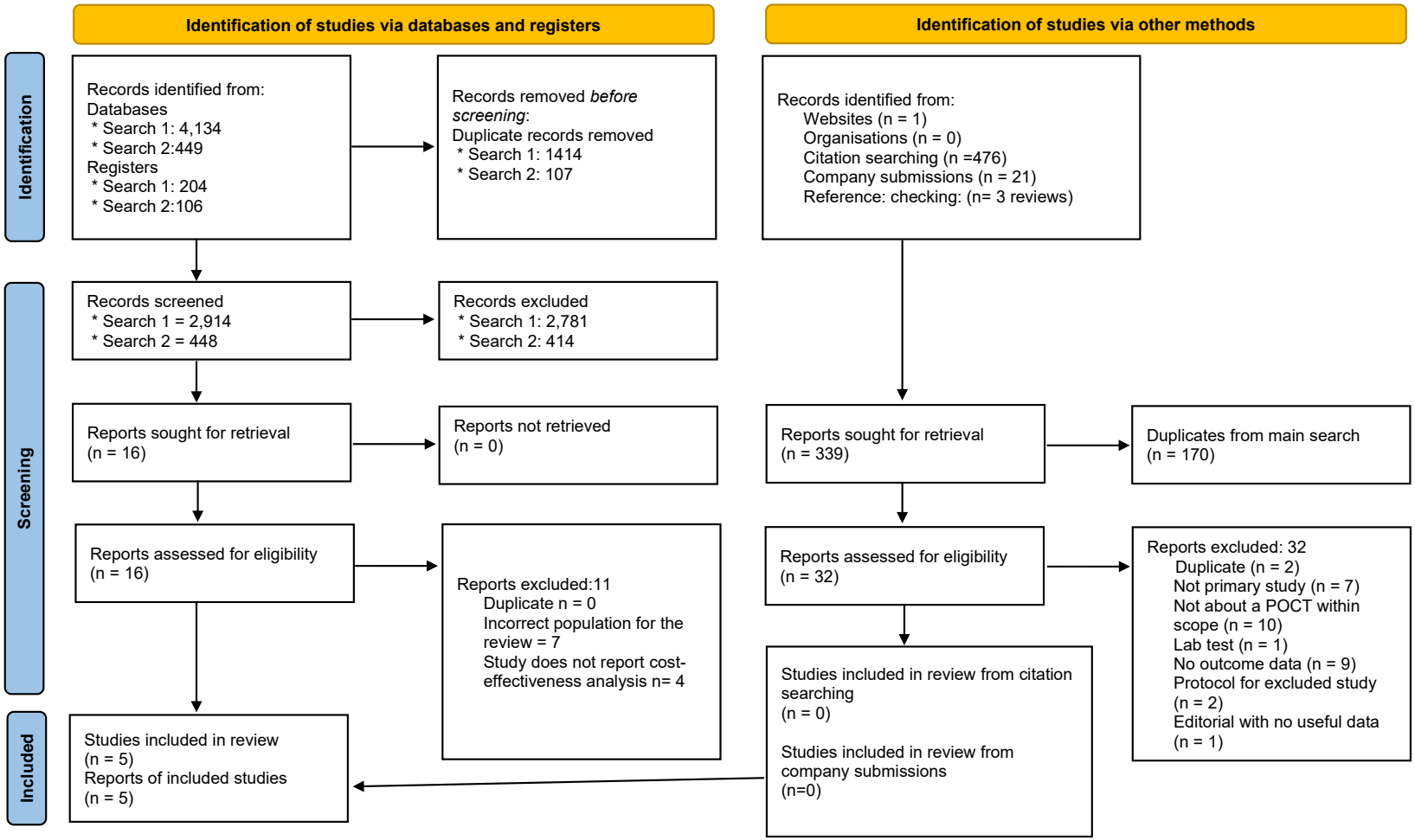
The quality of included cost-effectiveness studies was assessed using the Drummond checklist.[100]

Sources for parameter inputs for the model were identified from previous models, the studies identified in the clinical effectiveness reviews (objectives 1-5), and by running additional targeted searches to identify inputs to the economic model (as required). This included searching for previous network meta-analyses of antiplatelet treatments in general non-cardioembolic ischaemic stroke and TIA populations.

5.1.2 Results of the review of cost-effectiveness studies for *CYP2C19* testing strategies

Figure 26 shows the PRISMA flowchart showing the studies identified from the systematic review of cost-effectiveness studies for *CYP2C19* testing for patients who have had a non-cardioembolic ischaemic stroke and TIA, and reasons for exclusions.

Figure 21 PRISMA diagram showing the studies identified in the systematic review of cost-effectiveness studies for *CYP2C19* testing for patients who have had a non-cardioembolic ischaemic stroke or TIA



Five cost-effectiveness studies were identified for genetic testing for *CYP2C19* LOF followed by anti-platelet therapy in patients suffering from TIA / minor stroke. One study was from a UK NHS perspective [101] where a point-of-care test (POCT) was modelled and LOF carriers were assumed to be treated with Dipyridamole-aspirin instead of clopidogrel. Three studies modelled alternative treatment with ticagrelor [102] [103] [104] which is not licensed for this indication in the UK. The studies are summarised in Table 22.

Micieli (2020)[102]

This economic evaluation was undertaken to assess the cost-effectiveness of the GMEX point-of-care test (POCT) for *CYP2C19* LOF alleles followed by targeted dual antiplatelet therapy (DAPT) compared with no testing in patients living in Canada following TIA / minor stroke. It is assumed that the modelled population meet inclusion in the CHANCE protocol with either had an acute non-disabling ischemic stroke (NIHSS ≤ 3) or a high-risk TIA ($ABCD^2$ ≥ 4). [51] Under the testing strategy patients with LOF alleles receive ticagrelor with aspirin, whereas those without LOF alleles receive clopidogrel with aspirin. In the no-testing strategy all patients receive clopidogrel with aspirin. In all cases it is assumed that DAPT is given for 3 weeks followed by long-term aspirin monotherapy. The analysis was performed from a Canadian health policy decision-makers perspective. Many of the model inputs were based on the multi-centre, placebo controlled CHANCE-2 trial comparing the modelled strategies in China [49] and also from the CHANCE sub-study looking at the association between *CYP2C19* LOF and outcomes on clopidogrel with aspirin. [51] Both CHANCE and CHANCE-2 studies were identified in our clinical review (Objectives 2 and 3).

The decision model is a Markov state transition model for a cohort of patients average age of 65 years over a 20 year time horizon. The first stage model simulates patients outcomes at 90 days, where a proportion would transition into one of the following 4 health states:

- Survive without clinical event.
- Ischemic Stroke: mild (mRS 0-1), moderate (mRS 0-2), severe (mRS 3-5) and fatal (mRS 6).
- Haemorrhage: minor, major, ICH and fatal.
- Death

Patients were then modelled for the reminder of the 20 year time-horizon using a second stage of the Markov model which allows patients to have recurrent strokes by employing tunnel states, however the exact form of the model was not clear from the paper. Baseline age-specific probability of death was sourced from Canadian lifetables and modified to account for severity of health states with data obtained from the ACTIVE-W trial [105] of clopidogrel with irbesartan in atrial fibrillation patients.[102]

The costs of medicines and the costs of clinical events were from local sources specific to Alberta. Utility values were taken from the 'One thousand health-related quality-of-life estimates' systematic review. [106]

Testing for *CYP2C19* LOF was found to be cost-effective with an Incremental Cost Effectiveness Ratio (ICER) of 4,310 Canadian Dollars per Quality Adjusted Life Year (QALY) , with a probability of being cost-effective more than 0.99 at a willingness-to-pay threshold of 50,000 Canadian Dollars per QALY.

Cai (2021)[107]

This economic evaluation was undertaken to assess the cost-effectiveness of testing for *CYP2C19* LOF alleles using the Sequenom MassARRAY iPLEX laboratory test followed by targeted DAPT compared with no testing in Chinese patients following TIA / minor stroke. It is assumed that the modelled population matches that of the CHANCE study. [51] Under the testing strategy patients with LOF alleles receive dipyridamole with aspirin, and patents without the LOF alleles receive clopidogrel with aspirin. In the no-testing strategy all patients receive clopidogrel with aspirin. In all cases DAPT is given for 90days followed by long-term aspirin monotherapy. The analysis was performed from a Chinese health payer perspective.

This economic evaluation relies on two sources of clinical evidence. The efficacy of clopidogrel with aspirin according to *CYP2C19* LOF allele status is taken from a subgroup analysis from the CHANCE trial[51] which was identified in our clinical review (Objectives 2 and 3). The efficacy of dipyridamole with aspirin compared with clopidogrel with aspirin is estimated using an indirect comparison via common comparator aspirin monotherapy based on an individual patient data meta-analysis of 5 RCTs comparing dipyridamole with aspirin versus aspirin[108] and the CHANCE study comparing clopidogrel with aspirin vs aspirin. [51] The CHANCE study was included in our clinical review (objectives 1 and 2), and also used in our economic model.

The decision model is a combination of a decision tree and a Markov state transition model for a cohort of patients for a 30 year time horizon. The decision tree model simulates patients outcomes after the first 90 days, where a proportion would transition into one of the following 4 health states:

- Minor or no disability (mRS 0–2)
- Moderate disability (mRS 3–4)
- Severe disability (mRS 5)
- Death (mRS 6)

The Markov model covers the remainder of the 30-year time horizon patients experiencing recurrent strokes, intracerebral haemorrhage (ICH), major extracranial haemorrhage (ECH) and myocardial infarction (MI). Age-specific mortality rates for non-stroke death were derived from a published census of China and adjusted by the causes of death.

The costs of medicines were based on the retail prices according to the Beijing Municipal Commission of Development and Reform. The one-time hospitalisation costs associated

with clinical events were based on the China health statistics yearbook. [109] Utility values were based on a previous cost-effectiveness analysis of clopidogrel with aspirin vs aspirin alone for patients who have had a minor stroke or TIA. [110]

The ICER for the *CYP2C19* LOF testing strategy was 13,552.74 Chinese Yuan per QALY gained compared with no testing, and the probability of being cost-effective was 0.96 at a willingness-to-pay threshold 72,100 Chinese Yuan per QALY.

Narasimhalu (2020) [103]

This economic evaluation was undertaken to assess the cost-effectiveness of testing for *CYP2C19* LOF alleles using the Spartan RX POCT followed by targeted anti-platelet therapy compared with no testing in Singaporean patients who have had their first ischemic stroke. Under the testing strategy patients with LOF alleles receive ticagrelor whereas those without LOF alleles receive clopidogrel. In the no-testing strategy all patients receive clopidogrel. In all cases long-term anti-platelet monotherapy is given. The analysis was performed from a local healthcare provider's perspective.

This economic evaluation relies on two sources of clinical evidence. Outcomes for patients on clopidogrel according to *CYP2C19* LOF status (where LOF allele carriers were determined as *CYP2C19**2 and *CYP2C19**3) were taken from a prospective cohort study that evaluated the impact of *CYP2C19* polymorphisms on stroke recurrence and other vascular events in a cohort of Chinese patients receiving clopidogrel[67], identified in our clinical review (Objective 3). Outcomes on ticagrelor were taken from the ticagrelor arm of the multi-national multi-centre SOCRATES trial of ticagrelor versus aspirin in a subgroup of patients with a non-cardioembolic, non-severe acute ischemic stroke, or high-risk TIA. [111]

The decision model is a Markov state transition for a cohort of patients average age of 65 years over a 20-year time horizon. Patients transition into one of the following 3 health states:

- Non-recurrent Ischemic Stroke (the starting state)
- Post-Ischemic Stroke (after a recurrent stroke)
- Death

Local rates of ischemic stroke were sourced from the Singapore Stroke Registry, data from public hospitals between 2007 and 2016. [112] The standard mortality rates at every age were obtained from life tables for the Singapore Resident Population 2017–2018. The prevalence of LOF allele carriers was taken from previously reported values of 506 genomic samples of healthy Singaporean individuals. [113]

The cost of the genetic test and the costs of medicines were sourced from a local hospital. The total cost of ischemic stroke was sourced from administrative data. Utility values were sourced from an economic evaluation of primary stroke centres [114 3794] which based the values on a survey of preferences among persons at increased risk for stroke in the USA. [115]

CYP2C19 testing for LOF was found to be cost-effective with an ICER of $33,839/QALY compared with no-testing, with a probability of being cost-effective of 0.78 at a willingness-to-pay threshold of $60,000/QALY.

Kremers 2021[104]

This economic evaluation was undertaken to assess the cost-effectiveness of point-of-care test (POCT) for *CYP2C19* LOF alleles followed by targeted therapy compared with no testing in patients living in the Netherlands following minor acute stroke / TIA. Under the testing strategy patients with LOF alleles receive either aspirin monotherapy, prasugrel, ticagrelor or aspirin-dipyridamole instead of clopidogrel with aspirin, whereas in the no-testing strategy all patients receive DAPT clopidogrel with aspirin. Clinical inputs for the model are based on published studies, but this abstract does not give further details.[116]

The decision model is a Markov state transition 1-year cycle length for a cohort of patients over a life time horizon. Testing for *CYP2C19* LOF followed by prasugrel or ticagrelor were found to be cost-saving with incremental cost-savings of €461 or €438, and gains of 0.01 QALYs per patient compared to no testing and treatment with clopidogrel.

Wright et al (2022)[101]

This early economic evaluation was undertaken to assess the high-level cost-effectiveness of the Genedrive® *CYP2C19* ID Kit point-of-care test (POCT) for *CYP2C19* LOF alleles followed by targeted dual antiplatelet therapy (DAPT) compared with no testing in patients living in the UK following first stroke. Under the testing strategy patients with LOF alleles receive dipyridamole with aspirin instead of clopidogrel monotherapy, whereas in the no-testing strategy all patients receive clopidogrel. Patients who do not tolerate clopidogrel are switched to modified release dipyridamole, or to aspirin if the modified release dipyridamole is not tolerated. The analysis was performed from the UK NHS perspective.[101]

The treatment effects of clopidogrel on LOF carriers were based on a systematic review and meta-analysis of studies to assess the association between *CYP2C19* genotype and clopidogrel efficacy for ischemic stroke or TIA.[16] The treatment effects for LOF non-carriers were based on a network meta-analysis of treatments for first strokes and recurrent strokes in a general stroke/TIA population taken from the health technology assessment of clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events for NICE TA210.[117]

A decision tree and Markov model is used for a cohort of patients with average age of 67 years over a lifetime time horizon. In the first stage, the decision tree is used to capture the testing process and allocation to treatment. The proportion of patients who are LOF carries was based on data reported in the meta-analysis.[16] Patients then enter the Markov model and transition into one of the following 5 health states:

- No further stroke,
- one further stroke,
- greater than 1 further stoke,
- Vascular death,
- Other Cause of Death.

All-cause mortality was estimated from the Office of National Statistics mortality data.[118] The costs and utility values were taken from the economic evaluation of Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events.[117]

Testing for *CYP2C19* LOF was found to be dominate the no testing strategy, with lower mean costs (incremental savings of £170) and higher mean QALYs (incremental gain of 0.096 QALYs per patient), and a probability of being cost effective more than 0.77 at a willingness-to-pay threshold of £20,000 per QALY.[101]

Table 22 Summary of economic evaluations of genetic guided therapy for patients who've had a TIA / minor stroke

Author, year	Setting	Population	Model type	Time horizon	Interventions	Comparators	Perspective
Micieli (2022)[102]	Canada	TIA/minor stroke patients	Markov cohort model	Lifetime 20 years (30 day cycles)	**Genetic Test & Treat** GMEX POCT LOF non-carriers: Aspirin–clopidogrel. LOF carriers: DAPT aspirin (75-300mg on day 1 followed by 75mg daily) w/ ticagrelor (180mg on day 1 followed by 90mg twice daily) for 3 weeks, followed by single anti-platelet aspirin .	**Treat (No Test)** DAPT aspirin (75-300mg on day 1 followed by 75mg daily) w/ clopidogrel (300mg on day 1 followed by 75mg daily) for 3 weeks, followed by single antiplatelet aspirin.	Federal, Provincial, and Territorial Ministries of Health
Cai (2021)[107]	China	Acute minor stroke or high-risk TIA patients	Decision Tree & Markov Model	Lifetime 30 years	**Genetic Test & Treat** Sequenom MassARRAY iPLEX Lab Test LOF non-carriers: Clopidogrel (300mg on day 1 followed by 75mg daily) for 3 months plus aspirin (75-300mg on day 1 followed by 75mg daily) for 21 days. LOF carriers : Dipyridamole - aspirin sustained-release capsule (200 mg, 25mg, twice daily) for 3 months.	**Treat (No Test)** Clopidogrel (300mg on day 1 followed by 75mg daily) for 3 months plus aspirin (75-300mg on day 1 followed by 75mg daily) for 21 days.	Health Care Payer
Narasimhalu (2020)[103]	Singapore	Ischemic stroke patients	Markov Model	Lifetime 20 years	**Genetic Test & Treat** Spartan RX POCT LOF non-carriers: clopidogrel (300mg on day 1 followed by 75mg daily). LOF carriers: ticagrelor (180mg on day 1 followed by 90mg twice daily).	**Treat (No Test)** Clopidogrel (300mg on day 1 followed by 75mg daily).	Local Healthcare
Kremers (2022)[104]	Netherlands	Minor acute ischemic stroke / TIA patients	Markov Model	Lifetime (1-year cycles)	**Genetic Test & Treat** LOF non-carriers: DAPT Clopidogrel-aspirin. LOF carriers: receive either aspirin monotherapy, prasugrel, ticagrelor or DAPT aspirin-dipyridamole.	**Treat (No Test)** DAPT Clopidogrel-aspirin for 3 weeks followed by lifelong clopidogrel monotherapy.	NA

Author, year	Setting	Population	Model type	Time horizon	Interventions	Comparators	Perspective
Wright (2022)[101]	United Kingdom	Patients suffered first stroke	Decision Tree & Markov Model	Lifetime	**Genetic Test & Treat** Genedrive® *CYP2C19* ID Kit LOF non-carriers: Clopidogrel, if intolerant, switch to modified release. dipyridamole plus aspirin. LOF carriers: modified release dipyridamole plus aspirin.	**Treat Only (No Genetic Test)** Clopidogrel, if intolerant, switch to modified release dipyridamole plus aspirin.	NHS

Table 23 (contd) Summary of economic evaluations of genetic guided therapy for patients who've had a TIA / minor stroke

Author, year	Discount Rate	Health states	Source of effectiveness information	Results
Micieli (2022) [102]	1.50%	1. Survive without clinical event 2. Ischemic Stroke : Fatal (mRS 6), Severe (mRS 3-5), Moderate (mRS 0-2), mild (mRS 0-1) 3. Haemorrhage: Minor, Major, ICH , Fatal 4.Death	CHANCE trial subgroup data for non-carriers of LOF, and CHANCE-2 trial for LOF carriers.	The ICER for the *CYP2C19* testing strategy was CAD$4310 per QALY compared with no testing. *CYP2C19* testing was cost-effective in more than 99.99% of simulations using a willingness-to-pay threshold of CAD$50,000 per QALY.
Cai (2021)[107]	3%	1. Minor or no disability (mRS 0–2) 2. Moderate disability (mRS 3–4) 2. Severe disability (mRS 5) 4. Death (mRS 6)	*CYP2C19* subgroup data from the CHANCE trial. A meta-analysis of 5 RCTs of DAPT Dipyridamole-aspirin vs aspirin for secondary prevention after TIA or stroke.	The ICER for the *CYP2C19* testing strategy was CNY 13,552.74 (US$1,931) QALY compared with no testing. *CYP2C19* testing was cost-effective in more than 95.7% of simulations at a willingness-to-pay threshold CNY 72,100 (US$10,300) per QALY.
Narasimhalu (2020)[103]	3%	No recurrent ischaemic stroke Post- recurrent ischaemic stroke Death	The SOCRATES trial for Ticagrelor. For clopidogrel a prospective cohort study on the recurrent risk among stroke patients with *CYP2C19* phenotypes treated with clopidogrel from the Nanjing Stroke Registry Program.	The ICER for the *CYP2C19* testing strategy was S$33,839/QALY compared with no testing. *CYP2C19* testing was cost-effective in more than 77.68% of simulations at a willingness-to-pay threshold S$60,000/QALY threshold.
Kremers (2022)[104]	NA	NA	NA	Testing for *CYP2C19* LOF followed by prasugrel or ticagrelor were found to be cost-saving with incremental cost-savings of €461 or €438, and gains of 0.01 QALYs per patient compared to no testing and treatment with clopidogrel.

Author, year	Discount Rate	Health states	Source of effectiveness information	Results
				Probabilistic sensitivity analysis results were not reported.
Wright (2022)[101]	3.50%	No further stroke one further stroke >1 further stoke Vascular death Other Cause of Death	A meta-analysis investigating the effect of treatment with clopidogrel on stroke or TIA patients who are LOF carriers compared to LOF non- carriers. A systematic review and economic evaluation of the clinical and cost effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events.	The *CYP2C19* testing strategy was cost saving when compared with no testing. Incremental savings of £170 and gain of 0.096 QALYs per patient. The probabilistic sensitivity analyses demonstrated that testing was cost-effective in 77% of simulations at a willingness-to-pay threshold £20,000/QALY threshold.

Abbreviations: **CNY:** Chinese Yuan, **DAPT :** Dual Anti Platelet Therapy, **€**: Euros, **GBP £:** Great Britain Pound, **ICER:** Incremental Cost-Effectiveness Ratio, **ICH:** Intracranial haemorrhage, **LOF:** Loss of Function, **mRS:** Modified Rankin Scale, **NA:** Not Applicable, **NHS:** National Health Service, **POCT**: Point of Care Test, **QALY**: Quality Adjusted Life Year, **S$:** Singaporean Dollar, **TIA**: Transient Ischaemic Attack.

Quality assessment of cost-effectiveness studies

Table 24 shows the assessment of study quality of the cost-effectiveness studies using the Drummond checklist. [100] In general the studies were of high quality although the estimation of unit costs were not clear. Kremers 2021[104] was a conference abstract although limited detail is available, we confirmed treatment strategies via correspondence with authors.

Table 24 Study quality for economic evaluations of genetic guided therapy for patients who've had a TIA / minor stroke

	Micieli (2022) [102]	**Cai (2021)**[107]	**Narasimhalu (2020)**[103]	**Kremers (2021)**[104]	**Wright (2022)**[101]
Study Design					
The research question is stated	✓	✓	✓	✓	✓
The economic importance of the research question is stated	✓	✓	✓	✓	✓
The viewpoint(s) of the analysis are clearly stated and justified.	✓	✓	✓	×	✓
The rationale for choosing alternative programmes or interventions compared is stated	✓	✓	✓	✓	✓
The alternatives being compared are clearly described	✓	✓	✓	✓	✓
The form of economic evaluation used is stated	✓	✓	✓	✓	✓
The choice of form of economic evaluation is justified in relation to the questions addressed	✓	✓	✓	×	✓
Data Collection					
The source(s) of effectiveness estimates used are stated	✓	✓	✓	×	✓
Details of the design and results of effectiveness study are given (if based on a single study)	✓	✓	✓	×	✓
Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)	NA	NA	NA	NA	NA
The primary outcome measure(s) for the economic evaluation are clearly stated	✓	✓	✓	×	✓
Methods to value benefits are stated	✓	✓	✓	×	✓
Details of the subjects from whom valuations were obtained were given	✓	✓	✓	×	✓
Productivity changes (if included) are reported separately	NA	NA	NA	NA	NA
The relevance of productivity changes to the study question is discussed	NA	NA	NA	NA	NA

	Micieli (2022)[102]	Cai (2021)[107]	Narasimhalu (2020)[103]	Kremers (2021)[104]	Wright (2022)[101]
Quantities of resource use are reported separately from their unit costs	×	×	×	×	×
Methods for the estimation of quantities and unit costs are described	×	×	×	×	×
Currency and price data are recorded	✓	✓	✓	✓	✓
Details of currency of price adjustments for inflation or currency conversion are given	✓	✓	✓	×	✓
Details of any model used are given	✓	✓	✓	×	✓
The choice of model used and the key parameters on which it is based are justified	✓	✓	✓	×	✓
Analysis and interpretation of Results					
Time horizon of costs and benefitsis stated	✓	✓	✓	×	✓
The discount rate(s) is stated	✓	✓	✓	×	✓
The choice of discount rate(s) is justified	✓	✓	✓	×	✓
An explanation is given if costs and benefits are not discounted	NA	NA	NA	×	NA
Details of statistical tests and Cis are given for stochastic data	✓	✓	✓	×	✓
The approach to sensitivity analysis is given	✓	✓	✓	×	✓
The choice of variables for sensitivity analysis is justified	✓	✓	✓	×	✓
The ranges over which the variables are varied are justified	✓	✓	✓	×	✓
Relevant alternatives are compared	✓	✓	✓	✓	✓
Incremental analysis is reported	✓	✓	✓	✓	✓
Major outcomes are presented in a disaggregated as well as aggregated form	NA	NA	NA	NA	NA
The answer to the study question is given	✓	✓	✓	✓	✓
Conclusions follow from the data reported	✓	✓	✓	✓	✓
Conclusions are accompanied by the appropriate caveats	✓	✓	✓	×	✓

Summary of relevance of existing evidence to this economic evaluation

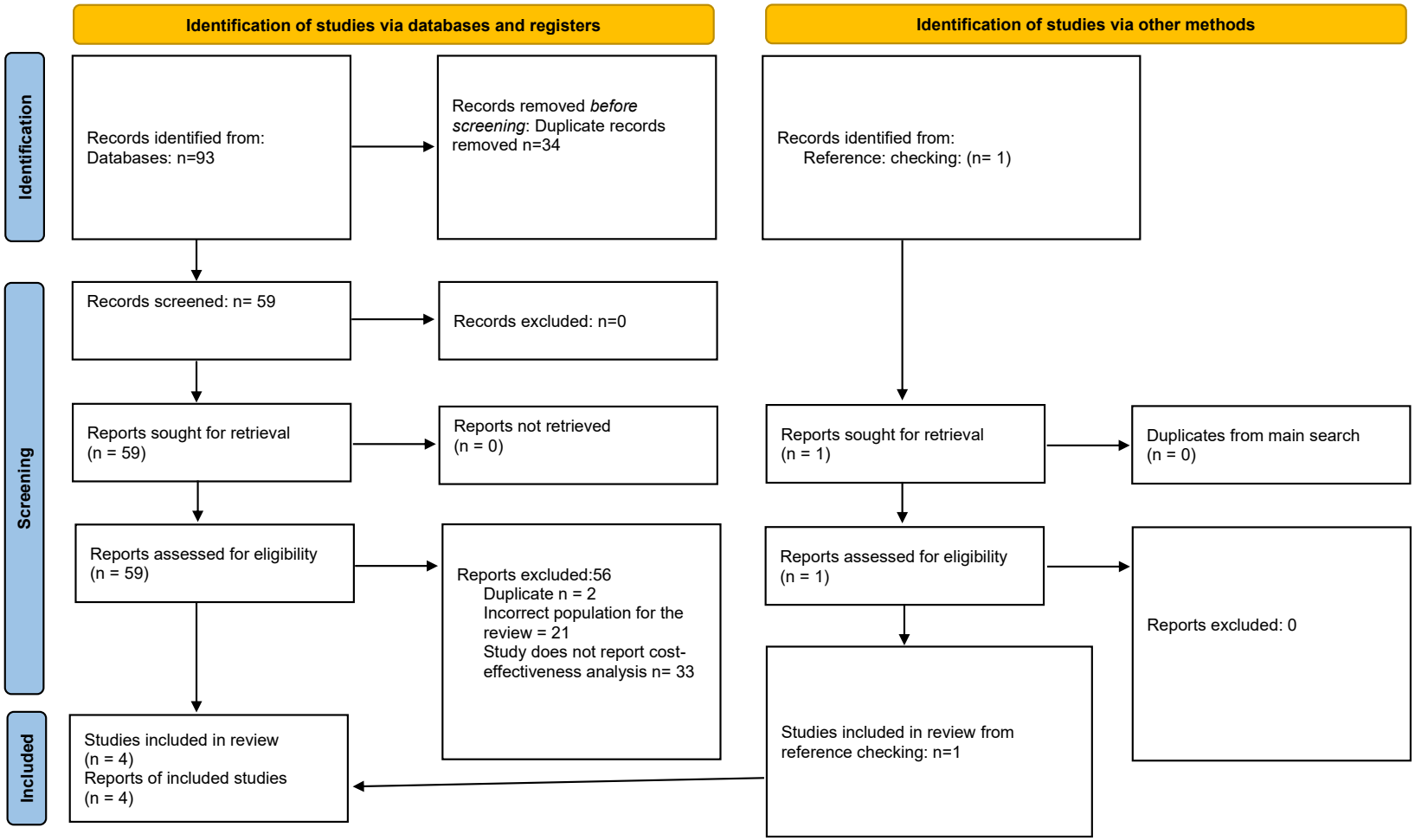
Of the previous models only Wright et al (2022)[101] was in a UK setting using an alternative treatment (dipyridamole) that would be used in UK clinical practise for LOF carriers. However, the model inputs used by Wright et al (2022)[101] were based on an old health

technology assessment[117] and a meta-analysis[16] that doesn't include some of the recent relevant evidence. None of the previous studies compared different types of *CYP2C19* tests. Most of the models used a decision tree structure for the short-term impacts of *CYP2C19* testing followed by a long-term Markov model, and all of the previous models found that *CYP2C19* testing is likely to be cost-effective.

5.1.3 Results of the review of cost-effectiveness studies of secondary prevention of ischaemic stroke

To supplement the review of cost-effectiveness studies for *CYP2C19* testing strategies, we also reviewed cost-effectiveness studies of secondary prevention of ischaemic stroke in a general population to help inform the structure of the long-term model for anti-platelet therapies in patients who had a previous ischaemic stroke or TIA, and also to help identify relevant evidence sources.

Figure 22 - PRISMA diagram showing the studies identified in the supplementary review of cost-effectiveness studies of secondary prevention ischaemic stroke in a general population



We identified 4 relevant cost-effectiveness studies which are summarised in Table 25.

Zhou (2022)[119]

This economic evaluation was undertaken to assess the cost-effectiveness of adding Cilostazol to aspirin or clopidogrel compared with aspirin or clopidogrel monotherapy in patients with non-cardioembolic stroke. A Markov state transition model was used to simulate a cohort of patients, average age of 70, over a 40 year time horizon between the following 4 health states:

- neurologically intact, (score of 0 mRS),
- mild disability (score of 1-2 on the mRS),
- moderate to severe disability (score of 3–5 on the mRS), and
- deceased (mRS score of 6)

The analysis was performed from a US payer/Medicare perspective.

Base rates of recurrent ischemic stroke for patients on aspirin and clopidogrel were derived from a subgroup analysis of the CAPRIE trial.[120] Neurological outcomes after intracranial haemorrhage while on antiplatelet therapy were derived from the results of the PATCH trial.[121]

Treatment effects for adding Cilostazol to aspirin or clopidogrel were based on the multi-centre, placebo controlled CSPS.com trial in Japan.[119] For those experiencing a recurrent ischaemic stroke or intracranial haemorrhage, the resulting mRS state was based on the results of the POINT trial.[122]

The costs of medicines and those associated with clinical events were from local sources specific to the USA. The annual costs of mild and severe health states was taken from a cost-effectiveness of Diagnostic Strategies.[123] The health utility scores associated with disability states was calculated using US-specific preference weights multiplied by utilities derived from the Virtual International Stroke Trials Archive (VISTA).[124]

Greenhalgh (2011)[117]

This economic evaluation was undertaken to compare the cost-effectiveness of different treatment sequences with aspirin, clopidogrel and modified release dipyridamole plus aspirin, compared with no treatment in patients who have had a recent stroke or TIA. The decision model is an individual patient simulation model over a lifetime horizon, where patient characteristics were based on data from the Health Survey of England 1996. Patients transition according to risks associated with disability status (disabled classified as mRS ≥3) through the following health states:

- new fatal or non-fatal ischaemic stroke event
- new fatal or non-fatal non-ischaemic stroke event (haemorrhagic stroke or intracranial haemorrhage)

- new fatal or non-fatal MI
- death from other vascular causes
- death from non-vascular causes

The analysis was performed from a UK health policy decision-makers perspective. Risk models for events and fatality due to events were based on confidential data from the CAPRIE[120] and PRoFESS[125] clinical trials. Treatment discontinuation is modelled by an exponential survival function which calculates the time of discontinuation for each patient.[117]

The treatment effects for first recurrent ischaemic stroke were estimated using a network meta-analysis of three clinical trials CAPRIE,[120] ESPIRIT[126] and PRoFESS.[125] The treatment effects for recurrent ischaemic stroke were estimated using a network meta-analysis of two clinical trials ESPS-2[127] and PRoFESS.[117] Furthermore the network meta-analyses were used to estimate death from all causes, vascular death, major bleeds and all bleeds.[117]

Treatment costs were drawn from the manufacture submissions,[128] [129] stroke event costs from a UK economic burden study,[130] and MI event costs from the UK Prospective Diabetes Study.[131]

Utility values for ischaemic stroke and related disability were taken from the PRoFESS trial,[125] and the utility for MI taken from a cost effectiveness study of the secondary prevention of stroke.[132] The utility decrement for minor bleeds taken from a cost-effectiveness study for stroke prophylaxis in atrial fibrillation.[133] The utility decrement of dyspepsia taken from an economic evaluation for a treatment of ankylosing spondylitis.[134] The utility decrement for intracranial haemorrhage taken from a cost effectiveness study of anticoagulation for haemodialysis patients with atrial fibrillation.[135]

Malinina (2007)[136]

This economic evaluation was undertaken to assess the cost-effectiveness of DAPT clopidogrel + aspirin or extended release dipyridamole + aspirin compared with aspirin in patients who have had a non-cardioembolic stroke or TIA. The decision model is a decision tree model for a cohort of patients average age of 65 years over a one year time horizon. The analysis was performed from a US payer perspective. Treatment effects for model were estimated by calculating the relative risk reductions derived from the randomized control trials ESPS-2, MATCH, CAPRIE and a meta regression of the effects of aspirin on stroke.[137] [136]

The proportion of stroke survivors was calculated from the Atherosclerosis Risk in Communities Study,[138] and the risk of recurrent stroke taken from the Oxfordshire Community Stroke Project.[139]The annual costs of stroke were based on a study of Medicare claims,[140] and the costs of minor bleeds were taken from a cost effectiveness study of the secondary prevention of stroke.[132] Utility values were not included in this model as the

primary aim of the model was to estimate the number of stokes averted over the time period.

Jones (2004)[141]

This economic evaluation was undertaken to compare the cost-effectiveness of different anti-platelets in patients who have had either a stroke or a TIA. Aspirin, clopidogrel, modified release dipyridamole, modified release dipyridamole + aspirin, and aspirin are compared for patients who have had a stroke. Aspirin, modified release dipyridamole, modified release dipyridamole + aspirin, and aspirin are compared for in patients who have had a TIA. The decision model is a Markov state transition for a cohort of patients average age of 60 years over a 40 year time horizon. The patients enter model after their initial stroke/TIA into one of the following 5 health states:

- TIA (starting state for the TIA population)
- Year 1 post-stroke (no further stroke / event free) (starting state for the ischaemic stroke population)
- New Stroke (recurrent stroke), either disabling or non-disabling
- Vascular death
- Non-vascular Death (Excluded by scenario analysis)

The analysis was performed from a UK NHS perspective. Baseline age adjusted event rates (recurrent stroke, vascular death) for stroke patients assumed to be on treatment with aspirin were calculated from patient-level data the South London Stroke Register.[142] Proportions of patients having disabling first stokes and disabling recurrent strokes were obtained from the ESPS-2[127] trial. Baseline risks of non-vascular death were estimated from the national statistics and excluding deaths due to diseases of the circulatory system.[141]

The treatment effects for the model are estimated from an indirect comparison [141] which connects the evidence on the treatment effects attributable to aspirin and risks of fatal/non-fatal bleeds reported in a meta-analysis by Baigent et al..[143] The treatment effects of clopidogrel vs aspirin estimated from the ESPS-2[127] trial, and treatment effects for dipyridamole, modified release dipyridamole + aspirin vs aspirin were estimated from the CAPRIE trial.

The annual cost associated with stroke was derived from study describing the economic burden of stroke to the UK.[130] The authors assumed that costs associated with mild and moderate strokes were attributable to non-disabled stroke patients and that costs associated with severe stroke were attributable to disabled stroke patients. Utility values were taken from a systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. [144]

Table 25 Summary of cost-effectiveness studies of antiplatelets for secondary prevention of ischaemic stroke in a general population

Author, year	Setting	Population	Model type	Time horizon	Interventions	Comparators / reference treatment strategy	Perspective
Zhou (2022)[119]	USA	Patients with non-cardioembolic stroke	Markov model decision tree	Lifetime (1 year cycles)	**DAPT** Cilostazol + aspirin or Cilostazol + clopidogrel	Aspirin or clopidogrel	US payer/Medicare
Greenhalgh (2011)[117] *TA 210 Stroke & TIA* subgroup*	United Kingdom	Patients that experienced a recent stroke or TIA.	Patient-level simulation model	Lifetime	**Sequences of the following treatments:** Clopidogrel, Aspirin, Modified release dipyridamole + aspirin	No treatment	NHS, Personal Social Services (PSS)
Malinina (2007)[136]	USA	Patients that experienced a non-cardioembolic stroke or TIA	Unclear	1 year	**DAPT** clopidogrel + aspirin or Extended release dipyridamole + aspirin	Aspirin	third-party payer perspective
Jones (2004)[141] *TA 90 Stroke & TIA subgroup*	United Kingdom	Patients that experienced stroke or TIA	Markov Model	Lifetime (40years)	<u>Stroke</u> clopidogrel modified release dipyridamole modified release dipyridamole + aspirin <u>TIA</u> modified release dipyridamole modified release dipyridamole + aspirin	Aspirin	NHS

Table 26 (contd) Summary of cost-effectiveness studies of antiplatelets for secondary prevention of ischaemic stroke in a general population

Author, year	Discount Rate	Health states	Source of effectiveness information	Results
Zhou (2022)[119]	3%	1) neurologically intact, (score of 0 mRS), 2) mild disability (score of 1-2 on the mRS), 3) moderate to severe dis-ability (score of 3–5 on the mRS), and 4) deceased (mRS score of 6) *Worsening of neurological disability was assumed to occur only through recurrent ischemic stroke or intracranial haemorrhage.*	CSPS.com Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischaemic stroke in Japan. POINT Platelet-Oriented Inhibition in New Transient Ischemic Attack and Minor Ischemic Stroke Trial PATCH Platelet Transfusion Versus Standard Care After Acute Stroke Due to Spontaneous Cerebral Haemorrhage Associated With Antiplatelet Therapy trial[121]. CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events) trial[120]. Cilostazol for Secondary Prevention of Stroke and Cognitive Decline Systematic Review and Meta-Analysis.	The dual therapy strategy resulted in mean costs savings of $13 488 and mean increase in QALYs of 0.585 compared with aspirin or clopidogrel alone in 100% of the simulations The average net monetary benefit resulting from the addition of cilostazol was $42 743 per patient over their lifetime at a willingness-to-pay threshold of $50,000/QALY At a willingness to pay of $50 000/QALY, the net monetary benefit was $42 743 ($13 488 +$29 255) per patient over their lifetime.
Greenhalgh (2011)[117]	3.5%	1) New (fatal / non-fatal) Ischaemic stroke 2) New (fatal / non-fatal) non-ischaemic stroke (haemorrhagic stroke or ICH) 3) MI 4) Other vascular death (total deaths excluding fatal strokes) 5) non-vascular death	A network meta-analysis of first strokes from the ESPRIT,[126] CAPRIE,[120] and PRoFESS[125] trials. A network meta-analysis of recurrent ischaemic stroke from the ESPS-2 and PRoFESS[125] trials.	The optimal treatment strategy clopidogrel → DAPT modified release dipyridamole + aspirin → aspirin with an ICER > £8,300/QALY compared to No Treatment. The optimal treatment strategy clopidogrel → DAPT modified release dipyridamole + aspirin → aspirin was cost-effective in 68% of the simulations using a willingness-to-pay threshold of £20,000 per QALY.

Author, year	Discount Rate	Health states	Source of effectiveness information	Results
		Adverse events: major/minor bleed, dyspepsia, new/worsened congestive heart failure.		PSA was limited to 100 replications. Each replication simulated 10,000 patients with up to 10 events.
Malinina (2007)[136]	NA	Recurrent stroke (Limited to only 1). Assumption; average stroke severity, to simplify stroke events.	ESPS-2 The second European Stroke Prevention Study.[127] CAPRIE The European trial of Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events.[120] The MATCH (Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients) trial.	Antiplatelet therapy with dipyridamole/aspirin prevents an additional 26 strokes per 1000 patients/year as compared with aspirin, with an incremental cost per stroke averted (cost-per-stroke averted ratio) per 1000 patients/year of $16,555. On the other hand, clopidogrel monotherapy, and clopidogrel plus aspirin combination, are not cost effective compared with ER-dipyridamole/aspirin since these therapies prevent less strokes at a higher cost.
Jones (2004)[141] *TA 90 Stroke & TIA subgroup*	Costs 6% QALYs 1.5%	Patients enter the model after initial stroke/ TIA into one of the following health states: 1) Year 1 post-stroke (no further stroke / event free) 2) New Stroke (recurrent stroke), either disabling or non-disabling 3) Vascular death 4) Non-vascular Death (Excluded by scenario analysis)	Indirect treatment comparison connecting evidence from the trials ESPS-2, [127] CAPRIE[120] and the Antithrombotic Trialists' Collaboration meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients.	**Scenario: 2-year treatment, only vascular related death.** The ICER for the treatment of stroke patients with DAPT modified release dipyridamole + aspirin was £5,500 compared with monotherapy aspirin. DAPT modified release dipyridamole + aspirin was cost-effective in 62% of the simulations higher than that of either aspirin (14%) or clopidogrel (12%) using a willingness-to-pay threshold of £10,000 per QALY. The results were similar for TIA patients.

Abbreviations: **DAPT :** Dual Anti Platelet Therapy, **ER-dipyridamole:** Extended Release Dipyridamole**, GBP £:** Great Britain Pound, **ICER:** Incremental Cost-Effectiveness Ratio, **ICH:** Intracranial haemorrhage, **MI:** Myocardial Infarction, **mRS:** Modified Rankin Scale, **NA:** Not Applicable, **NHS:** National Health Service, **PSA:** Probabilistic Sensitivity Analysis, **QALY**: Quality Adjusted Life Year, **TIA**: Transient Ischaemic Attack, **$:** United States Dollar.

5.2 Model structure and methods of economic evaluation

We developed a decision-analytic model to estimate the incremental costs and quality-adjusted life years (QALYs) for *CYP2C19* genetic testing for clopidogrel resistance in patients in England and Wales who have had a non-cardioembolic ischaemic stroke or TIA where treatment with clopidogrel is being considered, compared with no genetic testing. We refer to LOF carriers as LOF patients, and LOF non-carriers as NoLOF patients.

5.2.1 Populations

The model was developed for two distinct populations: patients who have had a non-minor ischaemic stroke; and patients who have had a TIA or minor stroke. This is to reflect the different treatment pathways (section 1.4) and different event rates in these two sub-populations. The key differences between the models are the event rates and transition probabilities, the costs and utilities for patients who have not had a recurrent stroke event (worse health state for non-minor stroke patients compared with TIA / minor stroke patients), and the time at which clopidogrel is initiated and LOF patients can benefit from targeted treatment (immediately for TIA / minor stroke patients, and after 2 weeks aspirin otherwise). Results are reported for the two sub-populations separately, and for a combined population using a weighted average over the sub-populations, according to prevalence. We conducted a scenario analysis for populations with high prevalence of clopidogrel resistance. We had planned to conduct a scenario analysis for children, however insufficient evidence was identified to do this. We instead conduct a scenario analysis for younger adults at time of index stroke or TIA.

5.2.2 Genetic testing and treatment strategies and comparators

We compared different *CYP2C19* testing strategies with a no testing strategy. We included the Genomadix Cube and the Genedrive *CYP2C19* POCT genetic tests included in the clinical effectiveness review (Section 3.1.1), and a single laboratory-based *CYP2C19* genetic test chosen to be representative of how laboratory-based tests are used in practice (based on our survey of genomic laboratory hubs (Section 3.5)). We note that there is very little information on the Genedrive POCT and so the results for this test are based on assumptions and should be interpreted with this in mind. We varied the time taken to receive results and the cost of the lab-based test in scenario analyses (see section 5.3.4). We assumed that the tests fail to provide a result in a proportion of cases (which depends on test type), and that for those cases a second test would be required, incurring additional costs.

Under the no-testing strategy it is assumed that all patients will be treated according to the treatment pathways in Figure 1, Section 1.4. Non-minor stroke patients receive aspirin 300mg daily for 2 weeks (starting within 24 hours), followed by long-term clopidogrel 75mg daily (after a loading dose of 300mg). TIA and minor stroke patients receive either DAPT aspirin 75mg daily plus clopidogrel 75mg or monotherapy clopidogrel 75mg daily (after a

loading dose of 300mg) for up-to 90-days (started within 24 hours), followed by long-term monotherapy clopidogrel 75mg daily.

For patients whose test indicates they are a *CYP2C19* clopidogrel LOF carrier, we assumed that clopidogrel is replaced with DAPT aspirin 75mg daily plus dipyridamole 200mg twice daily as recommended by NICE guidance [27] (see Figure 2, Section 1.4). We ran scenario analyses assuming that *CYP2C19* LOF carriers switch to different alternative antiplatelet therapy (Alt Tx). Based on clinical advice, other alternative antiplatelets included were low-dose aspirin 75mg daily or ticagrelor 90mg twice daily.

5.2.3 Model structure

The model structure was developed to capture the short- and long-term costs and benefits of *CYP2C19* genetic testing, based on our review of previous cost-effectiveness models (sections 5.1.2-5.1.3), results from the survey of laboratories (Section 3.5), information provided by Genedrive and Genomadix, and in discussion with specialist members of the Diagnostic Appraisal Committee (DAC).

The model utilises a hybrid decision-tree and Markov structure. Diagnostic decisions and short-term 90 day outcomes were modelled using a decision-tree structure, and long-term outcomes were modelled using a five state Markov model. The model is split into short-term (90 day) and long-term outcomes to reflect the elevated risk of a subsequent stroke in the short-term following an event, which is particularly relevant for patients who have had a TIA.

Decision tree

The decision tree (Figure – Figure) differs by test type according to the diagnostic outcomes for the test. For POCT tests there are 4 branches of the tree for patients who receive a true positive, false negative, true negative, and false positive result. We assume that the lab test is a gold standard test with perfect sensitivity and specificity, so there are just two branches of the tree for LOF patients and NoLOF patients who receive appropriate test results and corresponding treatment. For the no-testing strategy there are also two branches of the tree for LOF patients and NoLOF patients, but the event rates differ because all the LOF patients will receive clopidogrel rather than dipyridamole + aspirin. The proportion of the modelled population that are of LOF carriers is the same regardless of test.

The second part of the decision tree captures the 90 day outcomes, which are the same for each diagnostic outcome branch of the tree but with different event rates depending on treatment and LOF status. The 90 day health outcomes are:

- No further event
- Further minor stroke
- Major bleed / intracerebral haemorrhage (ICH)
- Further moderate stroke
- Further major stroke

- Death

The health outcomes are defined according to stroke severity which correspond to disability states. Advice from clinical members of the DAC suggested the mRS scores for the different stroke severity states given in Table 27. These are largely in line with the categories used in previous economic evaluations of *CYP2C19* testing.[102 119 107] We place major bleed / ICH between further minor and further moderate stroke in terms of severity, based on clinical advice and utility estimates (see section 5.2.5).

Table 27 Modified Rankin Scale ranges for different stroke health states in the model

Health State	mRS range
TIA	0
Minor stroke	0 – 1
Moderate stroke	2 – 3
Major stroke	4 – 5

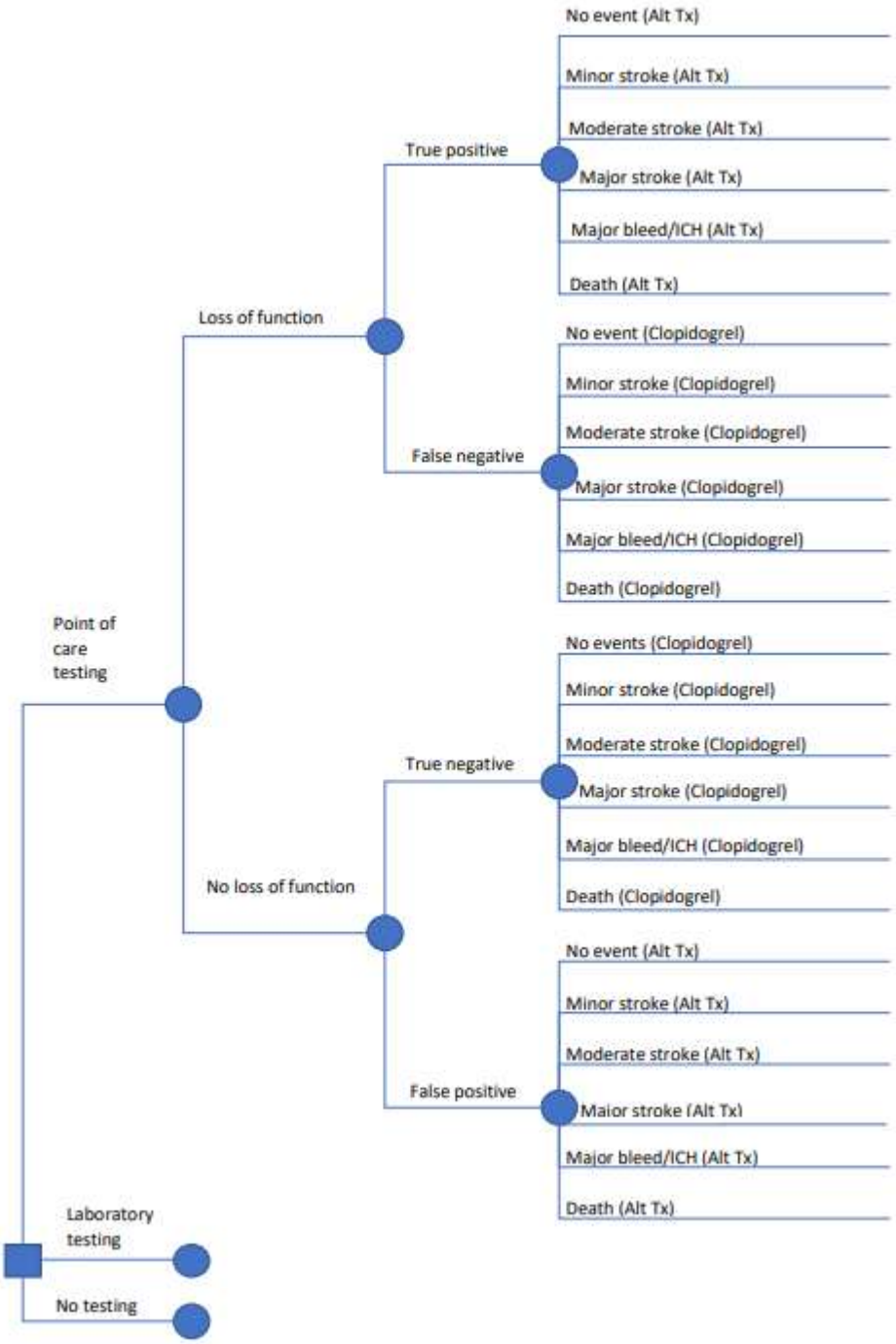
Under lab-based testing there may be a delay in receiving test results after which those identified as LOF carriers switch from clopidogrel to appropriate alternative treatment (Alt Tx). We assume that POCT test results are available within a day, so that there is no delay in starting appropriate treatment for LOF carriers. Treatment switches were modelled by averaging the event rates during the short term (90day) part of the model according to the time spent on different treatments.

For all strategies, patients may discontinue treatment as a result of treatment-related side-effects, and it is assumed that patients discontinuing would switch to low-dose aspirin monotherapy.

The model structure is the same for the non-minor ischaemic stroke and TIA / minor stroke sub-populations, but the model inputs and transition probabilities differ between populations.

As the decision tree models the first 90 days after the patient's initial ischaemic stroke or TIA, no discount rate is applied to costs and QALYs accrued in this period.

Figure 23 Point of care testing decision tree branch[1,2]

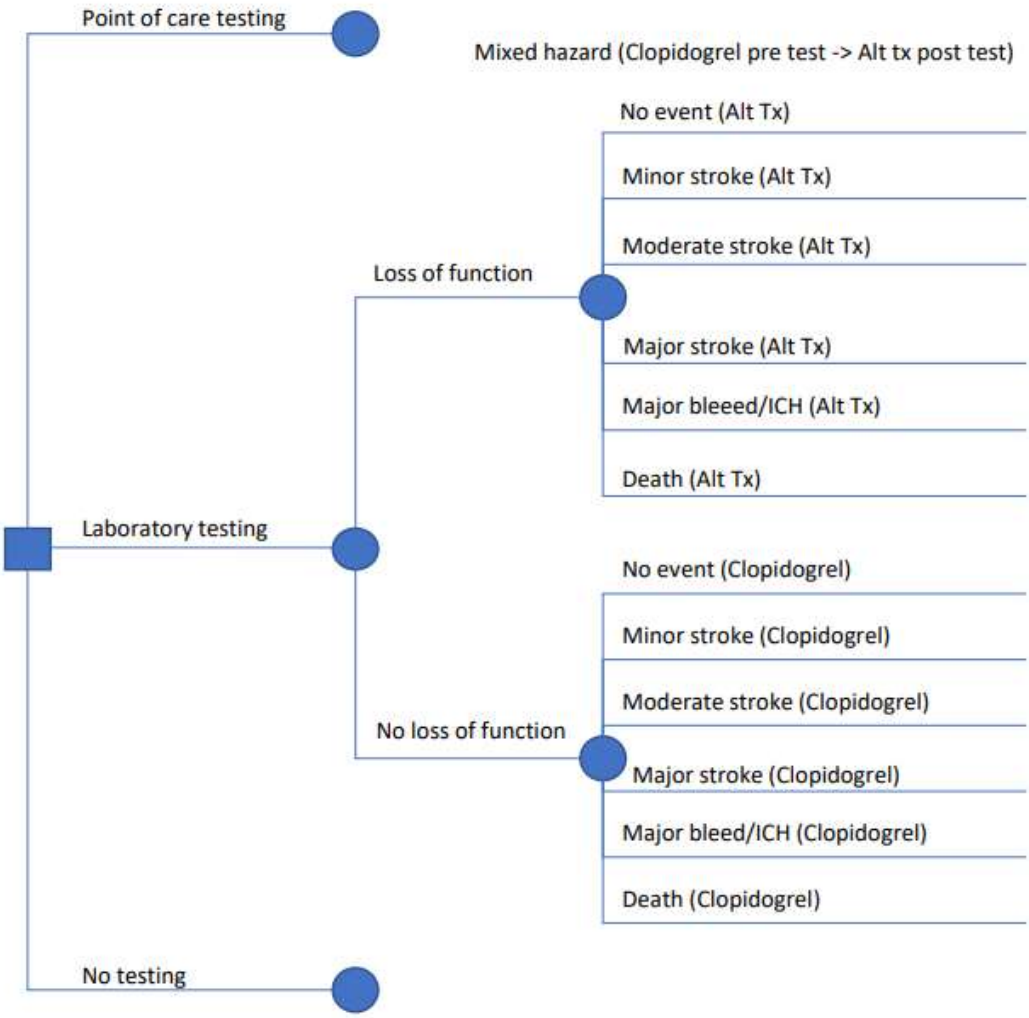


1 The timing of Clopidogrel treatment will depend on the indication. Those patients who have had a transient ischaemic attack/minor stroke may begin dual Clopidogrel-Aspirin treatment immediately. Those patients who have had a major stroke may initiate with 2 weeks of Aspirin before Clopidogrel treatment

2 Alternative treatment is Aspirin combined with Dipyridamole in the base-case, with scenarios for low-dose aspirin and ticagrelor.

Abbreviations: Alt Tx, alternative anti-platelet treatment regimen instead of clopidogrel; ICH, intracerebral haemorrhage.

Figure 24 Laboratory testing decision tree branch[1,2]

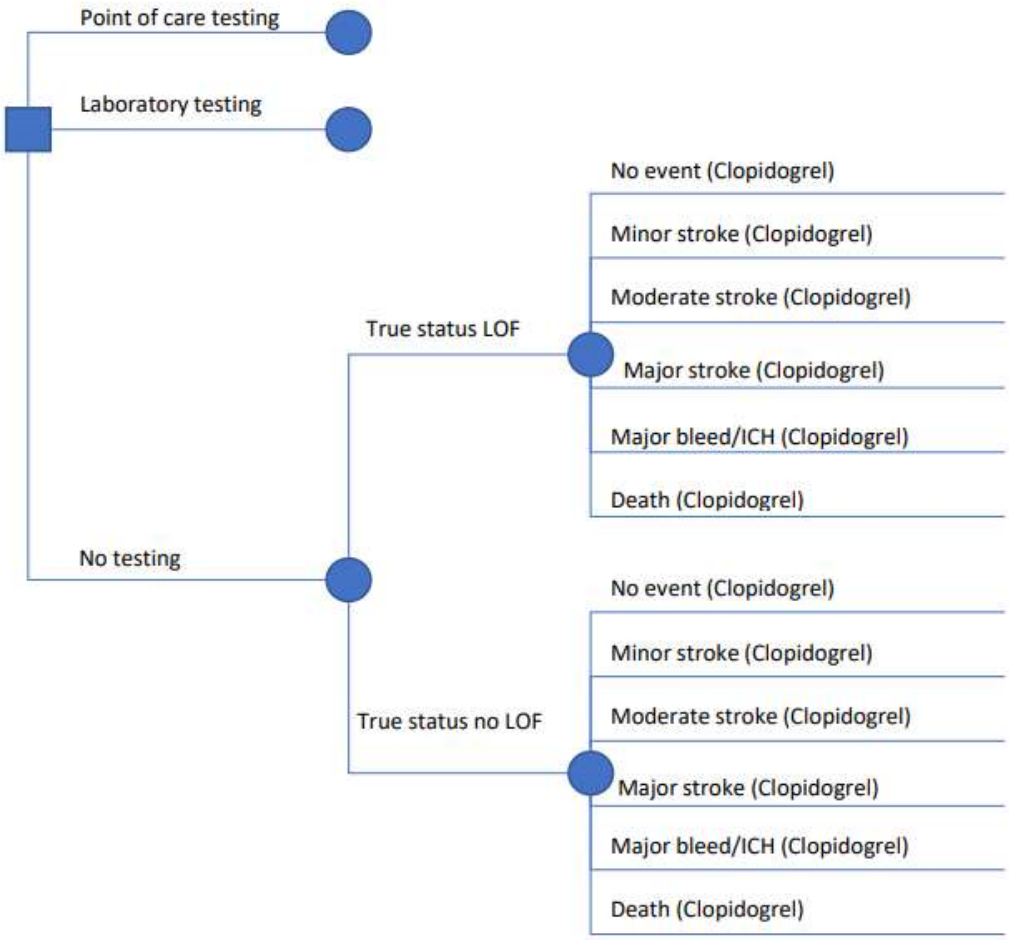


1 The timing of Clopidogrel treatment will depend on the indication. Those patients who have had a transient ischaemic attack/minor stroke may begin dual Clopidogrel-Aspirin treatment immediately. Those patients who have had a major stroke may initiate with 2 weeks of Aspirin before Clopidogrel treatment

2 Alternative treatment is Aspirin combined with Dipyridamole in the base-case, with scenarios for low-dose aspirin and ticagrelor.

Abbreviations: Alt Tx, alternative anti-platelet treatment regimen instead of clopidogrel; ICH, intracerebral haemorrhage.

Figure 25 No test decision tree branch



1 The timing of Clopidogrel treatment will depend on the indication. Those patients who have had a transient ischaemic attack/minor stroke may begin dual Clopidogrel-Aspirin treatment immediately. Those patients who have had a major stroke may initiate with 2 weeks of Aspirin monotherapy before Clopidogrel treatment

Abbreviations: ICH, intracerebral haemorrhage; LOF, loss of function

Markov model

Health states

Following the initial decision-tree, a Markov model was used to model long-term patient outcomes for a cohort of patients. In the model patients move between five possible health states: no recurrent stroke, post-minor stroke, post-major bleed / ICH, post-moderate stroke or post-major stroke. Health states were chosen based on discussion with clinical experts and inspection of the clinical and health economic literature on the most impactful and frequent events experienced by ischaemic stroke survivors. Health states differ in costs, health-related quality of life, mortality rate, and recurrent event rates. The ordering of the

health states by severity was motivated by consultation with patient and clinical experts and inspection of long-term health-related quality of life (HRQoL) measurements from studies which had measured this by health state (see section 5.2.5).

We assume that patients can progress to a more severe disease health state, but cannot move from a more severe health state to a less severe state. This was based on the nature of the long-term outcomes associated with the events included in the model (strokes, major bleeds) and the chronic nature of the disease. Patients are categorised into the most severe category that they have experienced.

The proportion of patients in each health state in the first Markov time cycle is determined by the proportion in each health state at the end of the 90day decision tree, according to true LOF status and treatment allocation.

Cohorts evaluated

The transitions in the Markov model depend on treatment and LOF status, and so four cohorts are evaluated corresponding to the paths in the decision tree:

1. Patients with LOF alleles undergoing clopidogrel treatment
2. Patients with LOF alleles undergoing a non-clopidogrel alternative treatment
3. Patients without LOF alleles undergoing clopidogrel treatment
4. Patients without LOF alleles undergoing a non-clopidogrel alternative treatment

We assume that patients stay on the same treatment they were on at the end of the decision tree period, and only switch treatment as a consequence of a bleeding event, which is modelled with a discontinuation rate set equal to the rate of new major bleeds / ICH each year for each treatment.

Time cycles, time horizon, and discounting

The initial time cycle in the Markov model takes the length of 275¼ days, calculated as a one year minus the 90 day period of the decision tree period. The second and subsequent time cycles take the length of a year (365¼ days). The Markov model utilises a lifetime time horizon so patient outcomes in the Markov model are followed until the general population life tables end (age 100).

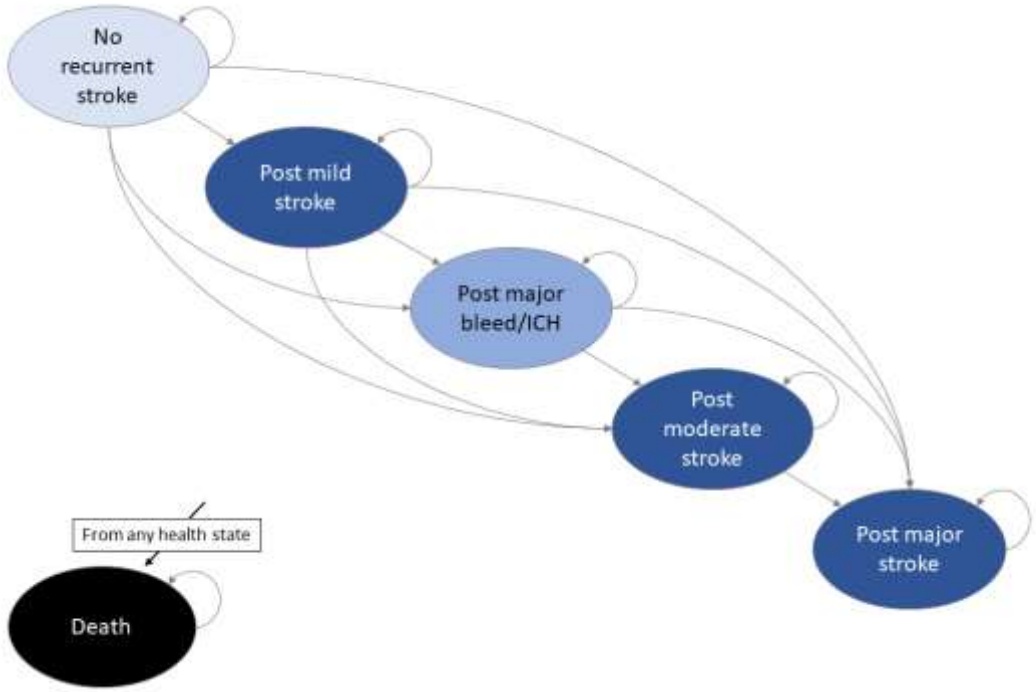
Costs and QALYs in the long-term Markov model are discounted at a rate of 3.5% per annum. Discounting begins in the second Markov time cycle which models the second year after the patient's initial stroke or TIA.

Model outcomes

Costs are accrued in the model through health state specific costs and treatment costs, which when summed over time spent in health states and time on treatment give total (discounted) expected costs over the model time horizon for each path in the decision tree.

QALYs accrue in the model through the health state utilities summed over time spent in each health state to give (discounted) total expected QALYs over the model time horizon for each path in the decision tree. The total expected costs and QALYs of the decision tree pathways are then averaged to calculate the total expected costs and QALYs associated with the point of care tests, laboratory testing, and no testing respectively. The cost-effectiveness results are summarised with incremental cost-effectiveness ratios (ICERs) and expected net-benefit.

Figure 26 Long-term Markov model structure



5.2.4 Perspective

An NHS and personal social services (PSS) perspective was taken with a life-time horizon where costs and QALYs are discounted at an annual rate of 3.5%. The model includes health effects for both patients and carers. A 2022 price year was used in the base case. Costs from previous years were inflated to the 2022 price year using the office for national statistics' CPIH index.

5.2.5 Model parameters and inputs

Model inputs were derived from the clinical effectiveness review, our review of previous cost-effectiveness models (sections 5.1.2-5.1.3), results from the survey of laboratories (Section 3.5), information provided by Genedrive and Genomadix, and additional targeted searches where required. Where it was necessary to make assumptions this was based on expert opinion and scenario analyses conducted to explore the impact of these assumptions on the results.

Test performance

Time to receive test results

The clinical review found that results were available within a matter of hours for the POCT tests (Table 17) and the companies confirmed that results will be available in 40mins to approximately 1 hour. We therefore assume that there would be no delay in patients receiving targeted therapy for the POCT test strategy.

The survey of laboratories (Section 4.6.2) indicated that there is likely to be some variability in the time until lab-based test results are available, and this would depend on capacity / resources. The most common estimate was approximately 1 week, but one lab reported it may be longer than 4 weeks. Our clinical advisors estimated it would take between 5 days and 6 weeks, which is in line with the survey responses. We assume a 1 week turnaround in the base-case, and 4 weeks in a sensitivity analysis.

Test failure rate

The clinical review found variation in the test failure rate (test result unavailable) ranging from 0.4% to 18.9% for studies on the Genomadix (Spartan) *CYP2C19* tests (Table 15). Pooling results from these studies in a random effects meta-analysis gives an estimated average failure probability of 0.08 (95% CI 0.05, 0.15). We assume a test failure rate of 8% and describe the uncertainty around this with a Beta distribution with parameters matched to the meta-analysis estimates. No studies were available for Genedrive, and so we assume this is equal to that seen for the Genomadix Cube, but note the uncertainty around this assumption.

The survey of laboratories (Section 4.6.2) found that most laboratories expected <1% of samples not to give valid results, although one laboratory estimated this to be 5%. We assume that all samples give a valid result in our model. Higher teat failure rates would increase the test cost slightly. We conduct a scenario analysis to the cost of the laboratory test.

Test accuracy of point-of-care tests

The bivariate meta-analysis for the Genomadix (Spartan) *CYP2C19* tests based on the studies identified in the clinical review estimates very high sensitivity of 100% (95% CI 94, 100%) and specificity of 100% (95% CI 99, 100%) (Figure 19, section 4.5.2). Note however, that these figures are based on detecting the *2, and *3 alleles that the Genomadix (Spartan) *CYP2C19* tests for. There are other LOF alleles (*4, *5, *6, *7, and *8), which would not be detected by the Genomadix Cube. The prevalence of these additional alleles are very small across ethnicities[145], but may reduce the sensitivity of the test very slightly. We therefore assume a sensitivity of 99% rather than 100% in the model. Genedrive tests for more alleles (Table 2), and so would have potential to detect *4 and *8, but not *5, *6, and *7. There was no diagnostic test accuracy data for Genedrive, so in the absence of data and due to the

very small prevalence for *4 and *8, we assumed that the diagnostic test accuracy for Genedrive was the same as for the Genomadix Cube. However, we note the uncertainty around the test accuracy for Genedrive.

Patient Characteristics, Prevalence of stroke, TIA, and *CYP2C19* LOF

Incidence of first stroke and patient characteristics

The prevalence and population characteristics of first ischaemic stroke are taken from the NICE Clinical Knowledge Summary (https://cks.nice.org.uk/topics/stroke-tia/background-information/prevalence/) and the data-sources it is based upon. The Public Health England (PHE) briefing document on incidence of first strokes in 2016 found a crude incidence rate of first strokes to be 107 per 100,000 population, with 49% females.[146] The mean age for first strokes was 68.2 for males and 73 for females. Ethnicity was only reported in approximately half of cases, but of these the proportions were 92%, 4%, 2.5%, and 1.5% for White, Asian, Black, and Other respectively. Note this distribution is different to the population split from the census due to a higher incidence of stroke in white people (due largely to differences in demographics). The PHE briefing document reports an incidence of first-ever transient ischaemic attack (TIA) of approximately 50 per 100,000 people per year. This gives the proportion of stroke/TIA cases that are TIA to be 50/157 = 31.8%.

Prevalence of CYP2C19 LOF

The clinical review identified a wide range of estimates of prevalence of LOF from studies of clopidogrel (Table 16), but these were not on UK populations and did not provide estimates of prevalence according to ethnicity from these studies. We ran additional searches to identify prevalence studies of LOF alleles. We found a UK-based study Pilling et al [147] which estimated a prevalence of having at least one *CYP2C19* LOF variant to be 28.7% in 7483 European-ancestry adults prescribed clopidogrel based on the UK Biobank study with genetic and linked primary care data. This is likely to be an underestimate of the prevalence of *CYP2C19* LOF in the UK due to a higher prevalence in those with non-European ancestry. The CHANCE study [51] found 58.8% of Chinese patients randomised to the trial had a LOF variant. A recent large-scale analysis of *CYP2C19* LOF status [148] by ethnicity in the US estimated prevalence of intermediate or poor metabolisers of 27.2% in Europeans, 56.8% for East Asians, and 31.9% for African Americans. These figures agree well with those from Pilling et al [147] and [51] for European and Chinese populations respectively. Applying these estimates to the ethnicity mix in the UK based on the PHE briefing report,[146] and assuming that the prevalence for those of non-European or Asian ancestry can be assumed to be 31.9%, we obtain a prevalence estimate of 0.92*27.2 + 0.04*56.8 + 0.04*31.9 = 32.1% in the UK population. We use this proportion of patients who are LOF carriers in the base case and conduct a scenario analysis to a higher proportion of 56.8% as estimated in East Asians.

Transition probabilities

In the decision tree and Markov model, the event transition probabilities according to treatment and LOF status are:

$$p_{trt,status}(t) = 1 - e^{-\lambda_{trt,status} t}$$

for time at risk t, where $\lambda_{trt,status}$ is the event rate. We estimate the baseline event rates for patients without LOF alleles who are taking clopidogrel, $\lambda_{clop,NoLOF}$, and then estimate hazard ratios for each treatment / LOF status relative to NoLOF on clopidogrel

$$HR_{trt,status} = \frac{\lambda_{trt,status}}{\lambda_{clop,NoLOF}} .$$

Because patients may switch treatments, the hazard will be a weighted average of the hazards for the different treatments they have taken according to time on each treatment. For example, if a patient with LOF alleles starts clopidogrel and then switches to DAPT dipyridamole + aspirin after 6 weeks, then their hazard rate will be $0.47\lambda_{clop,LOF} + 0.53 * \lambda_{dyp+asp,LOF}$.

The transition probabilities in the Markov model were derived in exactly the same way as for the decision tree probabilities, however the baseline event rates are assumed to differ in the longer term, and it is assumed that after 90 days patients only switch treatment as a result of a major bleed or ICH, modelled with a discontinuation rate set to the rate of major bleed / ICH.

Baseline recurrence rates (for patients with no LOF on clopidogrel)

We searched for large recent UK-based cohort studies to estimate the baseline event rates for the outcomes in the decision tree model (Figure - Figure) in patients who have experienced a stroke or TIA. We assume that event rates depend on the severity of primary stroke experienced, but that relative treatment effects (hazard ratios) do not vary by stroke severity.

Mohan et al 2009 [149] reports stroke recurrence rates based on 2874 patients following their first stroke with 8311 person-years follow-up from the South London Stroke Register (SLSR), for cases registered between 1 January 1995 and 31 December 2004. They estimate a cumulative risk of recurrence of 7.1% (95% CI 6.0 to 8.3%) in the first year, 16.2% (95%CI 14.4%, 18.1%) by 5-years, and 24.5% (95%CI 21.3%, 27.9%) by 10 years. These correspond to hazard rates per person year of 0.074, 0.044, and 0.056 in years 1, 2-5, and 6-10 respectively, computed using $\lambda = -\ln(1 - p_{\text{int}}) / t_{\text{int}}$ where λ_{int} is the hazard rate, p_{int} the probability of recurrence on the time interval, and t_{int} the length of the time interval in years.

More recent data is available from the Sentinel Stroke National Audit Programme (SSNAP).[150] SSNAP provides national audit data on stroke patients from every acute hospital in England, Wales and Northern Ireland with longitudinal data collection on outcomes for

up-to 6 months post-stroke, plus longer term information on stroke recurrence. We prefer to use the SSNAP data to estimate short-term recurrence rates in our model, as it is most representative of a contemporary stroke population in England and Wales, and provides detailed results specifically for patients who have had an ischaemic stroke. In the SSNAP health economics report,[151] recurrence probability estimates are provided for up to 5 years based on the SSNAP data for the short-term and SLSR in the longer term. However, it is not clear how the SLSR data has been used to form these estimates, and they do not align with the estimates reported in Mohan et al 2009.[149] Table 28 shows the estimated cumulative probability of recurrence, and the hazard rate per person year on each time interval from the two sources of evidence. We use the hazard rate of 0.092 from SSNAP for the first 90 days in our model, and beyond 90 days we use a hazard rate of 0.056 which is in line with the first year from SSNAP and the longer term data from SLSR.

Table 28 Stroke recurrence estimates for stroke patients based on the South London Stroke Registry (SLSR) and the Sentinel Stroke National Audit Programme (SSNAP).

Time from index event (years)	Cumulative percentage recurrence	Time Period (Interval)	Recurrence rate per person year
South London Stroke Registry (Mohan et al 2009) [149]			
1	7.1% (95% CI 6.0 to 8.3%)	0-1 (1 years)	0.074
5	16.2% (95%CI 14.4%, 18.1%)	1-5 (4 years)	0.044
10	24.5% (95%CI 21.3%, 27.9%)	5-10 (5 years)	0.056
Sentinel Stroke National Audit Programme (ischaemic stroke patients)* [151]			
0.25	2.28%	0 – 0.25 (0.25 years)	0.092
1	6.37%	0.25 – 1 (0.75 years)	0.056
2	11.41%	1-2 (1 year)	0.052
3	19.29%	2-3 (1 year)	0.082
4	28.50%	3-4 (1 year)	0.097
5	41.05%	4-5 (1 year)	0.134

*Survival and Recurrence sheet in HE-NHSE-RCP-Appendix-1.xslx [rows 54-63]

For TIA patients we identified a recent retrospective cohort study using the Framingham Heart Study data which reports recurrence rates for 435 patients who had an index first TIA. Lioutas et al (2021) report a crude hazard rate of recurrent stroke of 1.29 per 1000 person years, and give the proportion of recurrent events occurring over time from the index TIA.[152] Based on this we estimated an annualised hazard rate in the time periods following the index TIA (Table 29). There is an elevated rate of stroke in the first week following TIA and a high rate for the first 90 days, falling to a lower rate beyond 90 days. In the model we use a weighted average rate per person year of 0.0838 for the first 90 days, and 0.0064 for day 90 onwards.

Table 29 Stroke rates following an index TIA based on Lioutas et al 2021[152], who report an overall stroke rate of 1.29 per 1000 person years.

Time Period (Interval)	Percentage of strokes in time period	Stroke rate per person year
0-7 days (7 days)	21.5%	0.586
8-30 days (23 days)	9.2%	0.076
31-90 days (60 days)	8.5%	0.027
91-365 days (274 days)	12.3%	0.009
1-5 year (4 years)	48.5%	0.0064
Average over 0-90 days		0.0838

Stroke severity

SSNAP provides the breakdown of recurrent strokes into NIHSS categories. [151] We classified NIHSS 0-4 as mild, NIHSS 5-15 as moderate, and NIHSS >15 as severe to estimate the proportion of recurrent strokes that fall into each category (Table 30). We assume that the proportion of recurrent strokes in each category does not depend on the initial stroke category. However, the movement between states in the model depends on the current state, with patients attributed to the worst severity state that they have experienced.

Table 30 Number of recurrent strokes by type from the Sentinel Stroke National Audit Programme (SSNAP) [151] and resulting estimates of severity of recurrent strokes

NIHSS range	Recurrent Strokes by Severity	Total Recurrent Strokes	Proportion
0	0	101	0
1-4 (Mild)	43	101	0.426
5-15 (Moderate)	48	101	0.475
16-42 (Severe)	10	101	0.0495

Baseline mortality rates (for patients with no LOF on clopidogrel)

Mortality rates were assumed to depend on model state via the mRS score. The health economics report for SSNAP fits a Cox survival analysis to data from SSNAP and the SLSR to estimate survival over a 5-year time period. [151] The survival probabilities are provided for a reference category of a 65 year old male patient with mRS 0 following an ischaemic stroke (Table 31), from which we form the hazard rate per person year. SSNAP also provide the hazard ratios to adjust for age, sex, and mRS status (Table 31). We applied the hazard ratios to the reference hazard rates, to obtain the estimated hazard for an average cohort matching our population (the population was assumed to be 49% female patients with average age 68.2 years for males and females 73 years). The hazard ratios by mRS category only show an elevated mortality rate for those with mRS=4 or 5, which corresponds to our severe stroke state. We therefore apply a hazard ratio (averaged over mRS=4 and mRS=5) to reflect the increased mortality rate for those in the severe stroke state (Table 32). For TIA it is assumed that mortality is equal to that for mRS=0. Mortality increases with age as patients progress through the model which we capture using the rates by age and sex based on Office for National Statistics (ONS).[153]

Table 31 Estimated survival probabilities for a 65year old male patient with mRS=0 following an ischaemic stroke, and hazard ratios for age, sex, and mRS status estimated in the SSNAP health economics report using data from SSNAP[151] and SLSR[149]

Time (years)	Survival probability	Mortality rate (hazard) per person year	Covariate	Hazard Ratio	Confidence Interval
0	1		**Female**	1.001152	(0.924, 1.084)
0.0847	0.999	0.011812	**age (y)**	1.026459	(1.023, 1.030)
0.506	0.981	0.043114	**mRS1**	0.9557	(0.822, 1.112)
0.669	0.977	0.024589	**mRS2**	0.832645	(0.692, 1.003)
0.93	0.969	0.030775	**mRS3**	0.941297	(0.834, 1.063)
1.24	0.962	0.02266	**mRS4**	1.037715	(0.934, 1.153)
1.55	0.954	0.02591	**mRS5**	1.277252	(1.113, 1.465)
1.64	0.95	0.044534			
1.92	0.943	0.025088			
2.1	0.938	0.027847			
2.31	0.932	0.028657			
2.63	0.921	0.034565			
2.79	0.917	0.02505			
3.03	0.909	0.033467			
3.26	0.903	0.026166			
3.56	0.896	0.023415			
3.83	0.884	0.044713			
4.24	0.872	0.029445			
4.73	0.858	0.028773			
4.98	0.851	0.028098			
5	0.847	0.200401			

Table 32 Mortality rates per person year for different time intervals following a stroke by mRS category (stroke severity), based on estimated hazards and hazard ratios from the SSNAP health economics study[151] using data from SSNAP[150] and SLSR[149] (Table 31)

Time Period	mRS 0-3 (Mild / Moderate Stroke)	mRS 4-5 (Severe Stroke)
0-30 days	0.0128	0.0157
31 - 91 days	0.0467	0.0574
90days – 5 years	0.0329	0.0407

Baseline rate of major bleeds / ICH (on clopidogrel)

We assumed that bleeding and ICH adverse events do not depend on LOF status, in line with findings from the clinical review (Figure 18). We did not find any data on bleeding rates in cohort or registry data, and so we relied on evidence from large RCTs which had sufficient

major bleed / ICH events for robust estimation. Based on the studies identified in recent network meta-analyses[154 155] by far the largest study reporting bleeding rates on clopidogrel monotherapy is the multi-centre global PRoFESS RCT[156]. In the clopidogrel arm of PRoFESS there were 365 major haemorrhagic events with 25377.5 person years follow-up (10151 patients x 2.5y mean follow-up), giving a hazard rate of 0.0144 per person year. The proportion of major haemorrhagic events that were ICH was 103/365 = 0.282, and the proportion of ICH that were fatal was 29/55=0.527. We use these estimates for clopidogrel in the model.

Hazard ratios

The baseline event rates described above are assumed to represent patients with NoLOF taking clopidogrel monotherapy. For the model we need to know the event rates for each treatment option for LOF and NoLOF patients for all treatments in the pathways (ie clopidogrel, dipyridamole + aspirin, aspirin, and in the scenario analysis ticagrelor).

Ideally we would have studies comparing the different testing and targeted treatment strategies. Objective 1 of the clinical review (Section 4.2) searched for comparative studies of targeted testing and treatment strategies, however only found 2 small studies[45 46] that had very limited power to estimate relative effects. Furthermore the targeted treatment strategy varied by number of LOF alleles in Xia et al.[45] which does not align to the testing strategies in our model, and in Lan et al.[46] the targeted treatment strategy is to use aspirin 100 mg/day in LoF patients, which is not used in our base-case model.

An alternative approach is to use results from studies that compare treatment effects for LOF and No LOF patients. Objective 2 of the clinical effectiveness review (section 4.3) identified studies that compare the relative efficacy of different treatments for LOF patients. The studies relevant to the treatments in our model are the CHANCE study[51] which compares clopidogrel vs aspirin for LOF and No LOF patients, and the CHANCE-2 study[49] which compares ticagrelor vs clopidogrel in LOF patients. These two studies have been the main source of relative effects used in previous cost-effectiveness analyses of *CYP2C19* testing.[102 107] Objective 2 also identified a phase-II study[52] comparing ticagrelor vs clopidogrel by LOF status, however this study was under-powered for the outcomes of interest for our model, and so we prefer to use results from the much larger phase-III CHANCE-2 study[49], in line with previous models of *CYP2C19* testing.

For mortality, there was very limited evidence available, and the estimates that were available were very uncertain. We therefore made the assumption that differences in mortality between the treatments are a result of differences in the proportion of patients having a major stroke (which has a higher mortality rate), and the proportions of patients with a major bleed / ICH of which a proportion are fatal.

To obtain hazard ratios for LOF carriers on clopidogrel relative to NoLOF on clopidogrel we use the results from Objective 3 (Section 4.4.2) using the meta-analysis for any recurrent

stroke (Figure 14). We assume that the rate of major bleed / ICH on clopidogrel does not vary with LOF status.

For dipyridamole plus aspirin, no comparative evidence was identified by LOF status (Figure 6, Objective 2). However, because we do not expect outcomes on dipyridamole plus aspirin to vary by LOF status, we conducted a pragmatic literature search to identify network meta-analyses comparing treatments for secondary prevention of stroke in a general ischaemic stroke/TIA population. We identified two network meta-analyses addressing this question, Greving et al[154] and Del Giovane et al.[155] These two recent reviews of RCTs identified a single study comparing dipyridamole plus aspirin vs clopidogrel monotherapy, the PRoFESS trial[156], which is a large global trial of 20,095 patients. We use the results from this trial to inform the relative effect of dipyridamole plus aspirin (LOF or NoLOF) relative to clopidogrel NoLOF for recurrent stroke, and major bleed/ICH.

For low-dose aspirin the CHANCE study[51] , identified in Objective 2, gives hazard ratios for aspirin vs clopidogrel monotherapy by LOF status. Our baseline hazards are for NoLOF on clopidogrel, which we wish to estimate hazard ratios against. For aspirin NoLOF the CHANCE study provides this directly. For aspirin LOF, CHANCE provides a hazard ratio for aspirin vs clopidogrel in patients with LOF, $HR_{Asp,LOFvClop,LOF}$. To estimate a hazard ratio for aspirin LOF vs clopidogrel NoLOF patients, we use the relation:

$$HR_{Asp,LOFvClop,NoLOF} = HR_{Asp,LOFvClop,LOF} * HR_{Clop,LOFvClop,NoLOF} \quad (1)$$

using the hazard ratio for LOF vs NoLOF on clopidogrel obtained from Objective 3 (Figure 14). We assume that the rate of major bleed / ICH does not vary with LOF status.

For ticagrelor, the CHANCE-2 study[49] , identified in Objective 2, gives hazard ratios for ticagrelor vs clopidogrel monotherapy for LOF carriers. We use the same approach as described above using equation (1) to obtain a HR for ticagrelor LOF vs clopidogrel NoLOF (replacing Asp with Tic in (1)). We assume that the rate of major bleed / ICH does not vary with LOF status.

The hazard ratios used in the model for each treatment, LOF status, and outcome are summarised in

Table 33 and Table 34.

Table 33 Hazard Ratios (HR) for recurrent stroke for each treatment and LOF combination relative to NoLOF on Clopidogrel monotherapy

Treatment, LOF Status	HR recurrent stroke relative to clopidogrel NoLOF	Source
Clopidogrel monotherapy, NoLOF	1	-
Clopidogrel monotherapy, LOF	1.46 95%CI (1.09, 1.95)	Objective 3 (Figure 14)
Dipyridamole + Aspirin, No LOF	1.01 95%CI (0.92, 1.11)	PRoFESS[156]
Dipyridamole + Aspirin, LOF	1.01 95%CI (0.92, 1.11)	PRoFESS[156]
Aspirin, No LOF	1.96 95%CI (1.33, 2.857)	CHANCE[51]
Aspirin, LOF	1.387 95%CI (0.8947, 2.054)	CHANCE[51] with hazard ratio from Objective 3 (Figure 14) applied
Ticagrelor, No LOF	1.142 95%CI (0.7967, 1.587)	CHANCE-2[49] with hazard ratio from Objective 3 (Figure 14) applied

Table 34 Hazard Ratios for major bleed/ICH for each treatment and LOF combination relative to NoLOF on Clopidogrel monotherapy

Treatment, LOF Status	HR major bleed/ICH relative to Clopidogrel (LOF or NoLOF)	Source
Clopidogrel monotherapy (LOF or NoLOF)	1	Assumption that independent of LOF status
Aspirin + Dipyridamole (LOF or No LOF)	1.15 95%CI (1, 1.32)	PRoFESS[156]
Aspirin (LOF or No LOF)	0.637 95%CI (1.087, 0.373)	CHANCE[51]
Ticagrelor, No LOF	0.82 95%CI (0.34, 1.98)	CHANCE-2[49]

Uptake of targeted treatment and discontinuation rates

We heard from our clinical advisers that only a proportion of patients diagnosed as *CYP2C19* LOF may receive targeted treatment for a variety of reasons, such as physician or patient preference, issues with results not being made available to prescribers, or failure for the test to produce a result. Swen et al 2023[157] found that physician adoption of pharmacogenetic recommendations was for a range genes including *CYP2C19* was only 69.9%. In our base-case we assume that there is 100% uptake of alternative treatment for patients diagnosed as LOF carriers and vary this in a scenario analysis to 69.9%.

We assumed that patients may switch treatment in the short-term decision-tree model due to side-effects. We used data from large RCTs to estimate the discontinuation rates (Table 35), and assume that patients discontinuing switch to aspirin monotherapy.

Table 35 Discontinuation rates assumed for treatments in the model

Treatment	No. discontinue	Total	Probability of discontinuation	Source
Aspirin + Dipyridamole	1650	10055	0.164	PRoFESS[156]
Clopidogrel	1069	10040	0.106	PRoFESS[156]
Ticagrelor	1148	6550	0.175	SOCRATES[111]
Aspirin	965	6580	0.147	SOCRATES[111]

Health state utilities

Stroke-state utilities

Three of the reviewed cost-effectiveness studies accounted for health state utility values according to whether stroke status was disabling or non-disabling [158 141 117]; and the other three accounted for health state utility values according to the severity of disability [102 119 107]. Disability categories were Mild (mRs 0–1), moderate (mRs 2–3) and severe (mRs 4–5) in the study by Micieli et al[102]; Neurologically intact (mRs 0), mild (mRs 1–2) and moderate to severe (mRs 3–5) in the study by Zhou et al [119]; and Minor or no disability (mRs 0–2), moderate disability (mRs 3–4) and severe disability (mRs 5) in the study by Cai et al [107].

Because utility studies in this disease area commonly report results by modified Rankin scale (mRs), our preferred approach was to model the utility based on the mRs which could be mapped onto severity of stroke to assign appropriate utilities for the different health states in the model using the categorisation in Table 27.

A pragmatic literature review identified six studies which reported utility values based on the modified Rankin scale [159 160 161 124 162 163], of which two were studies on UK patients. The study by Whynes et al [161] reported EuroQol 5 dimensions (EQ-5D) scores (UK tariff) for 1462 acute stroke patients enrolled on the Efficacy of nitric Oxide in Stroke (ENOS) trial. The study by Rivero-Arias et al [160] reported EQ-5D scores for 2425 stroke/TIA patients from the Oxford Vascular (OXVASC) observational study. The utility values from the two studies reporting EQ-5D utilities relevant to the UK are presented in Table 36. These values are very similar, but we use the more recent figures from Whynes et al [161], which is line with the economic evaluation for the Sentinel Stroke National Audit Programme (SSNAP). [151] For each state in the model we assume an mRs range according to Table 27 and attribute an average utility over the mRs range from Whynes et al [161] (Table 36).

The utilities for the No Recurrent Stroke state depend on the population, assumed the average of the utilities for mRs 0-1 in the TIA / minor stroke population, and the average of the utilities for mRs 2-3 in the non-minor stroke population.

Table 36 EQ-5D utility values on the modified Rankin Scale

mRs	Whynes et al [161] utility (se)	Rivero-Arias et al [160] utility (se)
0	0.93 (0.04)	0.936 (0.003)
1	0.85 (0.03)	0.817 (0.004)
2	0.71 (0.03)	0.681 (0.004)
3	0.55 (0.03)	0.558 (0.006)
4	0.28 (0.03)	0.265 (0.006)
5	-0.15 (0.03)	–0.054 (0.005)

Major bleed / ICH utilities

Two of the reviewed cost-effectiveness studies accounted for bleeds by applying a temporary utility decrement [117] [101]; and the other 3 studies accounted for intercranial haemorrhage (ICH) by assigning a health state specific utility value;[102] or allowing for ICH severity by mapping to the mRs scale, and then using the utility values assigned to stroke severity [107] [119]. Cai et al [107] assume an mRs range of 0-2 for ICH. Micieli et al[102] estimates a utility of 0.62 for ICH which is a little lower than the utility for TIA / minor stroke in their model, suggesting ICH corresponds to mRs values of 1-2. Zhou et al [119] assume a distribution of mRs states (0-5) with an average of 3.4. Because we combine major bleed and ICH, we assume an mRs range of 1-2 in line with Cai et al [107] and Micieli et al[102] . Major-bleed / ICH therefore has a utility that lies between minor stroke and moderate stroke, which is in line with feedback from our clinical experts.

Carer disutilities

There can be substantial impact on the quality of life of those caring for patients who have had a stroke, which we included in our model as a utility decrement. None of the cost-effectiveness studies identified in our review included carer quality of life, and so we undertook a pragmatic literature review. Two studies were identified that reported very similar carer utility values [164] [165]. The utility reported for 928 caregivers enrolled on structured training programme for caregivers of inpatients after stroke in the TRACS trial was 0.791 95% CI (0.790 to 0.792) [165]. The utility reported for 414 carers enrolled on the Organising Support for Carers of Stroke Survivors (OSCARSS) trial was 0.78 95% CI (0.75 to 0.81) [164]. Assuming that the utility for mRs 0 is equivalent to that of the general population, the utility decrement for carers is estimated as (0.936 – 0.791) = 0.145 which is applied for 1 carer per patient who has experienced stroke. This included all patients in the ischaemic stroke population and all patients who experienced a minor, moderate, or severe stroke in the TIA population. This meant that patients could be assigned negative QALYs if the carer's utility decrement was greater than the patients health state utility.

Resource use and costs

Medicine costs

Costs of medicines used in the model are sourced from the British National Formulary (BNF) using the cheapest available option, detailed in Table 37.

Table 37 Treatment costs

Treatment	Dose per day (mg)	Cost (£) per day
Aspirin	300	£0.1071
	75	£0.0268
Clopidogrel	300	£0.1757
	75	£0.0439
Modified-release dipyridamole	400	£0.4383
	200	£0.2192
Ticagrelor	180	£1.950

Test costs

The assumed costs and resources for the Genedrive and Genomadix Cube POCTs are detailed in Table 38. The per test device cost was obtained by dividing the cost of acquiring and maintaining the device by the estimated number of tests that it will conduct over its lifetime using estimates provided by the companies. We assume that an extended warranty will be taken out to cover device failure and maintenance costs within the extended warranty period. Administration costs per test were estimated by multiplying the staff time required to run a test and record the results by the average hourly rates of the staff involved. The main consumable cost required for each test is the single use test kit which is listed per unit. Periodically control tests are required which incur the cost of a single-use control kit, which we turn into a per test cost by dividing by the number of tests that would be conducted within the period between control tests.

The clinical review found that staff would require minimal training to conduct POCTs, and given that training costs would be incurred once for each member of staff who will then conduct many tests, the per test training cost would be negligible, and is omitted from our model. The Genomadix Cube requires freezer space, and this is likely to require purchase and maintenance of an appropriate freezer. However, the cost of this is again negligible per test and is omitted from our model.

The total cost per test using the inputs from Table 38 was £104 per Genedrive test, and £197 per Genomadix Cube test. In the absence of estimates of uncertainty around these costs we assume a Gamma distribution with a standard deviation of 10% of the estimated total cost.

Table 38 Resource and cost parameters for the POCT tests

	Genedrive	Genomadix Cube	Source
Point of Care Device per unit cost (ex. VAT)	£4,995	£3,500	Company
Test kit per unit cost (ex. VAT)	£100	£175	Company
Control kit per unit cost (ex. VAT)	£100	£50	Company

	Genedrive	Genomadix Cube	Source
Warranty annual cost per year (after first 12 months)	£750 (5 years)	£700 (1 year)	Company
Device life in number of tests	6250 (Range 5000-7500)	2000 (at least 1500)	Company
Device lifetime in years	6 years	2 years	Company
Time to administer test	10 minutes		Company
Hourly rate of Band 5 nurse	£13.67		NHS Employers costs[166]
TOTAL COST			
Costs Per test	**£104**	**£197**	

The assumed costs and resource for the laboratory test are detailed in Table 39. In the survey (Section 4.6.2) the preferred platforms for conducting *CYP2C19* testing were variant detection using mass spectrometry, e.g. MassARRAY (Agena Bioscience) or Loop-mediated isothermal amplification (LAMP), e.g.LAMP (LaCAR MDx Technologies), with the former having more flexibility to test for multiple variants, and the latter being simpler and quicker to perform. We base our costs on the Agena MassARRAY iPlex, and estimate a per test device cost was obtained by dividing the device cost by the estimated number of tests it can conduct over its lifetime. In the absence of information on the device lifetime, we assume a 1 year lifetime, but explore the sensitivity of results of the laboratory test cost in a threshold analysis.

Each test also incurs a reagent cost and staff costs. Most responses to the survey were unable to provide detailed staff time per test, but there was agreement that 3 staff (band 5, band 6, and band 7) would be involved, and the most detailed response estimated 1.5h of band 5 for set-up, 2h of band 6 for analysis, and 2h of band 7 for checking and reporting. We assume these times for laboratory staff, plus an additional cost of a member of hospital staff (Band 5) to send the test and process results.

The total cost for the laboratory test was estimated to be £139 per lab test. In the absence of estimates of uncertainty around these costs we assume a Gamma distribution with a standard deviation of 10% of the estimated total cost, but run a sensitivity (threshold) analysis to the laboratory test cost.

Table 39 Resource and cost parameters for the Laboratory test

	Parameter	Source
Device per unit cost (Agena MassARRAY iPlex)	£414,800 (Range: £248,880-£663,680)	Xu et al (2019)[167]
Reagent per unit cost	£40 per test	Survey of laboratories (Section 4.6.2)
No of tests per day	40,000 samples	Svidnicki et al (2015) Le Hellard et al (2002) [168, 169]

	Parameter	Source
Device lifetime in years	1 year	Assumption
Time to set up test (band 5 nurse)	90 minutes	Survey of laboratories (Section 4.6.2)
Time for analysis of test (band 6 nurse)	120 minutes	
Time to check and report results (band 7 nurse)	120 minutes	
Time to process test (band 5 nurse)	10 mins	Assumption
Hourly rate of Nurse (band 5)	£13.67	NHS Employers costs[166]
Hourly rate of Nurse (band 6)	£17.00	
Hourly rate of Nurse (band 7)	£21.00	
TOTAL		
Cost per test	**£139**	

Health-state costs

Three of the cost-effectiveness studies reviewed modelled costs specific to the UK [141] [117] [101], all of which are based the health state costs from the economic burden of stroke in the UK study by Youman et al. [130] This cost-of illness model estimates the 5-year stroke related formal and informal costs by severity, however is now over 20 years old. We therefore searched for and identified the more recent Sentinel Stroke National Audit Programme (SSNAP) study representing all stroke hospitalisations in the UK for 2016. [150] We selected this to be the base case in our model because it is more recent, captures health-state costs for both in-hospital stay and out-of-hospital rehabilitation, and provides costs according to severity of stroke.[151] Mean costs are reported over a 1 year period and over a 5 year period post-stroke, which allows us to capture differences in short-term and long-term costs following a recurrent stroke (Table 40).

Table 40 Stroke Health State Costs in 2014 prices[150]

	1-year costs		5-year costs	
Stroke Severity (NIHSS)	**Mean NHS costs**	**Mean social costs**	**Mean NHS costs**	**Mean social care costs**
No stroke (0)	£8,632	£4,085	£13,702	£14,204
Minor stroke (1-4)	£10,035	£5,829	£15,103	£19,244
Moderate stroke (5 -15)	£16,419	£9,741	£20,799	£29,972
Moderate/Severe stroke (16-20)	£20,061	£16,179	£23,180	£47,898
Severe stroke (21-42)	£17,382	£16,063	£19,368	£45,809

We use the 1-year costs from SSNAP (Table 40) in the first year following stroke, and annualised costs calculated from the 5-year costs from SSNAP (Table 40) for subsequent years. Health state costs are calculated according to severity as follows:

- In the No Recurrent Stroke state we assume only rehabilitation costs are incurred which are equal to the social care costs from SSNAP, using NIHSS=0 for the TIA population and NIHSS= 5-15 for the ischaemic stroke population.
- In the Post-Secondary Minor Stroke state we include both NHS costs and social care costs, where the NHS costs are for NIHSS=1-4 for both TIA and Ischaemic stroke populations. Social care costs for the TIA / minor stroke population who have had a minor stroke are those for NIHSS = 1-4, whereas for the non-minor stroke who have a minor stroke, the social care costs are those for NIHSS= 15.
- In the Post-Secondary Moderate Stroke (NIHSS=5-15) and the Post-Secondary Severe Stroke (NIHSS=21-42) states both NIHS costs and social care costs are applied for the corresponding NIHSS range, and this is the same for both the TIA / minor stroke and non-minor stroke populations.
- Major Bleed / ICH costs were modelled as a single cost on the cycle when the event occurs that applied in addition to the cost of the health state the patient is in. In the absence of more recent data, the cost of a Major Bleed / ICH were taken from the economic evaluation conducted for NICE TA90. [141]

The resulting assumed costs are shown in Table 41 for the first and subsequent years for both modelled populations in 2014 prices.

Table 41 Stroke Health State Costs assumed in the model for the two different populations (2014 prices)

Health States	TIA/Minor Stroke	Non-minor Ischaemic Stroke
Annual Costs in Year 1		
No secondary event	£4,085	£9,741
Post-secondary minor stroke	£15,864	£19,776
Post-secondary moderate stroke	£26,160	£26,160
Post-secondary major stroke	£33,445	£33,445
Post major bleed/ICH (additional Single cost when event occurs)	£2,010	£2,010
Annual Costs in Subsequent Years		
No secondary event	£2,841	£5,994
Post-secondary minor stroke	£6,869	£9,015
Post-secondary moderate stroke	£10,154	£10,154
Post-secondary major stroke	£13,035	£13,035
Post major bleed/ICH (additional Single cost when event occurs)	£2,010	£2,010

5.2.6 Uncertainty

To reflect uncertainty in model inputs, we conducted probabilistic sensitivity analysis (PSA), where parameter uncertainty is captured with probability distributions and simulation used to estimate expected (mean) costs, expected QALYs, and incremental cost-effectiveness ratios (ICERs). The impact of uncertainty is presented using cost-effectiveness planes and

cost-effectiveness acceptability curves. One way sensitivity analyses were performed for all key parameters. Variance in input parameters was taken from the input source where available. Where unavailable, model inputs were varied by a user-defined variation parameter to conduct deterministic and probabilistic sensitivity analyses (set to 10% variation in results reported here).

5.2.7 Model Validation

The model underwent internal validation by two members of the team not involved in the building of the model, following Büyükkaramikli et al. [170] The validation included face validity tests, checks of model calculations, examination of the model outputs, and comparison of results with previous models.

5.2.8 Scenario and sensitivity analyses

A summary of the scenario analyses is given in Table 42 together with a rationale for the each scenario.

Table 42 List of scenario analyses included

Scenario	Description	Model parameters changed	Rationale for analysis
1	Prevalence of clopidogrel resistance	Increased the proportion of patients with LOF variants from 32.1% to 56.8%	Prevalence of LOF variants varies across populations due to differences in ethnicity.
2	Aspirin as Alt Tx for LOF patients	Patients whose test indicates LOF receive aspirin instead of dipyridamole plus aspirin. Costs and hazard ratios for aspirin are used for the alternative treatment.	Dipyridamole may not be used due to tolerability issues.
3	Mean age of cohort	Mean age of cohort reduced to 40 and corresponding life-table values used	This is a long-term treatment, and so costs and benefits of targeted treatment may depend on age at index event
4	Low uptake of alternative therapy after POCT test results	A probability 0.699 of receiving alternative treatment for those with LOF test result is applied. Applied to Genomadix Cube only for illustration (but effects would be similar for Genedrive and laboratory tests)	Swen et al 2023[157] found that physician adoption of pharmacogenetic recommendations was for a range genes including *CYP2C19* was only 69.9%.
5	Extended time to lab-test results	For the lab-test, the time spent on clopidogrel before switching to alternative treatment for LOF patients is varied to 4 weeks	Our survey found there is variability between labs in how quickly results are produced, and this can change with capacity
6	Ticagrelor (following DAPT ticagrelor + aspirin) as Alt Tx for LOF patients	Patients whose test indicates LOF receive ticagrelor (following DAPT ticagrelor + aspirin) instead of dipyridamole plus aspirin. Costs and hazard ratios for ticagrelor are used for the alternative treatment.	Ticagrelor has not been approved for use in England and Wales but it may be used off-label

Scenario	Description	Model parameters changed	Rationale for analysis
7	Early clopidogrel introduction	In the non-minor ischaemic stroke population clopidogrel treatment begins immediately. LOF carriers can benefit from alternative treatment sooner.	Some non-minor ischaemic stroke patients may begin clopidogrel immediately (for example if they are already taking aspirin)
8	Price year 2021	Prices are inflated to 2021 prices instead of 2022	High levels of inflation in 2022 may be impactful
9	Lab-based test costs	The cost of laboratory tests are varied in a threshold analysis	Uncertainty and heterogeneity in labs-costs, which may change with changes in infrastructure
10	Genedrive efficacy analysis	The sensitivity and specificity of the Genedrive test was varied in a threshold analysis. A one-way analysis where sensitivity and specificity were set to the same rate was performed	Limited data was found reporting the efficacy of the Genedrive system in our clinical review

Table 43 Summary of model inputs, values assumed in base-case analysis, distribution used for the probabilistic sensitivity analysis (PSA), and source of evidence

Model parameter	Value in base-case [sensitivity analysis]	Distribution for PSA	Evidence source
Test Performance			
POCT: time to receive results	1 day	N/A	Clinical review (Table 17)
Lab-test: time to receive results	1 week [4 weeks]	N/A	Survey (section 4.6.2)
POCT test failure probability	0.08	N/A	Meta-analysis of studies identified in clinical review for Genomadix Cube (Table 15). No data for Genedrive.

Model parameter	Value in base-case [sensitivity analysis]	Distribution for PSA	Evidence source
Lab-test failure probability	0.00	N/A	Survey (section 4.6.2)
POCT: Sensitivity	99%	95% CI (94, 100%) Beta(33, 0.333)	Meta-analysis for Genomadix Cube (Figure 19), reduced from 100% to 99% to account for the small proportion of patients with LOF alleles not tested for. No data for Genedrive.
POCT: Specificity	100%	95% CI (99, 100) Beta(100, 1.01)	Meta-analysis for Genomadix Cube (Figure 19). No data for Genedrive.
Patient Characteristics, Prevalence of stroke, TIA, and *CYP2C19* LOF			
Incidence of first stroke and TIA, proportion TIA	Stroke: 107 per 100,000 TIA: 50 per 100,000 P(TIA) = 31.8%	N/A	PHE briefing report.[146]
Patient characteristics: proportion female, mean age	P(female) = 49% Mean age females: 73y Mean age males: 68.2y	N/A	PHE briefing report. [171]
Prevalence of *CYP2C19* LOF	32.1% [56.8%]	Normal (SE=10% of rate)	Ionova et al (2020) [148] and PHE briefing report. [146]
Baseline event rates (representing NoLOF patients on clopidogrel)			
Stroke recurrence rates (per person year, ppy) for stroke patients	0-90 days 0.092 90+ days 0.056	Normal distribution 0-90 days (0.075-0.113) 90+ days (0.044-0.072)	Sentinel Stroke National Audit Programme (SSNAP)[150] [151] and South London Stroke Register Mohan et al 2009.[149]

Model parameter	Value in base-case [sensitivity analysis]	Distribution for PSA	Evidence source
Stroke rates (per person year, ppy) for TIA patients	0-90 days 0.0838 90+ days 0.0064	Normal (SE=10% of rate)	Lioutas 2021.[152]
Proportion of recurrent stroke by severity	Minor 0.426 Moderate 0.475 Severe 0.0495	Dirichlet(43, 48, 10)	Sentinel Stroke National Audit Programme (SSNAP)[150] [151]
Mortality rate by time for mRS 0-3	0-30 days 0.0128 31-90 days 0.0467 90+days 0.0331	Normal (SE=10% of rate)	Sentinel Stroke National Audit Programme (SSNAP)[150, 151] and South London Stroke Register Mohan et al 2009.[149]
Mortality rate by time for mRS 4-5	0-30 days 0.0157 31-90 days 0.0574 90+days 0.0407	Normal (SE=10% of rate)	Sentinel Stroke National Audit Programme (SSNAP)[150] [151] and South London Stroke Register Mohan et al 2009.[149]
Major Bleed or ICH (per person year)	0.0144	Normal (SE=10% of rate)	PRoFESS trial [156]
Proportion of Major Bleed or ICH that is ICH	0.282	Normal (SE=10% of rate)	PRoFESS trial [156]
Proportion of ICH which is fatal	0.527	Normal (SE=10% of rate)	PRoFESS trial [156]
Relative Treatment Effects (Hazard Ratios) al relative to Clopidogrel monotherapy, NoLOF			
Recurrent stroke			
Clopidogrel monotherapy, LOF	1.46	95%CI (1.09, 1.95)	Objective 3 (Figure 14)
Dipyridamole + Aspirin, No LOF	1.01	95%CI (0.92, 1.11)	PRoFESS[156]
Dipyridamole + Aspirin, LOF	1.01	95%CI (0.92, 1.11)	PRoFESS[156]
Aspirin, No LOF	1.96	95%CI (1.33, 2.857)	CHANCE[51]

Model parameter	Value in base-case [sensitivity analysis]	Distribution for PSA	Evidence source
Aspirin, LOF	1.387	95%CI (0.8947, 2.054)	CHANCE[51] with hazard ratio from Objective 3 (Figure 14) applied
Ticagrelor, No LOF	1.142	95%CI (0.7967, 1.587)	CHANCE-2[49] with hazard ratio from Objective 3 (Figure 14) applied
Major bleed/ICH			
Clopidogrel monotherapy (LOF or NoLOF)	1	1	Assumption that independent of LOF status, in line with clinical review (Figure 18)
Aspirin + Dipyridamole (LOF or No LOF)	1.15	95%CI (1, 1.32)	PRoFESS[156]
Aspirin (LOF or No LOF)	0.637	95%CI (1.087, 0.373)	CHANCE[51]
Ticagrelor, No LOF	0.82	95%CI (0.34, 1.98)	CHANCE-2[49]
Treatment discontinuation			
Discontinuation probability for clopidogrel	0.106	Normal (SE=10% of rate)	PRoFESS trial [156]
Discontinuation probability for DAPT dipyridamole+ aspirin	0.164	Normal (SE=10% of rate)	PRoFESS trial[156]
Discontinuation probability for aspirin	0.147	Normal (SE=10% of rate)	SOCRATES[111]
Discontinuation probability for ticagrelor	0.175	Normal (SE=10% of rate)	SOCRATES[111]
Utilities			
No secondary events	0.89	Normal distribution mean= 0.89, SE= 0.03	Whynes et al [161]
Post minor stroke - mRs 0-1	0.89	Normal distribution mean= 0.89, SE= 0.03	Whynes et al [161]

Model parameter	Value in base-case [sensitivity analysis]	Distribution for PSA	Evidence source
Post major bleed/ICH	0.62	Normal distribution mean= 0.62, SE=0.107	Micieli et al[102]
Post moderate stroke - mRs 2-3	0.63	Normal distribution mean= 0.63, SE=0.03	Whynes et al [161]
Post major stroke - MRs 4-5	0.065	Normal distribution mean= 0.065, SE=0.03	Whynes et al [161]
Carer disutility for patients with moderate or major stroke	-0.145	Normal distribution mean= -0.145, SE=0.03	TRACS [165]
Test Costs			
Genedrive per test cost	£104	Gamma with mean=104 and sd=10.4	Company
Genomadix Cube per test cost	£197	Gamma with mean 197 and sd=19.7	Company
Laboratory per test cost	£139	Gamma with mean 139 and sd=13.9	Survey (Section 4.6.2)
Health-State Costs (2014 prices)			
Annual Health State Costs in Year 1 (non-minor ischaemic stroke population)			
No secondary event	£9,741	Gamma with sd = 10% of cost	SSNAP[150 151]
Post-secondary minor stroke	£19,776	Gamma with sd = 10% of cost	SSNAP[150 151]
Post-secondary moderate stroke	£26,160	Gamma with sd = 10% of cost	SSNAP[150 151]

Model parameter	Value in base-case [sensitivity analysis]	Distribution for PSA	Evidence source
Post-secondary major stroke	£33,445	Gamma with sd = 10% of cost	SSNAP[150 151]
Post major bleed/ICH (additional Single cost when event occurs)	£2,010	Gamma with sd = 10% of cost	NICE TA90 [141]
Annual Health State Costs in Year 1 (TIA / minor ischaemic stroke population)			
No secondary event	£4,085	Gamma with sd = 10% of cost	SSNAP[150 151]
Post-secondary minor stroke	£15,864	Gamma with sd = 10% of cost	SSNAP[150 151]
Post-secondary moderate stroke	£26,160	Gamma with sd = 10% of cost	SSNAP[150 151]
Post-secondary major stroke	£33,445	Gamma with sd = 10% of cost	SSNAP[150, 151]
Post major bleed/ICH (additional Single cost when event occurs)	£2,010	Gamma with sd = 10% of cost	NICE TA90 [141]
Annual Health State Costs Subsequent Years (non-minor ischaemic stroke population)			
No secondary event	£5,994	Gamma with sd = 10% of cost	SSNAP[150 151]
Post-secondary minor stroke	£9,015	Gamma with sd = 10% of cost	SSNAP[150 151]
Post-secondary moderate stroke	£10,154	Gamma with sd = 10% of cost	SSNAP[150 151]
Post-secondary major stroke	£13,035	Gamma with sd = 10% of cost	SSNAP[150 151]

Model parameter	Value in base-case [sensitivity analysis]	Distribution for PSA	Evidence source
Post major bleed/ICH (additional Single cost when event occurs)	£2,010	Gamma with sd = 10% of cost	NICE TA90 [141]
Annual Health State Costs Subsequent Years (TIA / minor ischaemic stroke population)			
No secondary event	£2,841	Gamma with sd = 10% of cost	SSNAP[150 151]
Post-secondary minor stroke	£6,869	Gamma with sd = 10% of cost	SSNAP[150 151]
Post-secondary moderate stroke	£10,154	Gamma with sd = 10% of cost	SSNAP[150 151]
Post-secondary major stroke	£13,035	Gamma with sd = 10% of cost	SSNAP[150 151]
Post major bleed/ICH (additional Single cost when event occurs)	£2,010	Gamma with sd = 10% of cost	NICE TA90 [141]

5.3 Model Results

All results are reported separately for (i) the TIA / minor stroke population and (ii) the non-minor ischaemic stroke population. Key summary results are also reported for a mixed TIA / ischaemic stroke population using a weighted average using the proportions of the population in each group. Due to the paucity of clinical efficacy data for the Genedrive system, we assumed that sensitivity, specificity, and test failure rates are set equivalent to those for the Genomadix cube. For this reason, the results for Genedrive should be considered exploratory only, and only key summary results are reported for Genedrive. Deterministic base case results are outlined in Section 5.3.1, with deterministic sensitivity analyses reported in Section 5.3.2. Probabilistic sensitivity analyses, scenario analyses, and diagnostic test cost and accuracy threshold analyses are reported in sections 5.3.3 - 5.3.5.

5.3.1 Deterministic base-case analyses

Table 44 - Table 46 show the fully incremental results for the three populations. Overall total costs are lower and total QALYs are higher in the TIA / minor stroke population compared with the non-minor ischaemic stroke population. All laboratory and point of care *CYP2C19* testing strategies dominated no testing, i.e. *CYP2C19* testing generated more quality adjusted life-years (QALYs) and lower costs compared with no testing. Based on these results Genedrive dominates laboratory testing, and the ICER for Genomadix relative to Genedrive was £42,123, £5,023, and £24,387 in the non-minor stroke, TIA/minor stroke, and mixed populations respectively. However, the results for Genedrive are based on strong assumptions on accuracy and test performance, so these results need to be interpreted with this in mind.

Total QALYs were very similar between the different testing strategies make interpretation of ICERs challenging. For this reason we prefer to compare the *CYP2C19* testing strategies in terms of net monetary benefit presented in the pairwise results in Table 47 - Table 49 for a willingness to pay of £20,000 per QALY, preferring tests with the highest net monetary benefit. In the non-minor ischaemic stroke population the net monetary benefits were £6,159, £6,112, and £6,066 for Genedrive, the laboratory test, and the Genomadix Cube *CYP2C19* Test respectively. In the TIA / minor stroke population the expected net monetary benefits were £2,737, £2,584, and £2,644 for Genedrive, the laboratory test, and the Genomadix Cube *CYP2C19* Test respectively. Net monetary benefit is greatest in the non-minor ischaemic stroke population due to the higher event rate in the long-term, and hence greater benefit of appropriate treatment in this population. In the combined TIA / ischaemic stroke population the net monetary benefits were £5,069, £4,988, and £4,976 for Genedrive, the laboratory test, and the Genomadix Cube *CYP2C19* Test respectively. In all populations net monetary benefit is similar, suggesting little difference between the tests, but it is slightly higher for Genedrive, followed by laboratory test, then the Genomadix Cube *CYP2C19* Test.

Table 44 Base Case Fully Incremental Analysis for the Non-Minor Ischaemic Stroke Population

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Lab-test	vs Genomadix cube
POCT: Genedrive	£98,557	6.55					
Laboratory genetic test	£98,563	6.55	Yes	N/A	Dominated		
POCT: Genomadix cube	£98,650	6.55	Yes	N/A	Dominated	£42,123	
No test	£100,472	6.34	Yes	N/A	Dominated	Dominated	Dominated

Table 45 Base Case Fully Incremental Analysis for the TIA / Minor Stroke Population

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Lab-test	vs Genomadix Cube
POCT: Genedrive	£44,864	8.66					
Laboratory genetic test	£44,936	8.65	Yes	N/A	Dominated		
POCT: Genomadix cube	£44,957	8.66	Yes	N/A	Dominated	£5,023	
No test	£46,005	8.58	Yes	N/A	Dominated	Dominated	Dominated

Table 46 Base Case Fully Incremental Analysis for a Mixed TIA / Ischaemic Stroke Population

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Lab-test	vs Genomadix cube
POCT: Genedrive	£81,457	7.99					
Laboratory genetic test	£81,485	7.98	Yes	N/A	Dominated		
POCT: Genomadix cube	£81,550	7.99	Yes	N/A	Dominated	£24,387	
No test	£83,126	7.87	Yes	N/A	Dominated	Dominated	Dominated

Table 47 Pairwise Comparisons vs No Testing for the Non-Minor Ischaemic Stroke Population.

Comparator vs no test	Incremental costs (discounted)	Incremental QALYs (discounted)	ICER (£)	Net monetary benefit
POCT: Genedrive vs No test	-£1,915	0.21	-£9,027	£6,159
POCT: Genomadix cube vs No test	-£1,823	0.21	-£8,590	£6,066
Laboratory test vs No test	-£1,909	0.21	-£9,084	£6,112

Table 48 Pairwise Comparisons vs No Testing for the TIA / Minor Stroke Population.

Comparator vs no test	Incremental costs (discounted)	Incremental QALYs (discounted)	ICER (£)	Net monetary benefit
POCT: Genedrive vs No test	-£1,141	0.08	-£14,306	£2,737
POCT: Genomadix cube vs No test	-£1,048	0.08	-£13,143	£2,644
Laboratory test vs No test	-£1,069	0.08	-£14,105	£2,584

Table 49 Pairwise Comparisons vs No Testing for the Mixed TIA / Ischaemic Stroke Population.

Comparator vs no test	Incremental costs (discounted)	Incremental QALYs (discounted)	ICER (£)	Net monetary benefit
POCT: Genedrive vs No test	-£1,669	0.17	-£9,816	£5,069
POCT: Genomadix cube vs No test	-£1,576	0.17	-£9,270	£4,976
Laboratory test vs No test	-£1,641	0.17	-£9,808	£4,988

Table 50 and Table 51 show, for both populations, the contributions to total costs and total QALYs arising from each branch of the decision tree in the short-term (decision tree), long-term (Markov) components of the model, and in total. These figures incorporate the probability of taking each branch for each testing strategy. Sensitivity and specificity are very high, so the majority of costs and QALYs for POCT tests are from true negatives (the majority are NoLOF patients) followed by true positives (LOF patients).

Table 50 Base Case Contributions to Total Costs and QALYs by Branch of Decision Tree for the Non-Minor Ischaemic Stroke Population

	Short-term outcomes		Long-term outcomes (Discounted)		Total (Discounted)	
Branches	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**
POCT test; LOF; true positive	£1,058	0.06	£30,231	2.00	£31,289	2.06
POCT test; LOF; false negative	£11	0.00	£322	0.02	£332	0.02
POCT test; no LOF; true negative	£2,223	0.13	£64,713	4.34	£66,936	4.48
POCT test; no LOF; false positive	£0	0.00	£0	0.00	£0	0.00
Lab test; LOF	£1,090	0.06	£30,544	2.02	£31,634	2.08
Lab test; no LOF	£2,291	0.13	£64,639	4.34	£66,929	4.47
No test; true status LOF	£1,048	0.06	£32,167	1.82	£33,215	1.88
No test; true status no LOF	£2,194	0.13	£65,063	4.33	£67,257	4.46

Table 51 Base Case Contributions to Total Costs and QALYs by Branch of Decision Tree for the TIA / minor stroke population

	Short-term outcomes		Long-term outcomes (Discounted)		Total (Discounted)	
Branches	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**
PoC test; LOF; true positive	£422	0.06	£13,770	2.71	£14,192	2.78
PoC test; LOF; false negative	£4	0.00	£145	0.03	£150	0.03
PoC test; no LOF; true negative	£862	0.14	£29,660	5.72	£30,522	5.85
PoC test; no LOF; false positive	£0	0.00	£0	0.00	£0	0.00
Lab test; LOF	£447	0.06	£13,928	2.74	£14,375	2.80
Lab test; no LOF	£926	0.14	£29,636	5.71	£30,562	5.85
No test; true status LOF	£405	0.06	£14,519	2.68	£14,924	2.75
No test; true status no LOF	£829	0.14	£30,252	5.69	£31,081	5.83

5.3.2 Deterministic sensitivity analyses

We ran a deterministic sensitivity analysis by setting each parameter in turn at their lower and upper bounds and reporting the resulting change to the ICER in a tornado plots. Details of the parameter lower and upper bounds can be found in 5.2.8. Results are reported for the laboratory test and Genomadix cube vs no test and for both populations in Figure 27 - Figure 30. All parameters with an upper or lower bound over £500 difference from the base case were included.

In all cases, the base-case ICER changes by less that £3000 per QALY. For the non-minor ischaemic stroke population the parameters with the biggest impact were the health-state costs, and the hazard ratios for stroke for aspirin and clopidogrel in LOF patients relative to clopidogrel NoLOF, and mortality rates (Figure 27 and Figure 29). For the TIA / minor stroke population, the parameters with the biggest impact were the health-state costs, hazard ratios for stroke for aspirin and clopidogrel in LOF patients relative to clopidogrel NoLOF, hazard ratio for bleed on aspirin, health state utilities, mortality rates, and prevalence of LOF carriers (Figure 28 and Figure 30).

Figure 27 Deterministic Sensitivity Analysis Results for Parameters with Largest Impact on the ICER for Laboratory Test vs No Test for the Non-Minor Ischaemic Stroke Population

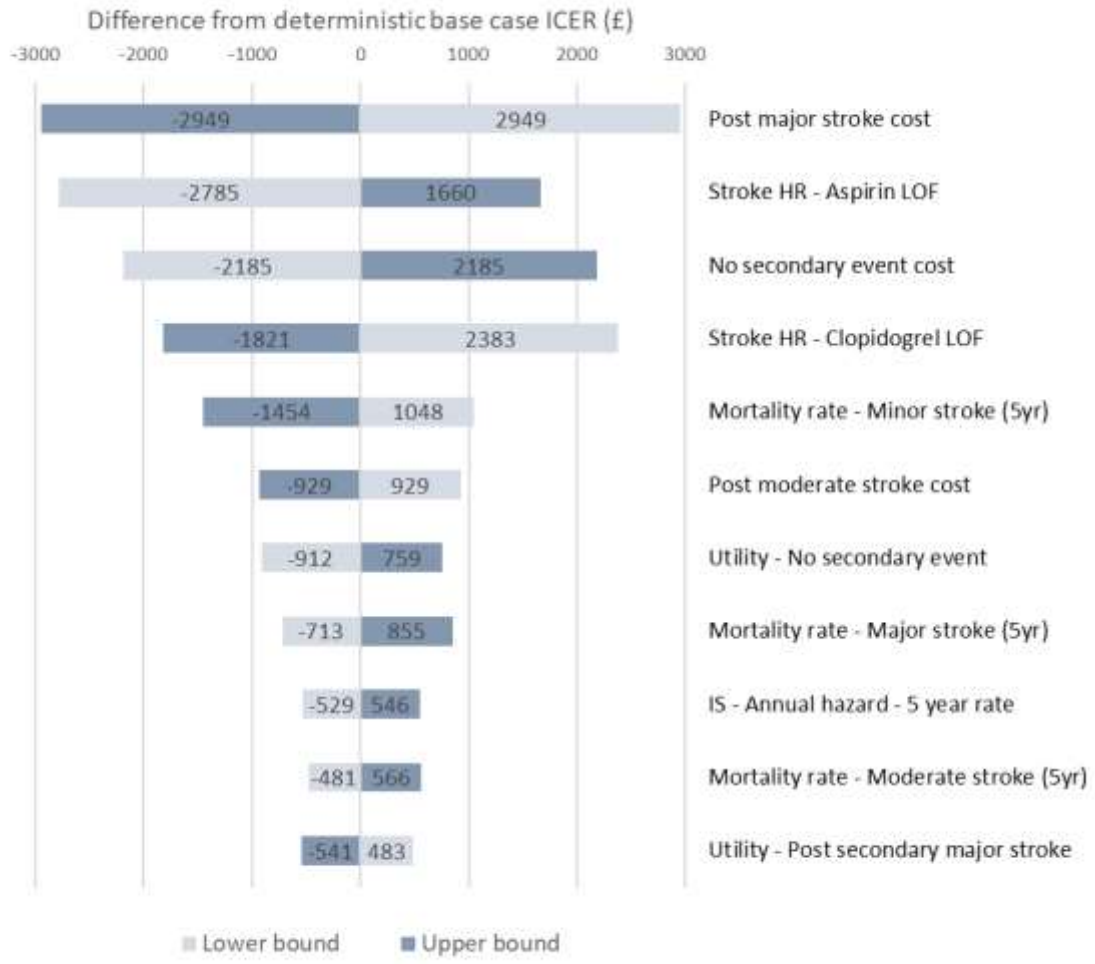


Figure 28 Deterministic Sensitivity Analysis Results for Parameters with Largest Impact on the ICER for Laboratory Test vs No Test for the TIA / Minor Stroke Population

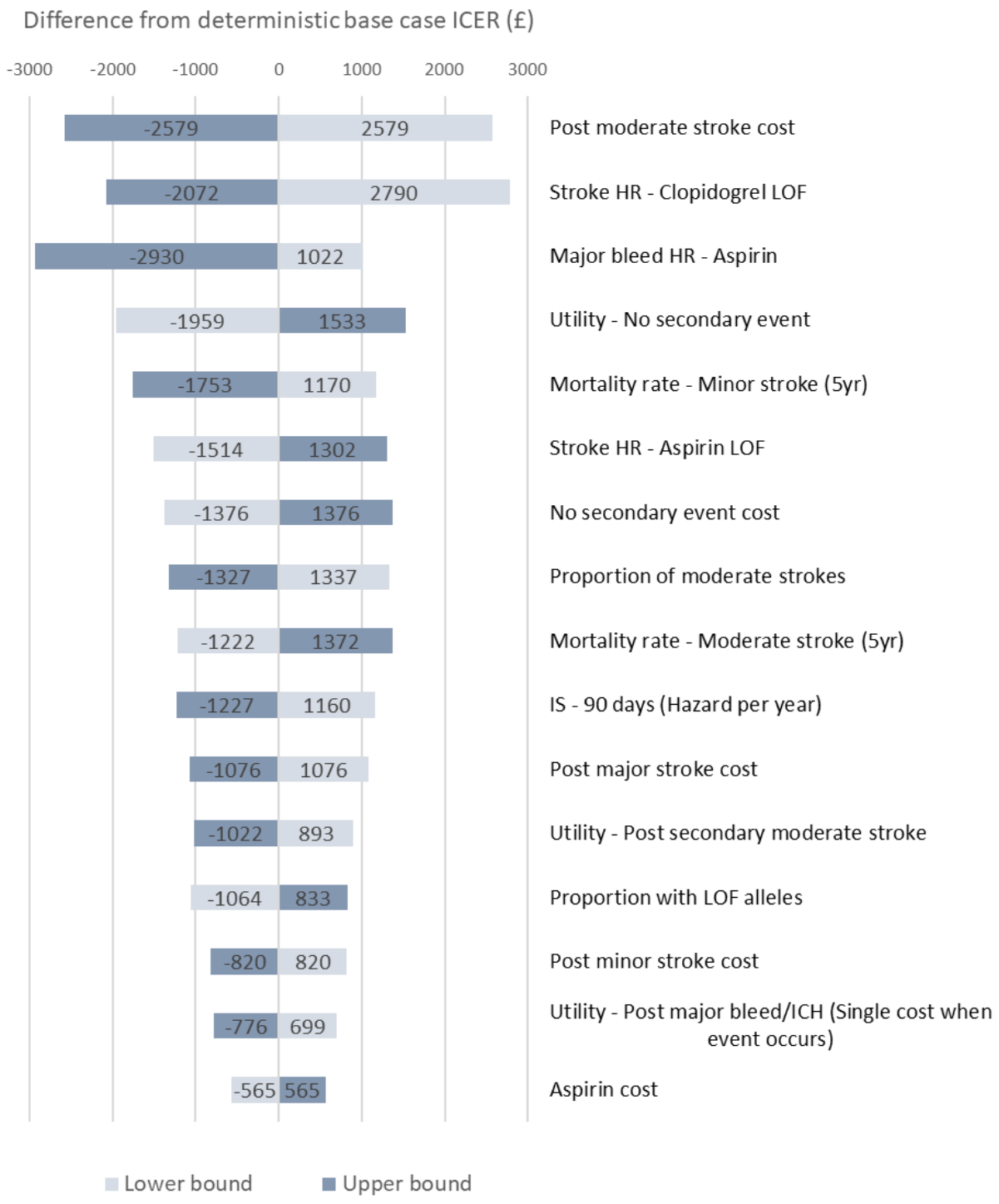


Figure 29 Deterministic Sensitivity Analysis Results for Parameters with Largest Impact on the ICER for Genomadix Cube vs No Test for the Non-Minor Ischaemic Stroke Population

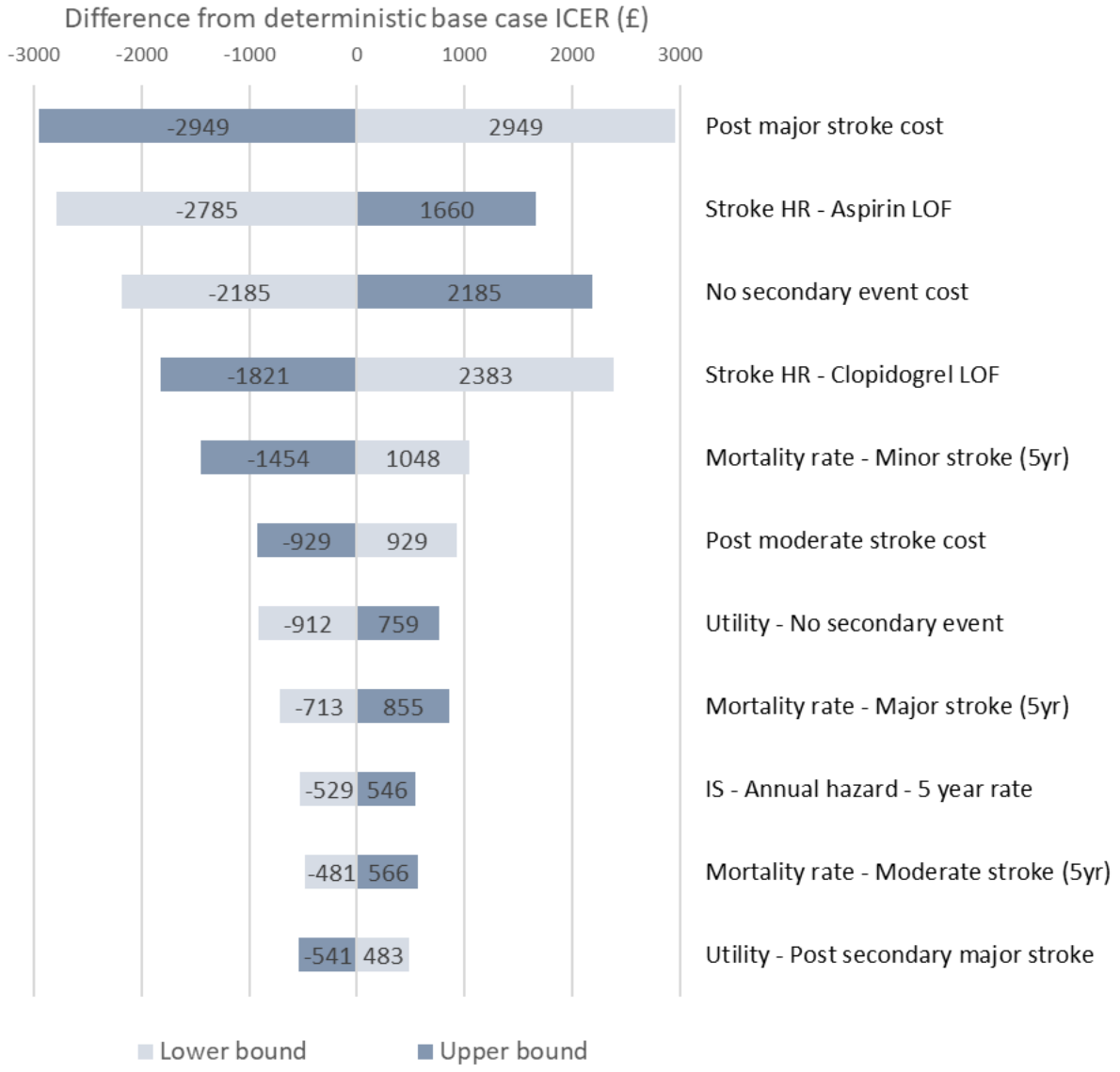
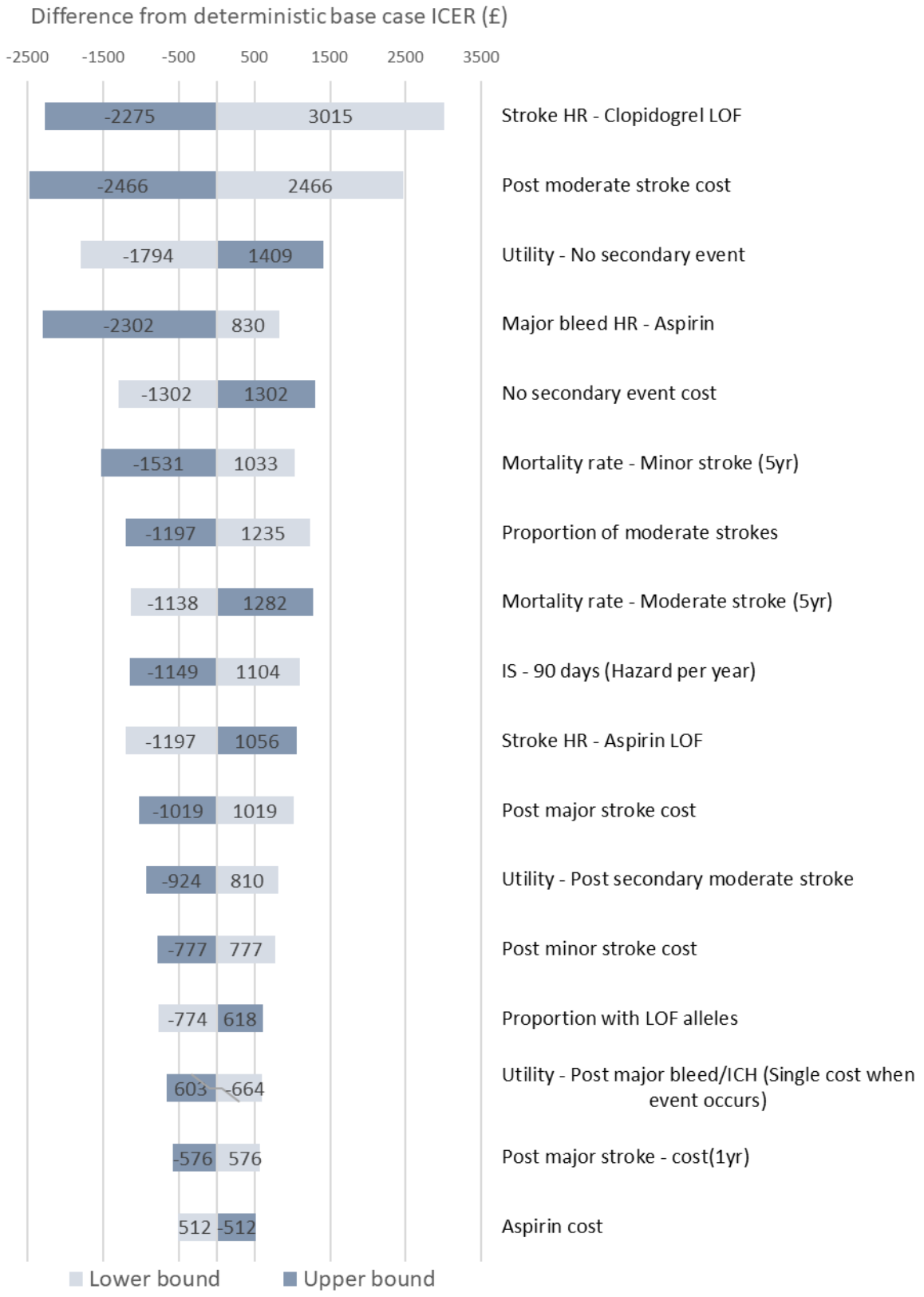


Figure 30 Deterministic Sensitivity Analysis Results for Parameters with Largest Impact on the ICER for Genomadix Cube vs No Test for the TIA / Minor Ischaemic Stroke Population



5.3.3 Probabilistic sensitivity analysis

The probabilistic sensitivity analyses were run for 5,000 iterations in each population (non-minor ischaemic stroke, TIA/minor stroke, and mixed). In the mixed population at each iteration the population was sampled with a probability 0.68 for non-minor ischaemic stroke 0.32 and the TIA/minor stroke population otherwise.

Incremental cost-effectiveness planes for the laboratory test and Genomadix cube are reported for the non-minor ischaemic stroke population (Figure 31, Figure 32), TIA / minor stroke population (Figure 34,
Figure 35) and mixed population (
Figure 37, Figure 38), with a willingness to pay thresholds of £20,000 per QALY indicated by the dotted lines. Cost-effectiveness acceptability curves are reported for the non-minor ischaemic stroke population (
Figure 33), TIA (Figure 36), and mixed populations (
Figure 39). In all cases there is a very high probability that one of the testing strategies is cost-effective, with the probability of no testing being cost-effective close to zero across all willingness to pay thresholds. Genedrive has the highest probability of being cost-effective for all populations, but note the lack of evidence on test accuracy and performance for Genedrive. The laboratory test has a low probability of being cost-effective in the TIA / minor stroke population due to the delay in receiving results.

Figure 31 Incremental Cost-Effectiveness plane for Laboratory Test vs No Test for the Non-Minor Ischaemic Stroke Population

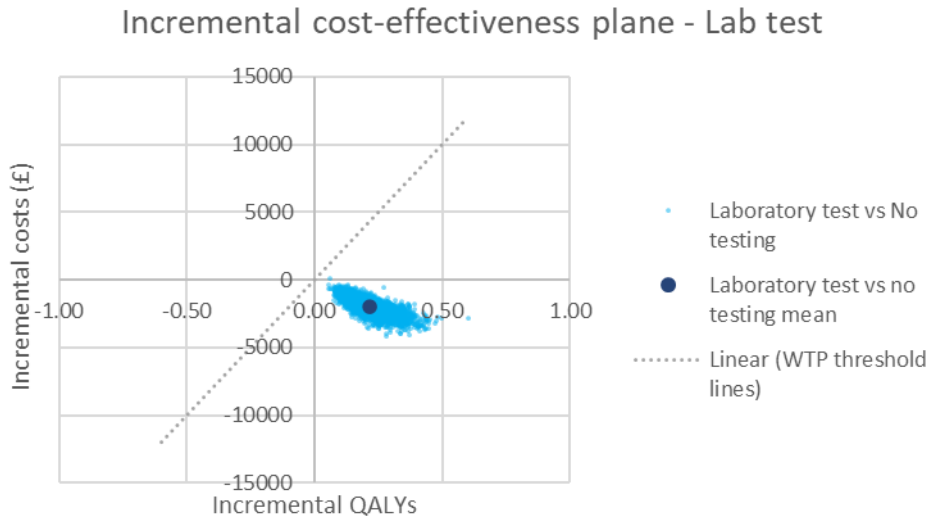


Figure 32 Incremental Cost-Effectiveness plane for Genomadix Cube vs No Test for the Non-Minor Ischaemic Stroke Population

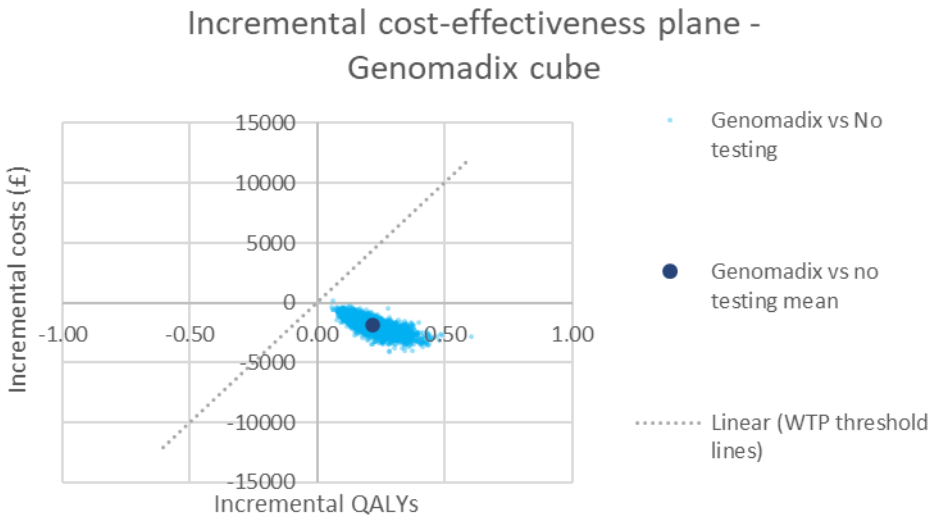


Figure 33 Cost-Effectiveness Acceptability Curve for the Non-Minor Ischaemic Stroke Population

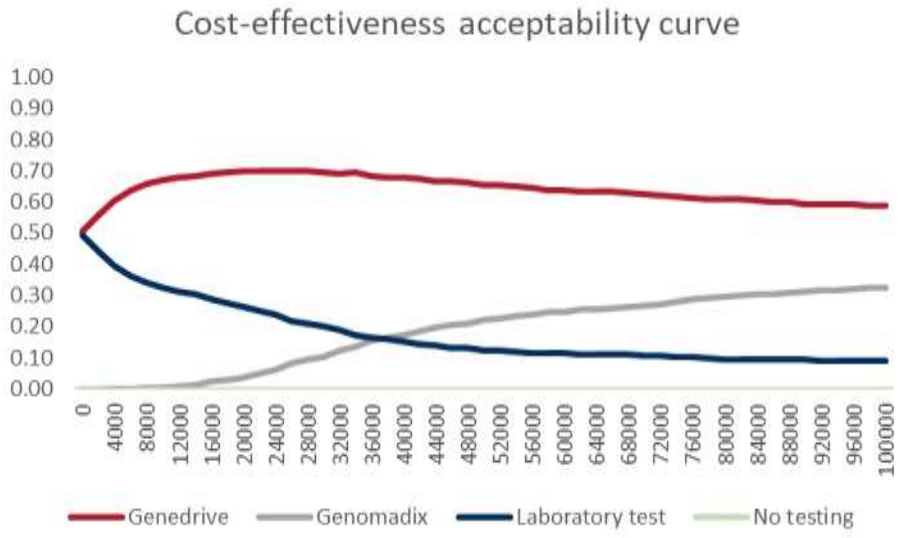


Figure 34 Incremental Cost-Effectiveness plane for Laboratory Test vs No Test for the TIA / minor stroke population

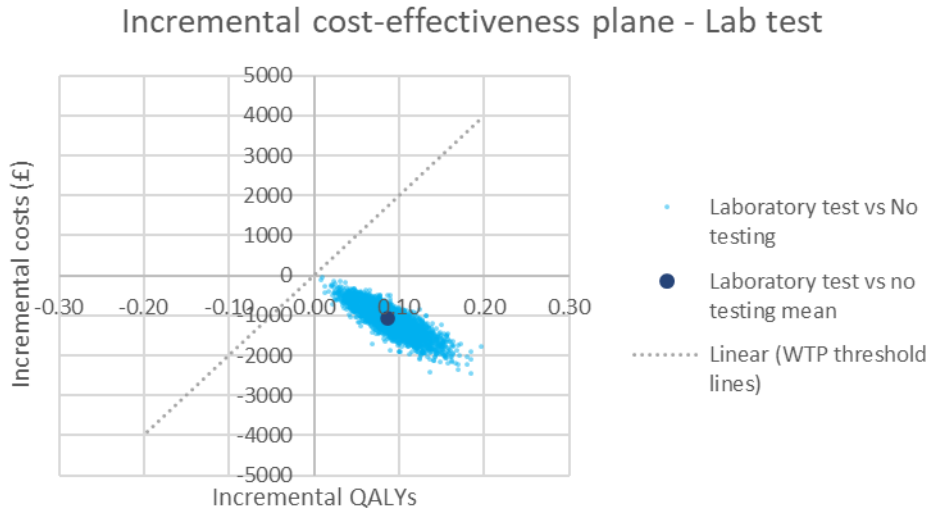


Figure 35 Incremental Cost-Effectiveness plane for the Genomadix Cube vs No Test for the TIA / minor stroke population

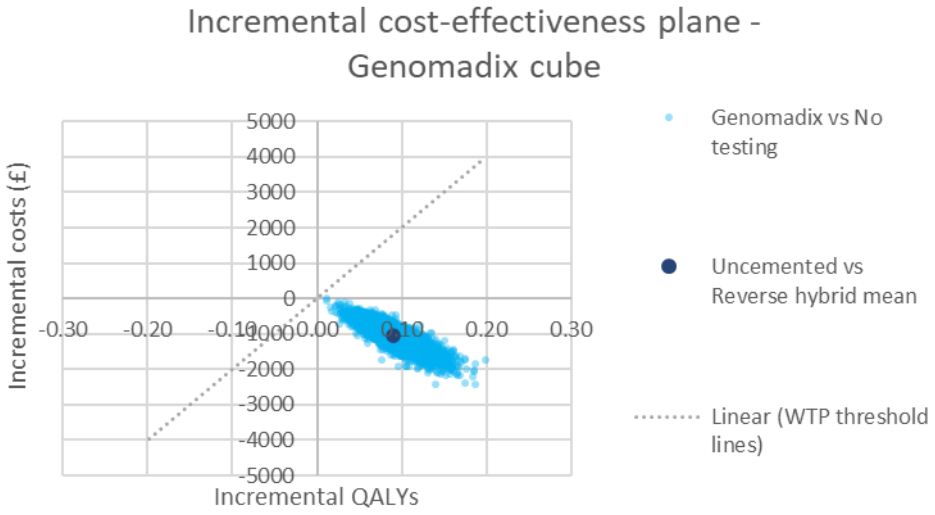


Figure 36 Cost-Effectiveness Acceptability Curve for the TIA / Minor Stroke Population

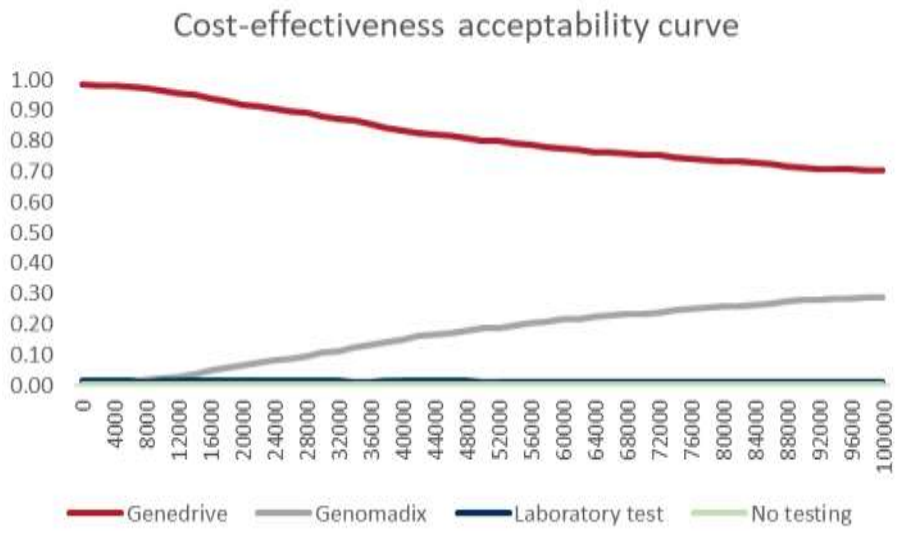


Figure 37 Incremental Cost-Effectiveness plane for Laboratory Test vs No Test for the Mixed Population

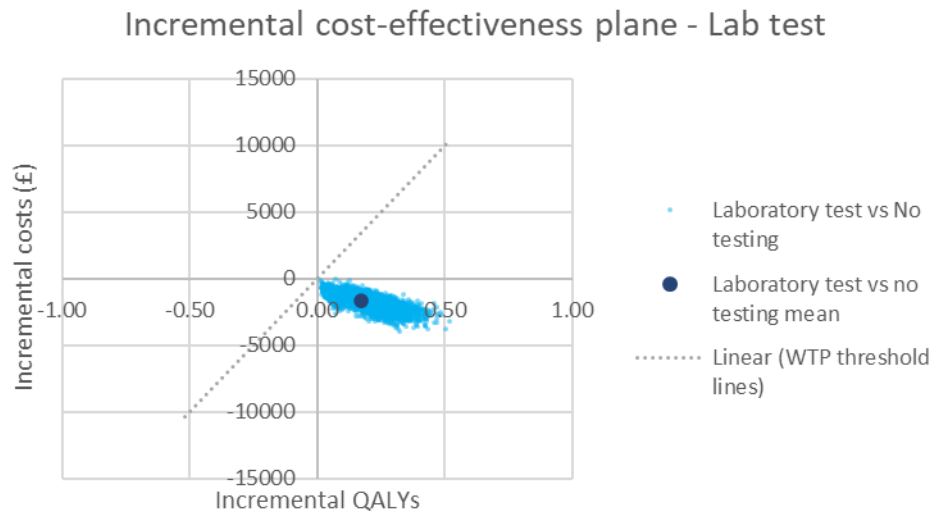


Figure 38 Incremental Cost-Effectiveness plane for the Genomadix Cube vs No Test for the Mixed Population

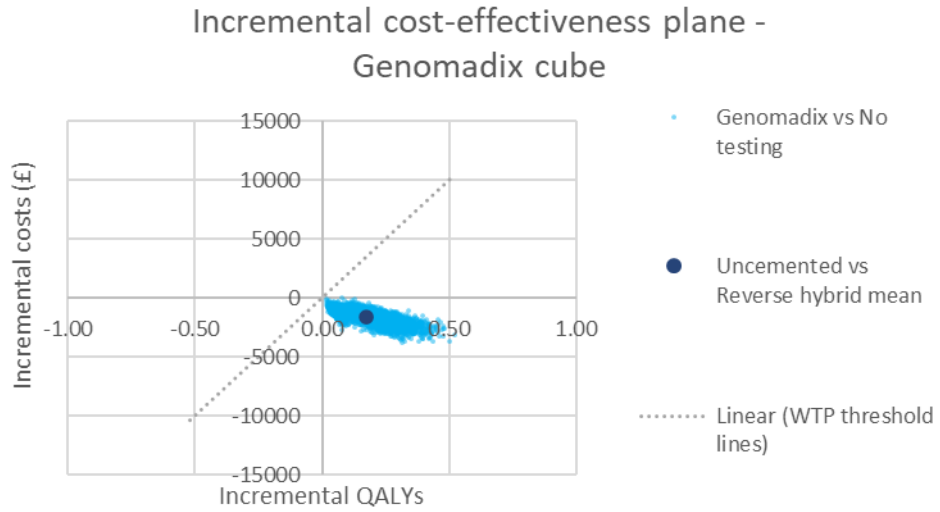


Figure 39 Cost-Effectiveness Acceptability Curve for the Mixed Population

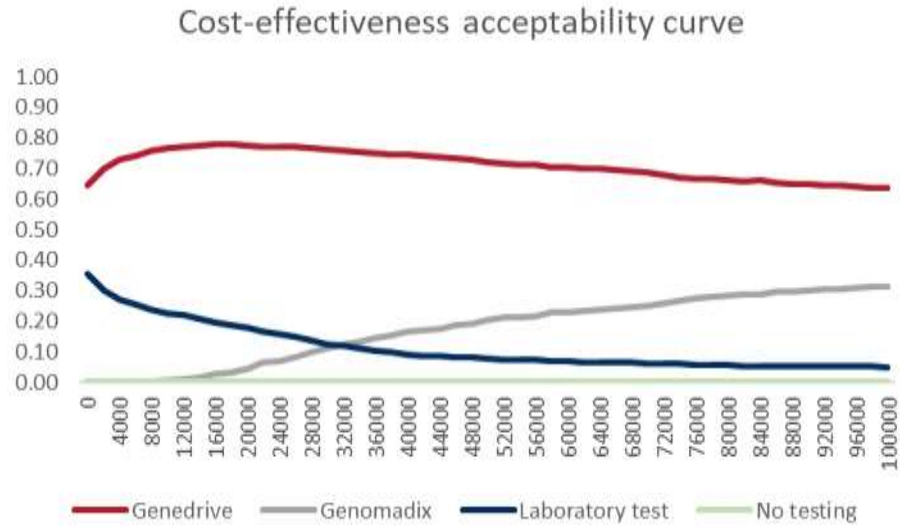


Table 52 - Table 54 report the probabilistic fully incremental analysis for the three populations. As for the deterministic analysis, all laboratory and point of care *CYP2C19* testing strategies dominated no testing in all populations. For the non-minor ischaemic stroke population, the Genomadix Cube had an ICER of £86,272 against lab test and £2,985,232 against Genedrive (owing to a very small difference in incremental QALYs), and the ICER for Genedrive relative to the lab-test was £5,530. For the TIA / minor stroke population and mixed population, lab test was dominated by Genedrive and the Genomadix Cube had an ICER £10,797 and £46,446 against the lab-test in the TIA / minor stroke population and mixed population respectively. Note however that the differences between

the tests in QALYs was very small making the interpretation of the ICERs challenging, so we prefer to compare the tests using expected net monetary benefit.

Table 55 - Table 57 report the pairwise comparisons from the probabilistic analysis of each *CYP2C19* testing strategy compared with no testing. In the non-minor ischaemic stroke population the expected net monetary benefits were £6,230 for Genedrive, £6,138 for the Genomadix Cube, and £6,214 for the laboratory test. In the TIA / minor stroke population the expected net monetary benefits were £2,932 for Genedrive, £2,829 for the Genomadix Cube, and £2,802 for the laboratory test. In the combined TIA / ischaemic stroke population the expected net monetary benefits were £5,211 for Genedrive, £5,119 for the Genomadix Cube, and £5,163 for the laboratory test.

Table 52 Probabilistic Fully Incremental Analysis for the Non-Minor Ischaemic Stroke Population

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Lab test	vs Genedrive	vs Genomadix cube
Laboratory genetic test	98,517	6.538					
POCT: Genedrive	98,523	6.539	No	No	5,530		
POCT: Genomadix cube	98,616	6.539	No	No	86,272	2,985,232	
No test	100,450	6.324	Yes	N/A	Dominated	Dominated	Dominated

Table 53 PSA Probabilistic Fully Incremental Analysis for the TIA / Minor Stroke Population

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Lab test	vs Genomadix cube
POCT: Genedrive	45,016	8.688					
Laboratory genetic test	45,086	8.685	Yes	N/A	Dominated		
POCT: Genomadix cube	45,118	8.688	No	No	3,1432,806	10,797	
No test	46,155	8.598	Yes	N/A	Dominated	Dominated	Dominated

Table 54 Probabilistic Fully Incremental Analysis for the Mixed Population

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Lab test	Vs Genomadix cube
POCT: Genedrive	81,341	7.106					
Laboratory genetic test	81,356	7.104	Yes	N/A	Dominated		
POCT: Genomadix cube	81,433	7.106	No	No	2,172,044	46446	
No test	83,031	6.930	Yes	N/A	Dominated	Dominated	Dominated

Table 55 Probabilistic Pairwise Comparisons vs No Testing for the Non-Minor Ischaemic Stroke Population

Comparator vs no test	Incremental costs (discounted)	Incremental QALYs (discounted)	ICER (£)	Net monetary benefit
POCT: Genedrive vs No test	-£1,927	0.215	-£9,118	£6,230
POCT: Genomadix cube vs No test	-£1,835	0.215	-£8,650	£ 6,138
Laboratory genetic test vs No test	-£1,933	0.214	-£9,214	£ 6,214

Table 56 Probabilistic pairwise comparisons - TIA population

Comparator vs no test	Incremental costs (discounted)	Incremental QALYs (discounted)	ICER (£)	Net monetary benefit
POCT: Genedrive vs No test	-£1,139	0.090	-£12,843	£2,932
POCT: Genomadix cube vs No test	-£1,036	0.090	-£11,592	£2,829
Laboratory genetic test vs No test	-£1,069	0.087	-£12,472	£2,802

Table 57 Probabilistic pairwise comparisons - Weighted population

Comparator vs no test	Incremental costs (discounted)	Incremental QALYs (discounted)	ICER (£)	Net monetary benefit
POCT: Genedrive vs No test	-£1,691	0.176	-£12,255	£5,211
POCT: Genomadix cube vs No test	-£1,598	0.176	-£11,450	£5,119
Laboratory genetic test vs No test	-£1,675	0.174	-£12,348	£5,163

5.3.4 Scenario analyses

Results from the scenario analyses for the non-minor ischaemic stroke and TIA / minor stroke populations can be found in Table 58 and Table 59 respectively. When compared against no test, the Genomadix cube and laboratory test had a positive net monetary benefit in all scenarios and populations modelled. The overall finding that *CYP2C19* testing is cost-saving and generates more QALYs compared with no-testing was robust in all the scenarios that we explored. The scenarios where *CYP2C19* testing was most cost-effective were when prevalence of *CYP2C19* LOF was high and for younger cohorts of patients. The scenarios where *CYP2C19* testing was least cost-effective were when we assumed that only 69.9% of LOF patients actually receive alternative treatment, and when the alternative treatment was ticagrelor. However, *CYP2C19* testing was still cost-saving but with a smaller increase in QALYs.

Table 58 Scenario Analyses: Deterministic Pairwise Results vs No Testing for the Non-Minor Ischaemic Stroke Population

		Genomadix Cube vs No testing				Laboratory test vs No testing			
		Incremental costs (£) (discounted)	Incremental QALYs (discounted)	ICER (£)	Net Monetary Benefit (£)	Incremental costs (£) (discounted)	Incremental QALYs (discounted)	ICER (£)	Net Monetary Benefit (£)
Deterministic base case		-£1,823	0.21	-8,590	£6,066	-£1,909	0.21	-£9,084	£6,112
1	Prevalence of clopidogrel resistance of 56.8%	-£2,941	0.36	-£8,204	£10,111	-£3,015	0.36	-£8,397	£10,196
2	Aspirin as Alt Tx for LOF patients	-£1,260	0.15	-£8,227	£4,322	-£1,352	0.15	-£8,995	£4,358
3	Mean age of cohort (including a scenario for young people) - 40 years old	-£2,553	0.34	-£7,547	£9,318	-£2,645	0.34	-£7,834	£9,398
4	Low uptake of alternative therapy after PoC test results	-£822	0.12	-£7,022	£3,162				
5	Extended time to lab-test results					-£1,879	0.21	-£8,990	£6,058
6	Ticagrelor + aspirin as Alt Tx for LOF patients	-£713	0.19	-£3,771	£4,496	-£760	0.19	-£4,064	£4,498
7	Early clopidogrel introduction	-£1,818	0.21	-£8,577	£6,058	-£1,901	0.21	-£9,054	£6,099
8	Price year 2021	-£1,688	0.21	-£7,956	£5,932	-£1,768	0.21	-£8,413	£5,971

Table 59 Scenario Analyses: Deterministic Pairwise Results vs No Testing for the TIA / Minor Stroke Population

		Genomadix vs No testing				Laboratory test vs No testing			
		Incremental costs (£) (discounted)	Incremental QALYs (discounted)	ICER (£)	Net Monetary Benefit	Incremental costs (discounted)	Incremental QALYs (discounted)	ICER	Net Monetary Benefit
Deterministic base case		-£1,048	0.08	-£13,143	£2,644	-£1,069	0.08	-£14,105	£2,584
1	Prevalence of clopidogrel resistance of 56.8%	-£1,296	0.12	-£11,259	£3,598	-£1,305	0.11	-£11,613	£3,551
2	Aspirin as Alt Tx for LOF patients	-£914	0.07	-£13,967	£2,223	-£947	0.06	-£15,500	£2,168
3	Mean age of cohort (including a scenario for young people) - 65 years old	-£1,614	0.13	-£12,851	£4,125	-£1,634	0.12	-£13,395	£4,074
4	Low uptake of alternative therapy after PoC test results	-£283	0.03	-£9,088	£907	-	-	-	-
5	Extended time to lab-test results	-	-	-	-	-£1,014	0.07	-£13,779	£2,485
6	Ticagrelor + aspirin as Alt Tx for LOF patients	-£149	0.07	-£2,077	£1,584	-£137	0.07	-£2,026	£1,493
7	Early clopidogrel introduction	-£1,048	0.08	-£13,143	£2,644	-£1,069	0.08	-£14,105	£2,584
8	Price year 2021	-£971	0.08	-£12,172	£2,567	-£990	0.08	-£13,063	£2,505

5.3.5 Threshold analyses

We conducted two threshold analyses, one varying the of laboratory test costs (cost per test) and the other varying the diagnostic accuracy for the Genedrive. For each threshold analysis and population we plot incremental net monetary benefit relative to the other *CYP2C19* testing strategies against different values of the parameter that is varied. All net monetary benefit figures presented here calculated using a £20,000 per QALY willingness to pay threshold.

Figure 40 and

Figure 41 present the incremental net benefit for the laboratory test compared against the other *CYP2C19* testing strategies non-minor ischaemic stroke and TIA / minor stroke populations, respectively. In the non-minor ischaemic stroke population the laboratory test was cost-effective vs Genedrive below £29, vs the Genomadix cube below £184 and vs no test below £6,251. In the TIA / minor stroke population the laboratory test was found to be as cost-effective at cost-per-tests below £79 vs the Genomadix cube, below £2723 vs no test and was strictly dominated at all costs against the Genedrive test.

Our reviews did not identify any evidence on the sensitivity and specificity of the Genedrive system. We explored the sensitivity of our results to assumptions on this by using a threshold analysis for the test accuracy of Genedrive system. We varied sensitivity and specificity together in a one-way threshold analysis, with sensitivity and specificity set to the same value, presented in Figure 42 and Figure 43. In the both populations the Genedrive system was found to be cost-effective at sensitivity and specificity equal and over 99% vs the Genomadix cube, equal and over 98% vs the lab test.

Figure 40 Incremental Net Monetary Benefit of the Laboratory Test vs Other Testing Strategies by Laboratory Test Cost for the Non-Minor Ischaemic Stroke Population

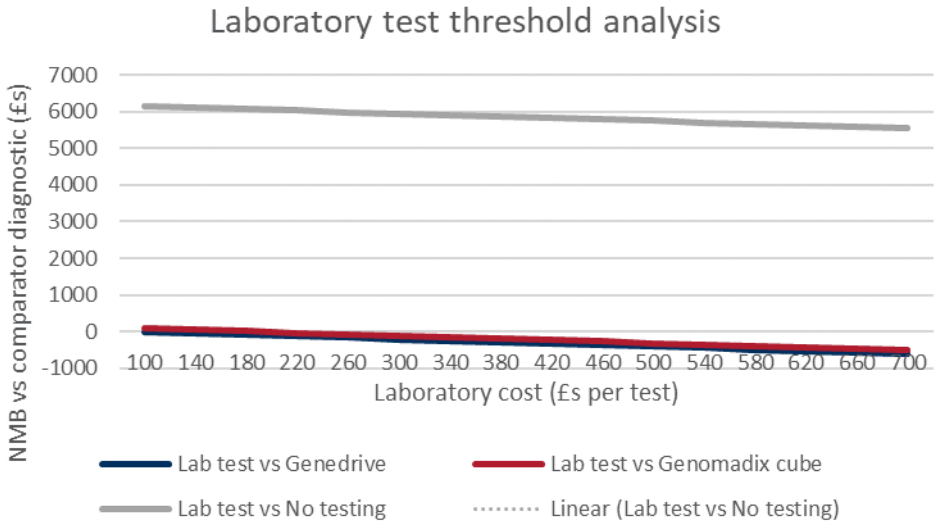


Figure 41 Incremental Net Monetary Benefit of the Laboratory Test vs Other Testing Strategies by Laboratory Test Cost for the TIA / Minor Stroke Population

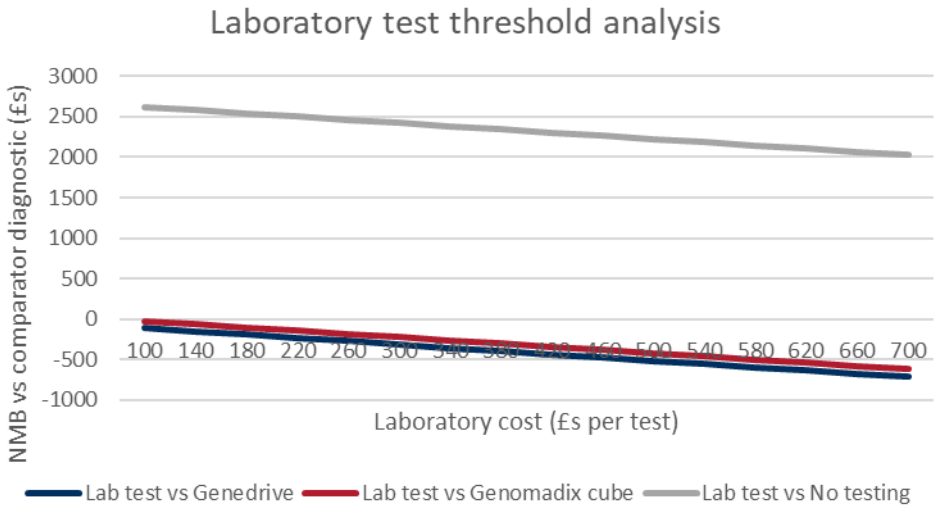


Figure 42 Incremental Net Monetary Benefit of the Genedrive vs Other Testing Strategies by Genedrive Test Accuracy for the Net monetary benefit of the Non-Minor Ischaemic Stroke Population

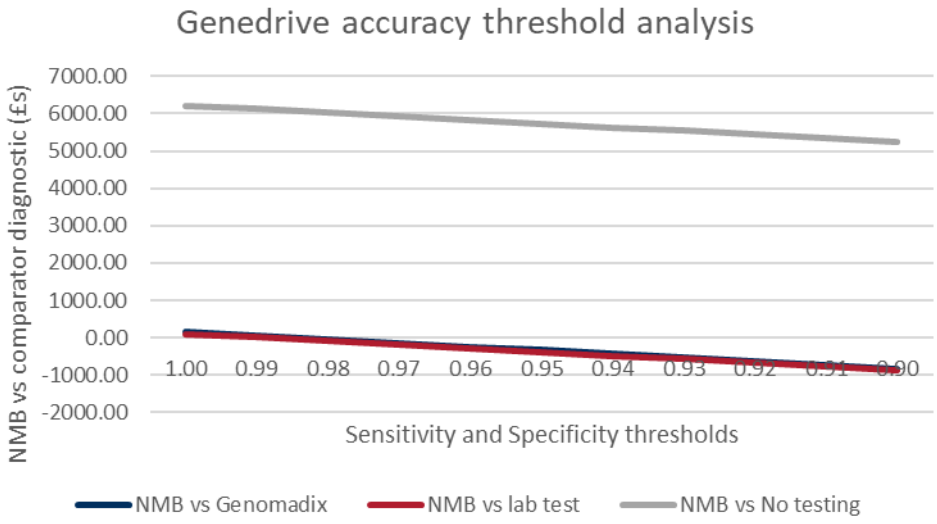
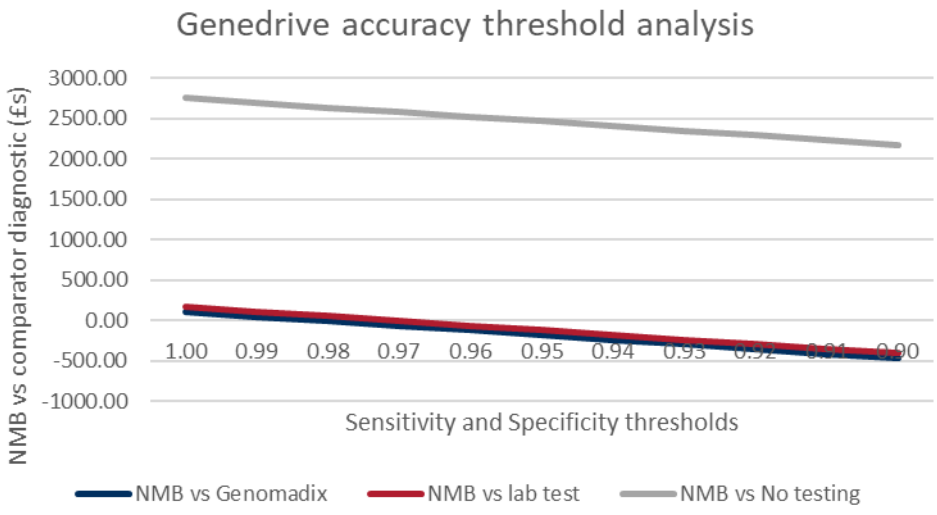


Figure 43 Incremental Net Monetary Benefit of the Genedrive vs Other Testing Strategies by Genedrive Test Accuracy for the TIA / Minor Stroke Population



5.3.6 Summary of findings of economic evaluation

In summary in our base-case for all populations we found that laboratory and point of care *CYP2C19* testing strategies dominated no testing, i.e. *CYP2C19* testing generated more quality adjusted life-years (QALYs) and lower costs compared with no testing. This finding was robust to the sensitivity and scenario analyses that we conducted. The scenarios where *CYP2C19* testing was most cost-effective were when prevalence of *CYP2C19* LOF was high and for younger cohorts of patients. The scenarios where *CYP2C19* testing was least cost-effective were (i) when we assumed that only 69.9% of LOF patients actually receive alternative treatment due to reluctance to use alternative treatment or due to the test results not being visible to physicians; and (ii) when the alternative treatment was ticagrelor. However, *CYP2C19* testing was still cost-saving in these scenarios, but with a smaller increase in QALYs.

It was challenging to compare the different types of test due to very small differences in QALYs between the different *CYP2C19* testing strategies. Because sensitivity and specificity were so high in our model, the main difference between the *CYP2C19* testing strategies was their per-test cost, which suggest a cost-minimisation approach may be appropriate. The laboratory test has the disadvantage that there could be a delay in receiving test results, however we found our results were not sensitive to the time until test results were received. This is because the period of time waiting for test results represents only a small part of the time-horizon over which costs and QALYs accrue. We conducted a threshold analysis to the cost of the laboratory test, which provides costs below which the laboratory test is cost-effective compared with the two POCTs for each population.

Due to limited information on Genedrive, we assumed all model inputs were the same as for the Genomadix Cube *CYP2C19* Test with the exception of the costs, which is why Genedrive appears the more cost-effective of the POCTs. The results for Genedrive should therefore be considered exploratory only and this finding may change as further evidence on the accuracy and performance of Genedrive becomes available. We conducted a threshold analysis for the diagnostic test accuracy of Genedrive, reducing sensitivity and specificity (but keeping them equal). We found that the Genedrive system was found to be cost-effective at sensitivity and specificity equal and over 99% vs the Genomadix cube, equal and over 98% vs the lab test.

6 Assessment of factors relevant to the NHS and other parties

We heard from our clinical advisers that only a proportion of patients diagnosed as *CYP2C19* LOF may receive targeted treatment for a variety of reasons, such as physician or patient preference, issues with results not being made available to prescribers, or failure for the test to produce a result. Swen et al 2023[157] found that physician adoption of pharmacogenetic recommendations was only 69.9% for a range genes including *CYP2C19*. If *CYP2C19* testing is introduced in the NHS it may need to be accompanied with training and education of staff on the benefits of targeted treatment, and systems in place to ensure that results are visible to those prescribing antiplatelet therapy, to realise the full value for money of testing.

Our survey of laboratories indicated that whilst facilities are available for *CYP2C19* testing, there would be capacity issues to incorporate routine testing into existing workflow. If laboratory testing is adopted then investment would be required to ensure sufficient capacity. An alternative option that we have not modelled is to consider performing the tests in local labs rather than sending to national laboratories.

The POCTs that we evaluated only detect some *CYP2C19* variants, whilst laboratory testing has the potential to test for more variants as research evolves on the impact of *CYP2C19* genetic variants on clopidogrel metabolism. It is also worth noting that if pharmacogenetic panel testing is introduced in the future to test for a range of genetic variants associated with adverse treatment reactions, then the benefits of specific *CYP2C19* testing in a TIA / ischaemic stroke population may be diminished.

The Genomadix Cube would require appropriate storage in a freezer which would require an investment in both freezers and space, if adopted.

CYP2C19 LOF is more prevalent in some populations than others, with particularly high prevalence in Asian populations. We found that testing was cost-effective (cost-saving and generating more QALYs than no-testing) across the range of prevalence observed for different ethnicities, although the benefits are greater in populations with higher prevalence of *CYP2C19* LOF. This should be kept in mind when considering adoption of routine testing for *CYP2C19* LOF.

7 DISCUSSION

7.1 Statement of principal findings

Our results suggest that *CYP2C19* testing followed by tailored treatment is likely to be effective and cost-effective in both adult populations modelled (non-minor ischaemic stroke and TIA/minor ischaemic stroke) providing cost-savings and increased QALYs compared with not testing. There was no evidence in children for any of the objectives.

Evidence identified for objectives 1 to 3 suggests that people with LOF alleles are more likely to experience a secondary vascular event and treatments with alternatives to clopidogrel may reduce this risk. Alternative treatments investigated included in the studies were short-term high dose clopidogrel (150mg) followed by long term aspirin alone, ticagrelor, aspirin, and triflusal. Some studies combined these either with an initial (up to 30 day) course of aspirin or with longer term aspirin. There were no studies of dipyridamole, one of the anti-platelets that is likely to be offered as an alternative to clopidogrel in the UK, if *CYP2C19* testing were to be introduced.

We only identified two small studies, both at high risk of bias, that evaluated a "test and treat" strategy (objective 1). This is the ideal study design to investigate the benefits of introducing genetic testing to identify *CYP2C19* LOF alleles. There was a suggestion that testing plus treating based on LOF allele status was associated with a reduced incidence of ischaemic stroke, TIA and a compositive outcome of secondary vascular events, but confidence intervals were wide and overlapped the null.

Objective 2 identified 7 studies investigating whether people who have LOF alleles have a reduced risk of secondary vascular occlusive events if treated with alternative antiplatelet therapies compared to treatment with clopidogrel. Four were judged at low risk of bias, three had concerns regarding the potential for bias due to missing data and lack of information on allocation concealment. There was evidence that ticagrelor was associated with a lower risk of secondary vascular events, including ischaemic stroke, than clopidogrel. One study suggested that ticagrelor was associated with an increased risk of any bleeding event; the other found no difference in the risk of bleeding with ticagrelor compared to clopidogrel. There was no statistical evidence for differences between antiplatelet treatment strategies for any of the other comparisons or bleeding outcomes.

Objective 3 identified 25 studies (20 cohort studies and 5 trials) that compared people with and without LOF alleles, all of whom were treated with clopidogrel (alone or combined with aspirin or other antiplatelet drugs) to see whether the risk of secondary vascular occlusive events differed between groups. Six studies were judged at high risk of bias due to loss to follow-up that could potentially be related to incidence of vascular events. There was strong evidence that people with LOF alleles treated with clopidogrel (or clopidogrel plus short-term aspirin) have a greater incidence of secondary vascular events (HR 1.72, 95% CI 1.43, 2.08), stroke (HR 1.46, 95% CI 1.09, 1.95) and ischaemic stroke (HR 1.99, 95% CI 1.49, 2.64) than those without LOF alleles. Meta-regression suggested that there was evidence

of a reduced effect of LOF alleles in patients given a loading dose of clopidogrel compared to those who were not; in patients taking clopidogrel plus long-term aspirin relative to those taking only clopidogrel or clopidogrel plus short-term aspirin; and in studies that included patients with stroke and TIA as primary events compared with only patients with stroke. The stratified analysis based on clopidogrel regimen suggested that there was no evidence of a difference in the risk of secondary vascular events between those taking clopidogrel plus aspirin (HR 0.92; 95% CI 0.50, 1.74). However, the analyses based on loading dose of clopidogrel and clopidogrel regimen should be considered exploratory as analyses were not pre-specified. There was no difference in the risk of bleeding between those with and without LOF alleles (HR 0.98, 95% CI 0.68, 1.40).

Objective 4 identified 11 relevant studies evaluating the accuracy of the POCT in scope. All evaluated Spartan versions of the Genomadix Cube – either Spartan Cube, Spartan RX or Spartan FRX, against a laboratory reference standard – there were no studies on the accuracy of Genedrive. All studies were judged at low risk of bias. None of the studies were conducted in a stroke population. The Genomadix (Spartan) *CYP2C19* tests were found to have very high accuracy with summary estimates of sensitivity and specificity both 100% (95% CI 94, 100% for sensitivity and 99, 100% for specificity) for the detection of *2 and/or *3 LOF alleles. There were very few disagreements between the Genomadix Cube and laboratory based reference standards – 8 of the 11 studies reported perfect agreement between the tests. There was no suggestion of a difference across the three different versions of the test evaluated.

Objective 5 identified 17 relevant studies evaluating the technical performance of the two POCT in scope and conducted a survey of genomic laboratories to gather information on the technical performance of laboratory based tests. One study evaluated Genedrive and the others all evaluated Genomadix (Spartan) *CYP2C19* tests. Only one of the studies was conducted in a stroke population. There was substantial variation in estimates of test failure rate for Genomadix (Spartan) *CYP2C19* tests which ranged from 0.4% to 19% across studies – the true test failure rate is therefore unclear, but has the potential to be a large proportion of samples. Some studies provided data on the prevalence of the different variant forms of *CYP2C19,* however these were relatively small samples with little information on ethnicity which is a major factor determining the prevalence of LOF alleles. Studies reporting time to results for Genomadix (Spartan) *CYP2C19* tests were consistent with the estimate provided by the manufacturer (64 mins) – most studies reported that time from buccal swab to results was around 1 hour, although two studies reported higher estimates of 90 mins and 90-120 mins. One study of Genedrive reported that it gives results in around 40 mins. Studies generally suggested that Genomadix (Spartan) *CYP2C19* tests were simple, user-friendly and can be conducted by staff who have received minimal training. Limitations highlighted include storage conditions (samples need to be frozen and stored between -15 and -80 degrees), only one sample can be genotyped at a time, and it only tests for *2, *3 and *17 alleles. The study that evaluated Genedrive, noted that the test is simple, portable, rapid and does not require analytes to be frozen, and tests for *2,

*3, *4, *8, and *17 alleles. One study estimated the cost per patient test at 225 Euros for Spartan (Genomadix) RX, but did not provide any information on how this estimate was reached. Genedrive and Genomadix provided information on the platform cost, assay cost, and cost of external control kits, which were used in our economic model.

The survey of genomic laboratory hubs had an excellent response rate with 8 of the 10 labs, including those in Northern Ireland, Scotland and Wales, to whom the survey was sent completing the survey. All but one of the labs reported that they had at least one form of sequencing technology and all had at least one form of targeted *CYP2C19* gene variant detection, most commonly PCR-based SNP genotyping assays using fluorescent reporter systems, such as TaqMan (ThermoFisher). Preferred technologies for performing *CYP2C19* testing varied across labs and included: next-generation sequencing (2 labs), MassARRAY(3 labs), LAMP (3 labs), PCR-based SNP genotyping assays using fluorescent reporter systems, such as TaqMan (ThermoFisher) and QuantStudio 12K Flex Real-Time PCR System or X9 Real-Time PCR System (1 lab). Resource requirements varied across labs, making it difficult to estimate the exact resources that would be required for *CYP2C19* testing, and this may vary according to the specific lab test that would be used. Costs per test varied from around £15 (MassARRAY, although another lab estimated this as £100) to £250 for Next-generation gene sequencing. Most labs reported that their preferred test could be performed by existing staff members with standard training or that the test was fully automated although one lab stated that their preferred test (QuantStudio 12K Flex Real-Time PCR System or X9 Real-Time PCR System) would be new to their lab and so training would be required. Most labs reported that it was difficult to estimate the proportion of samples that would not return a valid result, but most expected this to be <1%. Testing capacity and turnaround times also varied across labs. Current testing capacity ranged from 0 to 200 tests per week, and turnaround time ranged from 24-72 hours up to 1-2 weeks, although 5 laboratories estimate that this would be between 72 hours and 1 week. Most laboratories reported that additional testing capacity and faster turnaround time would be possible with additional resources – including staff, laboratory space, increased automation, and equipment. Most labs also confirmed that the test could be performed in local laboratories although additional staff training and/or equipment would be needed. The major barriers to implementing *CYP2C19* testing were the scale of the predicted activity and current capacity (4 labs), with one highlighting that they do not currently perform any tests of this scale in the NHS and so do not have the infrastructure for this. Most labs stated that whilst it should be possible to implement POCT tests within the laboratory workflow, this may not be the most efficient process for the number of samples that would need to be tested.

We developed a decision analytic model to evaluate the cost-effectiveness of POCT and laboratory tests compared with no testing (Objective 6), in two populations: (i) TIA / minor ischaemic stroke, and (ii) non-minor ischaemic stroke; to reflect the different treatment pathways and event rates in these populations. Results were also obtained for a mixed ischaemic stroke and TIA population. We modelled patients moving between 5 health states: no recurrent stroke, minor stroke, major bleed or ICH, moderate stroke, and severe

stroke, with a mortality rate depending on health state. A decision tree was used to capture short-term (90 day) outcomes, and a Markov model with a 1-year cycle captured outcomes beyond 90days over a patient's life-time.

In our base-case for all populations we found that laboratory and point of care *CYP2C19* testing strategies dominated no testing, i.e. *CYP2C19* testing generated more quality adjusted life-years (QALYs) and lower costs compared with no testing. The laboratory test and point of care tests gave very similar mean QALYs, and so we compare the tests in terms expected net monetary benefit at a willingness to pay of £20,000 per QALY from our probabilistic analysis, preferring tests with the highest expected net monetary benefit. In the non-minor ischaemic stroke population the expected net monetary benefits were £6,230, £6,214, and £6,138 for Genedrive, the laboratory test, and the Genomadix Cube *CYP2C19* Test respectively. In the TIA / minor stroke population the expected net monetary benefits were £2,932, £2,802, and £2,829 for Genedrive, the laboratory test, and the Genomadix Cube *CYP2C19* Test respectively. Net monetary benefit is greatest in the non-minor ischaemic stroke population due to the higher event rate in the long-term, and hence greater benefit of appropriate treatment in this population. In the combined TIA / ischaemic stroke population the expected net monetary benefits were £5,211, £5,163, and £5,119 for Genedrive, the laboratory test, and the Genomadix Cube *CYP2C19* Test respectively. In all populations expected net monetary benefit is similar, suggesting little difference between the tests, but it is slightly higher for Genedrive in both populations. The next highest expected net benefit is for the laboratory test in the non-minor ischaemic stroke population, and for the Genomadix Cube *CYP2C19* Test in the TIA / minor stroke population.

It should be noted that due to limited information on Genedrive, we assumed all model inputs were the same as for the Genomadix Cube *CYP2C19* Tests with the exception of the costs, which is why Genedrive appears the more cost-effective of the POCTs. The results for Genedrive should therefore be considered exploratory only and this finding may change as further evidence on the accuracy and performance of Genedrive becomes available. We conducted a threshold analysis for the diagnostic test accuracy of Genedrive, reducing sensitivity and specificity (but keeping them equal). We found that the Genedrive system was found to be cost-effective at sensitivity and specificity equal and over 99% vs the Genomadix cube, equal and over 98% vs the lab test.

The model inputs that have the biggest impact on the cost-effectiveness results were the costs of the different stroke states, and the treatment effects for stroke in patients with *CYP2C19* LOF, and the hazard ratio for major bleed / ICH on aspirin relative to clopidogrel. However, varying these parameters did not change the overall finding that *CYP2C19* testing is cost-saving and generates more QALYs compared with no-testing. Accounting for uncertainty in a probabilistic analysis gave very similar results. Cost-effectiveness acceptability curves show that there is a high probability that one of the testing strategies is the most cost-effective, with Genedrive having the highest probability of being cost-

effective. The laboratory test has a low probability of being cost-effective in the TIA / minor stroke population due to the delay in receiving results.
The overall finding that *CYP2C19* testing is cost-saving and generates more QALYs compared with no-testing was robust in all the scenarios that we explored. The scenarios where *CYP2C19* testing was most cost-effective were when prevalence of *CYP2C19* LOF was high and for younger cohorts of patients. The scenarios where *CYP2C19* testing was least cost-effective were when we assumed that only 69.9% of LOF patients actually receive alternative treatment, and when the alternative treatment was ticagrelor. However, *CYP2C19* testing was still cost-saving but with a smaller increase in QALYs.

7.2 Strengths and limitations of the assessment

Our systematic review followed published guidance on the conduct of systematic reviews and is reported according to PRISMA-2020 guidance [32] and PRISMA-DTA guidance, [33] making our review processes transparent and robust. The protocol was pre-registered on the PROSPERO database (CRD42022357661) and published on the NICE website for this appraisal.[172] Following protocol registration, we increased the scope of studies eligible for inclusion for objectives 4 or 5, from diagnostic cohort studies (only) to include primary studies of any design. This increased the scope of potentially eligible studies and we consider it a strength of the work.

We conducted extensive literature searches designed to maximise retrieval of relevant studies and did not apply any language or date restrictions to these searches. We included attempts to locate ongoing and unpublished studies through searches of trial registries and screening of the manufacturers' submissions. We defined clear, unambiguous inclusion criteria and documented reasons for exclusion of studies at full text review and for all studies included in the manufactures submissions to ensure transparency in how we applied our inclusion criteria. We conducted a formal assessment of the risk of bias of included studies using the RoB 2 tool for RCTs, [36] the ROBINS-E tool for observational studies,[37] and the QUADAS-2 tool for diagnostic test accuracy studies.[38] These tools are the most robust tools available for these study designs with a clear focus on the risk of bias within each study. We modified QUADAS-2 to exclude the assessment of applicability; the other tools do not include an applicability assessment. Instead of a formal assessment of applicability, we extracted details on information that could result in variation across studies and considered this in our synthesis of results. All stages of the review process involved at least two reviewers to minimise the risk of bias or error in the review. Our synthesis included a meta-analysis for objectives 2, 3 and 4. For objective 2, different studies evaluated different intervention comparisons. We investigated the potential to carry out an NMA, but the networks either did not connect, or were a simple chain of evidence, and so a NMA would give the same results as an analysis of each comparison pair separately. Most comparisons were made by a single study except for ticagrelor vs clopidogrel and aspirin vs clopidogrel where we pooled the results from two studies.

For objective 3, where all studies compared outcomes in those with and without LOF alleles taking clopidogrel, there was some evidence of heterogeneity which we explored using meta-regression. However, we did not pre-specify all variables that we later considered potential sources of heterogeneity; analyses based on these variables should be considered exploratory and interpreted with caution. There were too few studies to investigate differences across studies for objective 1 and 2. For objective 4, all studies reported consistently high estimates of the accuracy of Genomadix (Spartan) *CYP2C19* tests, and so there was no evidence of heterogeneity in outcomes across studies. We formally assessed the potential for publication bias/small study effects for objective 3, and found no evidence to suggest the presence of publication bias. We did not include a formal assessment of publication bias due to the small number of included studies for objectives 1 and 2, and for objective 4 due to the difficulties in assessing publication bias for diagnostic test accuracy studies where there is no clear threshold for "significance".

We assessed the accuracy of the two POCT in scope in relation to laboratory tests which were considered the reference standard for this appraisal, this assumes that they have 100% accuracy. Although there are a variety of laboratory tests available there is no clear "reference standard" amongst these, so it would not be possible to specify a reference standard for evaluation of laboratory based tests. Instead, we assumed that they all have 100% accuracy, following advice from our clinical experts. Given that we found the Genomadix (Spartan) *CYP2C19* tests to have close to 100% accuracy (objective 4), this assumption appears reasonable. For objective 5, we reviewed studies of the technical performance for our two POCT tests; however for laboratory based tests we took a different approach conducting a survey of genomic laboratories to obtain information on the technical performance of laboratory based tests. We considered that data obtained by a survey would be specific to our research question, provide information of direct relevance to the NHS and provide the most up to date data; which would be unlikely to be the case had we reviewed the existing literature on these tests. The survey of the genomic laboratories had a very high response rate with 8 of the 10 labs invited to participate completing the survey.
Whilst there have been previous economic evaluations of the cost-effectiveness of *CYP2C19* testing for targeted anti-platelet treatment for patients following a TIA or ischaemic stroke, [101] [102] [103] [104] there has only been one previous model in a UK population which compared Genedrive vs no testing. [101] Our model has a similar structure to that of Wright et al (2022) [101], but we model stroke severity state rather than number of strokes experienced, and have used more recent evidence sources as inputs to our model. Our conclusions are in line with those found by Wright et al (2022) [101] for Genedrive, but our model also includes the Genomadix Cube *CYP2C19* test and laboratory testing options.

We made a range of assumptions in our model (objective 6), but our scenario analyses suggest that the main conclusion that *CYP2C19* testing is cost-saving and generates additional QALYs was robust to these assumptions. The different testing strategies had similar QALYs under our model assumptions, and choice between them is largely one of

cost-minimisation and ease of implementation. To estimate per test costs, we needed to assume a life-time of the devices which was based on estimates from Genedrive, Genomadix, and an assumption for the lab-test. Some costs were excluded because they become negligible when evaluated per test, including freezers to store the Genomadix Cube *CYP2C19* test, and staff training costs, and changes to processes to ensure results are recorded in patient records. However, these would represent an up-front investment if testing is adopted in the NHS. Our survey suggested different laboratories would use different platforms; we used the Agena MassARRAY iPlex as a typical platform when estimating lab-test costs, but this cost is likely to vary across laboratories. We conducted a threshold analysis for the cost of the lab-test which provides lab-costs below which the lab-test is cost-effective compared with each POCT and for each population.

In our base case we assumed that all patients with a LOF test result would receive targeted treatment, however Swen et al 2023[157] found that physician adoption of pharmacogenetic recommendations was only 69.9% for a range of genes including *CYP2C19*. Our scenario analysis suggests that although costs increase and QALYs decrease as uptake falls, *CYP2C19* is still cost-saving and generates more QALYs compared with no-testing.

We assumed that the alternative treatment that *CYP2C19* LOF patients would receive is dipyridamole plus aspirin, and that the efficacy of dipyridamole plus aspirin does not depend on *CYP2C19* LOF status. This assumption was necessary because we did not identify any studies of dipyridamole plus aspirin in patients with *CYP2C19* LOF in our reviews and instead used evidence from the PRoFESS RCT. [156] The CHANCE study[51] found that the efficacy of aspirin varied with *CYP2C19* LOF status, and so it may be the case that dipyridamole plus aspirin also depends on *CYP2C19* LOF status. Further research would be required to assess this.

In the absence of test-and-treat studies, we used RCTs comparing treatments for LOF and NoLOF patients where these were available. For some treatments (aspirin, ticagrelor) relative to clopidogrel we had information for LOF patients, but no information for NoLOF patients. In these cases we used the result for LOF patients and then applied a HR for clopidogrel for LOF vs NoLOF estimated from the clinical review (objective 3). The results were not found to be sensitive to changes in this assumption.

We included treatment discontinuation due to treatment-related adverse events including major bleeds / ICH. It was assumed that in all cases patients would switch to low-dose aspirin following treatment discontinuation. If patients taking clopidogrel would instead switch to dipyridamole plus aspirin this may change the cost-effectiveness results, because dipyridamole plus aspirin is more effective at preventing future strokes than aspirin. However dipyridamole plus aspirin also has a high risk of bleeding events, so it is not clear how this would change the results.

Some patients may not take aspirin either due to drug sensitivity or patient or physician choice, and for these patients who have a *CYP2C19* LOF variant the alternative treatment is likely to be dipyridamole monotherapy. We did not explicitly model these patients, but the benefits of testing is likely to be reduced for these patients due to lower efficacy of dipyridamole monotherapy relative to dipyridamole plus aspirin.[127]

We incorporated the impact of stroke on carers by applying a utility decrement for carers of patients who had a moderate or major stroke (1 carer per patient). We assumed that patients do not require a carer following a minor stroke or TIA. Applying the carer utility decrement to patients in the major stroke state led to negative contributions to QALYs, which we felt was reasonable given the very low quality of life for patients who have had a major stroke.

For all objectives, we took a pragmatic approach where the presence of LOF alleles was considered to be the presence of at least one *2 or *3 LOF allele – these are the two most common LOF alleles, although the prevalence of *3 (0.3%) is much lower than the prevalence of *2 (16%). Genomadix Cube only detects these LOF alleles; Genedrive also detects *4 and *8, the prevalence of these is very low (0.2% and 0.1% respectively). Both tests are also able to identify the *17 allele, which is associated with increased function, we did not investigate how this could have impacted on outcomes (objective 1 to 3) or on the accuracy of the test (objective 4). Laboratory tests could in principle detect all LOF alleles. There has been some suggestion that having one LOF allele and one increased function allele (e.g. *2/*17 or *17/*3) could in effect cancel each other out and lead to normal function, but there is little evidence to support this.[14] It would be possible to offer alternative treatments to rapid metabolisers, those with one normal function allele and one increased function allele (e.g. *1/*17) or ultrarapid metabolisers, those with two LOF alleles (*17/*17). There is also the potential that having two LOF alleles (e.g. *2/*2 or *2/*3) could lead to poorer metabolism of clopidogrel than having only one LOF allele (e.g. *2/*1 or *1/*2). Whilst some studies included in the review did classify participants into normal (no LOF alleles), intermediate (one LOF allele) and poor (two LOF alleles), in these situation we combined data across categories to dichotomise into normal and poor (intermediate and poor combined) metabolisers. For example, one of the studies included for objective 1 applied different treatments for those carrying no LOF alleles, one LOF allele and two LOF alleles. There is potential for considerable complexity in how treatment is tailored based on *CYP2C19 testing*. In practice a similar pragmatic approach to the approach that we have taken is most likely to be adopted where individuals are dichotomised into low and normal metabolisers. For example, although the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidance[14] classifies people into five metaboliser categories, treatment is dichotomised so that standard treatment with clopidogrel is recommended for ultrarapid (2 increased function alleles), rapid (1 increased function alleles and 1 normal function allele) and normal metabolisers (2 normal function alleles); alternative treatment is recommended for poor (2 LOF alleles) or intermediate metabolisers (1 LOF allele, 1 normal function allele).[14] A related limitation is that some studies only evaluated the *2 LOF allele and did

not look for the presence of *3 mutations. Given the very low prevalence of *3 in most populations this is unlikely to have had a substantial impact on results.

Our review and model focused on evaluation of the accuracy of POCT tests against a laboratory reference standard. It could also be of interest to compare the accuracy of both POCT and laboratory *CYP2C19* tests (genotype tests) to P2Y12-pathway specific platelet function tests (phenotype test) as a reference standard, or to consider the potential utility of these tests as an alternative to genetic testing. Platelet function testing of blood samples can assess the response to antiplatelet medication and give information on whether the phenotype (in this case clopidogrel resistance) is encoded by the gene is expressed. These tests must be performed whilst a patient is taking clopidogrel. This was considered as part of the scoping process for this appraisal but it was determined that this was not in scope. Such testing is not currently in use in the NHS, and results can be difficult to interpret and are affected by factors other than the genotype alone, for example, a person's size.[173] Whilst such tests would potentially have a benefit in that they can predict response to clopidogrel based on both genetic and environmental factors, the prognostic value and clinical utility of platelet reactivity testing is still unclear.[174] Further, the need for patients to have started clopidogrel testing for these tests to be used, limits their potential usefulness within the setting of this appraisal.

There were a number of limitations in the evidence base. The ideal study to evaluate the potential impact of a new diagnostic test is an RCT where participants are randomised to either be tested and treated accordingly or to not test and receive standard care. We only identified two "test and treat" studies however neither of these were randomised and both appeared underpowered to detect differences in secondary vascular events between groups. We therefore needed to draw on less robust types of evidence to determine whether people with LOF alleles have better outcomes if treated with alternative anti-platelet drugs. There was also very little data for objective 2 which looked at whether people with LOF alleles had better outcomes when treated with alternative antiplatelet drugs compared to treatment with clopidogrel. A major limitation for our review was that none of the studies for objective 1 or 2 evaluated dipyridamole + aspirin, the most likely alternative treatment to clopidogrel that would be offered in the NHS. However, aspirin alone may potentially be considered as an alternative treatment option in the NHS, and we did identify two studies comparing clopidogrel plus aspirin for the first 21/30 days with aspirin alone. These studies suggested there was no difference in the risk of secondary adverse events between those taking clopidogrel plus aspirin and long-term aspirin alone, suggesting that aspirin alone may be an appropriate treatment option. Furthermore our scenario analysis found that test and treat with aspirin as an alternative treatment was cost-saving and generated more QALYs compared with no-test, although the cost-savings and QALY benefits were not as great as when the alternative treatment was dipyridamole plus aspirin. Whilst there was evidence that ticagrelor may reduce secondary vascular events compared to clopidogrel in those with LOF alleles who have had a stroke, this is not currently licensed for stroke patients in the UK. One study also suggested an increased risk

of bleeding with ticagrelor compared to clopidogrel, although a second study reported no difference in bleeding risk. We ran a scenario analysis using ticagrelor as an alternative treatment for LOF patients, and found that *CYP2C19* testing was still cost saving and gained QALYs, but that these were less than for dipyridamole plus aspirin as the alternative treatment. Triflusal was evaluated in two studies – this is not currently a realistic treatment option as it is unavailable in the UK.

7.3 Uncertainties

Our systematic reviews and economic modelling have identified several areas where uncertainties remain. As highlighted above, for this appraisal, we dichotomised into poor and normal metabolisers based on the presence of at least one *2 or *3 LOF allele. All studies that evaluated the accuracy of POCT evaluated their concordance with a laboratory based reference standard that was testing for the presence or absence of the same LOF alleles - *2 and/or *3. It is unclear how accuracy would have differed had the laboratory based reference standard tested for the presence of any LOF allele. As *2 and *3 are the most common LOF alleles, this may have had limited impact on findings. There were insufficient data to consider the impact of testing for other LOF alleles, or to evaluate whether treatment should take a more complex approach with different categories based on different combinations of LOF, normal function and increased function alleles – there are up to five categories that could be considered for this, but the benefit of treating each of these metaboliser categories separately is unclear, and in particular how those with increased function alleles (e.g. *17) should be treated. It is also unclear exactly which alleles should be tested for, whilst some alleles such as *2, *3, *4 and *8 have been clearly linked to LOF, for others such as *9 and *10 the evidence based is still evolving and these are currently categories as “indeterminate” or “likely LOF”.[14] These alleles are also much rarer than some of the other alleles and so the benefit of testing for alleles beyond those most frequently associated with LOF is unclear. This is of particular importance when considering which test would be most appropriate to implement within the NHS. Genomadix Cube only detects *2, *3 and *17, Genedrive detect *4 and *8 in addition to these alleles. There is more flexibility in which tests can be targeted by laboratory based tests. Some, such as Sanger sequencing, will detect all variants, others will target specific LOF alleles, although probes can potentially be developed for all alleles of interest.

There have been a number of other reviews looking at the role of *CYP2C19* testing to guide antiplatelet treatment. The most recent of these was the review by McDermott et al. published in 2022.[175] This non-systematic review included studies describing the interaction between *CYP2C19* genotype and clinical outcomes following ischaemic stroke or TIA. The authors concluded that there was good evidence that *CYP2C19* LOF allele carriers of Han-Chinese ancestry have increased risk of further vascular events when treated with clopidogrel. This is in line with our findings, and although the majority of our studies (13/25 for objective 3) were from China, we found that results from these studies was consistent with results from studies conducted in other settings. Most of the observed heterogeneity across studies for objective 3 was explained by whether a loading dose of clopidogrel was

applied and by whether clopidogrel was given alone or in combination with aspirin with a smaller difference seen between LOF and NoLOF carriers when a loading dose was applied and clopidogrel given in combination with aspirin. The McDermott review did not carry out a formal statistical synthesis of results across studies and so was not able to carry out the formal investigation of differences across studies that we conducted as part of our review. It also did not differentiate between the different objectives of the studies in the same way that we have done, which allowed us to draw conclusions both on whether people with LOF alleles have poorer outcomes when treated with clopidogrel compared to those without LOF alleles, and on whether those with LOF alleles have a reduced risk of secondary ischaemic events when treated with an alternative to clopidogrel.

Although our review showed consistently high estimates of accuracy across the included studies, a number of questions remain regarding the accuracy and technical performance of *CYP2C19* POCT. These included: accuracy of Genomadix Cube compared to Spartan versions of the test; accuracy of Genedrive; accuracy in stroke patients; and test failure rate.

All the evaluations that contributed data on Genomadix Cube were actually Spartan versions of the test. Two of these evaluated Spartan Cube, this appears equivalent to Genomadix Cube and was renamed when Spartan Bioscience's assets were acquired by Genomadix. Other studies evaluated Spartan RX and one study evaluated FRX. The difference between the RX and FRX versions is unclear, but it appears that FRX is either an earlier version of the RX or that the test was renamed – the study of the FRX version was earlier than other evaluations. Genomadix as part of their submission to NICE explained that "*the original Spartan RX CYP2C19 System and the subsequent Genomadix Cube CYP2C19 system both test for the same CYP2C19 alleles; however, the Genomadix Cube test is not a newer version of the Spartan RX test. Significant differences include the mechanisms used to heat and cool the samples, the storage, use, and stability of the specimens on the swab, the optical system, and the test workflow. A direct comparison of the performance of the two systems is not available*". A related NICE methods innovation briefing on Spartan Cube explained that this was released as a successor to Spartan RX and they differ in that *"the 3 reaction tubes are integrated into a single test cartridge, the swabs and test cartridges are packaged separately, and the DNA analyser device is smaller."*[176] It is therefore unclear whether the performance of the Genomadix Cube can be considered equivalent to that of the Spartan RX, however, there was no suggestion of a difference in performance between the two studies that evaluated Spartan Cube and those that evaluated Spartan RX. Further studies that directly compare the two tests, are required to confirm this. T[redacted]

The only data available on Genedrive was one small unpublished early evaluation of the test that did not report data on accuracy. The manufacturer confirmed that there were no studies currently ongoing, but these were planned to start from the first quarter of 2023; no details were provided on what these studies would evaluate. They also highlighted that the Genedrive System has been reviewed by NICE for an alternative assay - the Genedrive MT-RNR1 ID Kit, under the MIB290[20] and this is also currently under review as an Early Value Assessment, currently in progress.[20] Genedrive offers some potential benefits compared to Genomadix Cube: it is slightly quicker (40 mins vs 60 mins), cheaper (we estimated the cost at £104 per test for Genedrive and £197 for Genomadix), tests for a greater number of alleles - *8 and *35 in addition to the *2, *3 and *17 that are detected by Genomadix Cube. This is may be of particular value in ethnicities such as those with Asian and Jewish origins where these alleles are found at higher frequencies. A further benefit of this test is that it does not require the frozen storage of test kits that is required for Genomadix Cube. It also allows patient data to be uploaded directly into patient records, where data are only stored locally with Genomadix Cube. In the absence of data on accuracy and performance of Genedrive, we assumed these would be the same as for the Genomadix Cube in our economic model, which meant that Genedrive was slightly cheaper with the same benefits as Genomadix. However, these findings are uncertain and may change when data on the accuracy and performance of Genedrive become available.

None of the studies that evaluated the accuracy of the POCT evaluated these tests in our population of interest – people who have had an ischaemic stroke or TIA. Whilst for many tests the population in which the test is conducted can lead to substantial variation in estimates of accuracy,[177] we consider this less likely to be the case for genetic tests. With genetic markers the LOF alleles are either present or absent and will not be affected by other factors that could influence test performance such as comorbidities, age, sex, setting and disease prevalence.

There was substantial variation in test failure rate across studies – this ranged from 0.4% to 18.9% for studies of Genomadix (Spartan) *CYP2C19* tests. Reasons for this substantial variation were unclear and so it is difficult to determine the true failure rate. There was no information on the failure rate of Genedrive. Most laboratories expected their favoured laboratory test for *CYP2C19* testing to have a failure rate of <1%. Failure rate could be an important factor in deciding which *CYP2C19* test to implement and so further, accurate data is required on failure rate for all tests, both POCT and laboratory based. Another factor that could influence which test should be recommended for *CYP2C19* testing is how test results are recorded in patient records and communicated across settings. Genedrive allows results to be added directly to patient records; this is not possible with the Genomadix test. It is important that the results of *CYP2C19* testing are not just available at the point of testing, but are recorded in the patient's record for future reference in case they may need to be prescribed clopidogrel again in the future. It is also important that test results are not lost as patients are discharged from hospital after the test is requested but before results are available. This would reduce the uptake of appropriate targeted treatment, which we found

led to a large reduction in the cost savings and QALY benefits of testing in our scenario analyses.

There are proposals to implement pre-emptive panel testing across the NHS. A recent multi-national cluster randomised trial of a 12-gene pharmacogenetic panel found that guided treatment based on this panel significantly reduced the incidence of clinically relevant adverse drug reactions and was feasible across different European health-care systems organisation and settings, including the UK.[157] Panel testing may initially only be introduced in some areas as a pilot scheme but longer term could become standard - this may mean *CYP2C19* status is already available for certain patients. A recent report on "Personalised Prescribing" by the Royal College of Physicians and British Pharmacological Society produced a set of recommendations for embedding pharmacogenomics, including *CYPC19* testing, in the NHS.[178] It is currently unclear whether and when this will be commissioned in NHS care, but a pilot project, the PROGRESS project, is currently underway.[179] If such a programme were implemented, then it may reduce the appropriateness of specific *CYP2C19* testing. However, a potential limitation in implementing any form of pharmacogenetic testing is the potential unwillingness of clinicians to act upon pharmacogenetic test results. The multi-national trial of the 12-gene panel found that up to 30% of clinicians did not accept the recommendation of a treatment change based on the genetic test.[157]

We did not identify any studies comparing test and treat strategies with dipyridamole + aspirin as the alternative treatment, which is the most likely alternative treatment to clopidogrel that would be offered in the NHS. Nor did we identify any studies comparing the efficacy of dipyridamole + aspirin compared with clopidogrel according to *CYP2C19* LOF status. In order to include dipyridamole + aspirin as the alternative treatment in our model we assumed that the efficacy of dipyridamole + aspirin does not depend on *CYP2C19* LOF status. There is therefore uncertainty as to the costs and benefits of using dipyridamole + aspirin as the alternative treatment. Note however, that *CYP2C19* testing was still found to be cost-saving and have increased QALYs compared to no-testing in our scenarios where aspirin or ticagrelor were the alternative treatment. This suggests that a test and treat strategy with dipyridamole + aspirin as the alternative treatment is very likely to be cost-effective, regardless of the exact relative treatment effects by *CYP2C19* LOF status.

Genetic variability is not the only factor to affect the efficacy of clopidogrel. Other factors that may be associated with clopidogrel efficacy include other drugs, for example PPIs may inhibit clopidogrel,[2] smoking status, weight, diabetes, hypertension[13] and the influence of other rare genetic variants.

We did not find any evidence in a paediatric population in our searches, and did not have sufficient evidence to include children in our economic model. However, in children, aspirin rather than clopidogrel is currently recommended to prevent recurrence of stroke, and so in that case there would not be any benefit of testing for *CYP2C19* LOF status. We ran a

scenario analysis for a cohort of younger adults at index TIA / ischaemic stroke and found that the cost-saving and quality of life benefits improved. This suggests that if clopidogrel were to be considered for a child then *CYP2C19* testing is likely to be cost-effective.

7.4. Equality, Diversity and Inclusion

Our research was based on existing literature and so we had no control over the participants enrolled. We were broad in our inclusion criteria such that studies from any country and in any language of publication were eligible. *CYP2C19* LOF is more prevalent in some populations than others, and is particularly high in Asian populations. We explored ethnicity as a potential source of heterogeneity in our analyses for objective 3, where sufficient data were available to do so, but found that overall there was no association between ethnicity and how those with and without LOF alleles respond to clopidogrel. Our economic analysis found testing was cost-effective for the range of prevalence observed across ethnicities, suggesting that this would not introduce inequity.

Our survey received a broad response from laboratories across England, Wales, Scotland and Northern Ireland providing the full UK perspective on the potential for providing *CYP2C19* testing.

Our team included researchers with a broad range of experience and expertise. The lead authors are junior researchers within Bristol TAG, who were given the opportunity to lead on the writing of this report to help develop their research skills and portfolio. They were supported by the two senior authors, Professors and Co-Directors of Bristol TAG, who provided advice and mentorship to the junior researchers leading on the reviews and health economic modelling. The team included those with expertise in systematic reviews, health economics, and medical statistics. We also included two clinical experts from the South West Genomic Medicine Genomic Medicine Service Alliance who provided clinical expertise, particularly around genetic testing. Where needed, we were able to draw on the broader expertise of the seven specialist Diagnostic Appraisal Committee (DAC) member.

7.5. Patient and Public Involvement

Our team included two patient representatives who have lived experience of stroke. The patients attended a meeting near the beginning of the project with the full team to share their experience of stroke and gave suggestions of important outcomes to be considered in the economic model. They also helped to ensure the findings of the review are comprehensible by giving feedback on the plain language summary.

8 CONCLUSIONS

8.1 Implications for service provision

Our results suggest that *CYP2C19* testing followed by tailored treatment is likely to be effective and cost-effective in both populations modelled (non-minor ischaemic stroke and TIA/minor ischaemic stroke) providing cost-savings and increased QALYs compared with not testing. There was very little difference in cost-effectiveness estimates between the three tests, although Genedrive had slightly higher expected net monetary benefit, followed by laboratory tests then the Genomadix Cube. The choice of test to be adopted is therefore likely to be based on practical considerations as to which test would be most appropriate and practical within an NHS setting. Our survey of laboratories suggested that, given the high volume of testing required, it may be more appropriate to implement testing through the genomic labs, or in local labs to allow batching of tests; POCT are only able to run a single test at a time. However, POCT have the potential advantage of providing results more quickly (<1 hour compared to around 1 week), this ensures appropriate treatment can be started as soon as possible and reduces the risk of results not being actioned if the patient has been discharged from secondary care. There are logistical difficulties to implementing POCT in stroke care. The Genomadix Cube would require appropriate storage in a freezer which would require an investment in both freezers and space. Considerations on how results would be integrated into patient's medical records both for future prescribing where clopidogrel may be considered, but also on the impact of *CYP2C19* variants on a wide range of other medicines. Genedrive is able to add results directly to patient records; this is not currently possible for Genomadix Cube. Our survey of laboratories indicated that whilst facilities are available for *CYP2C19* testing, there would be capacity issues to incorporate routine testing into existing workflow. There was also substantial variation in preferred laboratory test for *CYP2C19* testing. If laboratory testing is adopted, this would require investment in equipment, staff, laboratory space, and automation of processes.

There is some suggestion of reluctance by clinicians to act on pharmacogenetic variations. Implementation of *CYP2C19* testing would therefore need to be accompanied by training and education of staff on the benefits of targeted treatment, to ensure that results are acted upon. There is also a question of what should happen to those already on clopidogrel treatment. Consideration needs to be given as to how such patients should be treated – it may be appropriate to test all those currently on clopidogrel treatment and adapt treatment as necessary.

As discussed above, there are proposals for introducing pharmacogenetic panel testing to test for a range of genetic variants associated with adverse treatment reactions. It is currently unclear when and if such programmes would be introduced in the NHS, but a pilot programme is currently in process. If such panel testing is likely to be introduced into the NHS, then the benefits of specific *CYP2C19* testing in a TIA/ischaemic stroke population at this point need to be carefully considered.

8.2 Suggested research priorities

The section on uncertainties (section 7.3) highlights a number of areas where further research is needed. A clear gap in the evidence is on the clinical effectiveness of alternative antiplatelet strategies, in particular on dipyridamole plus aspirin, in a stroke population with LOF alleles. Further studies are required to determine the true effectiveness of dipyridamole plus aspirin in this population. The ideal study would randomised patients to be tested and treated based on LOF status – those with LOF alleles would receive dipyridamole plus aspirin, those without would receive clopidogrel. Outcomes would then be compared across groups.

There is a lack of data on Genedrive. For the health economic model we assumed that accuracy and test failure rate would be equivalent to that of Genomadix Cube, however it is unclear how likely this is to be the case. Further test accuracy studies that also provide information on the technical performance of the test (e.g. test failure rate, cost, time to perform the test) are needed; Genedrive highlights that testing will be starting this quarter but details on what studies are proposed are not available. The true test failure rate of Genomadix Cube remains unclear; there was substantial variation in estimates of test failure rate. Further studies are required to determine what the test failure rate would be if the test were to be implemented into routine practice in the NHS.

The value of testing additional alleles beyond *2 and *3 is unclear, as is the clinical significance of the *17 LOF allele. Our review and economic model took a pragmatic approach where we dichotomised action based on testing such that those with at least one LOF allele were considered, however, it remains unclear whether this is the appropriate approach. Future studies should consider how those with *17 LOF allele respond to clopidogrel and whether those with two LOF alleles have worse outcomes than those with one LOF allele. This would inform whether the dichotomy used in our appraisal is the appropriate strategy to implement in practice.

9 Acknowledgements

We would like to thank the following specialist Diagnostic Appraisal Committee (DAC) members for clinical advice relating to this project: Dr Dagan Lonsdale (St George's, University Of London), Prof Albert Ferro (Kings College London), Dr Daniel Burrage (Whittington Health NHS Trust), Dr Alexander Doney (University Of Dundee), Dr Dheeraj Kalladka (Imperial College Healthcare NHS Trust), Mr Paresh Parmar (London North West University Healthcare NHS Trust), And Dr Salim Elyas (Royal Devon University Healthcare NHS Foundation Trust)

We would also like to thank:
Professor Katherine Payne and Dr Stuart Wright (University of Manchester) for discussions on their health economic model of CY219Y testing

Dr Cinzia Del Giovane (UniMore, Università degli Studi di Modena e Reggio Emilia) and Dr Irene Tramacere (Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta) for providing data from their Network Meta-Analysis of antiplatelets for secondary prevention in stroke / TIA patients.

Those that responded to our survey on behalf of each of the 5 regional genomic laboratory hubs (Central and South; East; North West; South East; and North East and Yorkshire) and the Scottish (NHS North Tayside), Welsh and Irish services.

Charlene Wisdom-Trew, Bristol TAG, for providing administrative support.

9.1 Contributions of authors

Catalina Lopez Manzano led the review of objectives 1-3. Eve Tomlinson led the review of objectives 4-5, contributed as second reviewer to objectives 1-3, and checked the literature searches. Chris Cooper designed and undertook the literature searches, acted as second reviewer for objectives 4 and 5 (including review of company submissions), and worked on the review of cost-effectiveness. Penny Whiting drafted the clinical effectiveness sections of the protocol, led the survey of laboratories, oversaw and contributed to the reviews of effectiveness (objectives 1-3) and accuracy (objectives 4-5). Hayley Jones provided statistical supervision for objectives 1-4. The clinical effectiveness section of the report was drafted by Catalina Lopez Manzano, Eve Tomlinson, Chris Cooper and Penny Whiting. Joe Carroll developed and coded the health economic model, produced all model results, and drafted the sections of the report describing the model, sensitivity and scenario analyses, and cost-effectiveness results. Ayman Sadek conducted the reviews of previous economic evaluations of *CYP2C19* testing for clopidogrel resistance and previous models of secondary prevention of recurrent stroke, reviewed evidence for model inputs, contributed to model validation, and drafted the cost-effectiveness review and model inputs sections of the report. Nicky Welton provided oversight of the cost-effectiveness analysis, contributing to model conceptualisation, protocol development, review of previous models, identification of inputs to the model, model validation, interpretation and discussion of results of the cost-

effectiveness analysis. Will Hollingworth contributed to model conceptualisation and protocol development. The cost-effectiveness section of the report was drafted by Joe Carroll, Ayman Sadek, and Nicky Welton.

Lorraine Rowsell and John Knight provided a patient perspective on the project and edited the plain language summary.

Andrew Mumford and Rachel Palmer provided clinical advice for the project, particularly on genetic testing.

All authors were involved in commenting on the final report. Penny Whiting is the senior author and guarantor.

9.2 Ethics Statement

The majority of the research included in this report is secondary research and as such did not require ethical approval. The survey of genomic laboratory hubs was shared with the Health Sciences Faculty Research Ethics Officers from the University of Bristol Research Ethics Committee to determine whether ethical approval was required. They determined that the survey constituted an audit of practice/service evaluation and so ethical review was not required.

9.3 Information Governance Statement

There were no personal data involved in the production of this report.

9.4 Data-sharing statement

All data extracted for the systematic review and the results of the risk of bias assessments are provided in full in the appendices to this report. The economic model will be shared upon reasonable request for academic collaboration.

10 REFERENCES

1. The National Institute for Health and Care Excellence (NICE). *Stroke and TIA: What causes stroke and TIA?* ; 2022. URL: https://cks.nice.org.uk/topics/stroke-tia/background-information/causes/ (Accessed July 2022).
2. Zerna C, Thomalla G, Campbell BCV, Rha JH, Hill MD. Current practice and future directions in the diagnosis and acute treatment of ischaemic stroke. *Lancet* 2018;**392**
3. The National Institute for Health and Care Excellence (NICE). *[NG128] Stroke and transient ischaemic attack in over 16s: diagnosis and initial management* 2022. URL: https://www.nice.org.uk/guidance/ng128/chapter/Context (Accessed July 2022).
4. Stroke Association. *Are you at risk of stroke?* URL: https://www.stroke.org.uk/what-is-stroke/are-you-at-risk-of-stroke (Accessed July 2022).
5. The King's Fund. *The health of people from ethnic minority groups in England* 2021. URL: https://www.kingsfund.org.uk/publications/health-people-ethnic-minority-groups-england (Accessed 13 July 2022).
6. Boysen G, Truelsen T. Prevention of recurrent stroke. *Neurological Sciences* 2000;**21**(2)
7. Hankey GJ. Impact of Treatment of People with Transient Ischaemic Attacks on Stroke Incidence and Public Health. *Cerebrovascular Diseases* 1996;**6(suppl 1)**
8. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *British Medical Journal* 2004;**328**(7435)
9. The National Institute for Health and Care Excellence (NICE). *[TA210] Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events*. 2010. URL: https://www.nice.org.uk/guidance/ta210/chapter/1-guidance (Accessed July 2022).
10. European Medicines Agency (EMA). *Plavix (Clopidogrel)*. URL: https://www.ema.europa.eu/en/medicines/human/EPAR/plavix (Accessed July 2022).
11. Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: A review of the evidence. *Journal of the American College of Cardiology* 2005;**45**(8)
12. Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G*, et al.* Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *Journal of the American College of Cardiology* 2008;**51**(3)
13. Feher G, Koltai K, Alkonyi B, Papp E, Keszthelyi Z, Kesmarky G*, et al.* Clopidogrel resistance: Role of body mass and concomitant medications. *International Journal of Cardiology* 2007;**120**(2)
14. Lee CR, Luzum JA, Sangkuhl K, Gammal RS, Sabatine MS, Stein CM*, et al.* Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update. *Clinical Pharmacology & Therapeutics* 2022; 10.1002/cpt.2526
15. Botton MR, Whirl-Carrillo M, Del Tredici AL, Sangkuhl K, Cavallari LH, Agúndez JAG*, et al.* PharmVar GeneFocus: CYP2C19. *Clinical Pharmacology & Therapeutics* 2021;**109**(2)
16. Pan Y, Chen W, Xu Y, Yi X, Han Y, Yang Q*, et al.* Genetic Polymorphisms and Clopidogrel Efficacy for Acute Ischemic Stroke or Transient Ischemic Attack: A Systematic Review and Meta-Analysis. *Circulation* 2017;**135**(1)
17. National Institute of Health. *dbSNP Reference SNP*. URL: https://www.ncbi.nlm.nih.gov/snp/ (Accessed February 2023).

18. PharmVar: Pharmacogene Variation Consortium. *CYP2C19*. URL: https://www.pharmvar.org/gene/CYP2C19 (Accessed February 2023).
19. Medicines and Healthcare products Regulatory Agency. *Management and use of IVD point of care test devices*; 2021. (Accessed July 2022) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/957967/Management_and_use_of_IVD_point_of_care_test_devices.pdf:
20. National Institute of Health and Care Excellence (NICE). *[GID-DG10057] Genedrive MT RNR1 ID Kit for detecting a genetic variant to guide antibiotic use and prevent hearing loss in babies: early value assessment*. 2023. URL: https://www.nice.org.uk/guidance/indevelopment/gid-dg10057 (Accessed February 2023).
21. National Institute of Health and Care Excellence (NICE). *Clopidogrel genotype testing after ischaemic stroke (provisional title): request for information (Genomadix)*. 2022 (Accessed July 2022).
22. Royal College of Physician. *National clinical guideline for stroke*; 2016. (Accessed July 2022) https://www.strokeaudit.org/SupportFiles/Documents/Guidelines/2016-National-Clinical-Guideline-for-Stroke-5t-(1).aspx:
23. Royal College of Paediatrics and Child Health (RCPCH). *Stroke in childhood: Clinical guideline for diagnosis, management and rehabilitation* 2021. URL: https://www.rcpch.ac.uk/sites/default/files/2021-02/Stroke%20guideline%2008.04.19%20updated%202021.pdf (Accessed January 2023).
24. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL*, et al.* Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *The Lancet* 2007;**369**(9558)
25. Dawson J, Merwick A, Webb A, Dennis M, Ferrari J, Fonseca AC*, et al.* European Stroke Organisation expedited recommendation for the use of short-term dual antiplatelet therapy early after minor stroke and high-risk TIA. *European Stroke Journal* 2021;**6**(2)
26. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D*, et al.* 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke* 2021;**52**(7)
27. The National Institute for Health and Care Excellence (NICE). *Stroke and TIA: Scenario: Secondary prevention following stroke and TIA*. 2022. URL: https://cks.nice.org.uk/topics/stroke-tia/management/secondary-prevention-following-stroke-tia/ (Accessed July 2022).
28. The National Institute for Health and Care Excellence (NICE). *[ID2689] Ticagrelor for preventing stroke after previous ischaemic stroke or high-risk transient ischaemic attack*. TBC. URL: https://www.nice.org.uk/guidance/indevelopment/gid-ta10663 (Accessed July 2022).
29. Centre for Reviews and Dissemination (CRD). *CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination.* York: University of York 2009. URL: https://wwwyorkacuk/media/crd/Systematic_Reviewspdf. (Accessed May 2022).
30. Bossuyt PM, Deeks JJ, Leeflang MM, Takwoingi Y, Flemyng E. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*. Oxford: Cochrane; 2022.
31. The National Institute for Health and Care Excellence (NICE). *Developing NICE guidelines: the manual* 2022. URL: https://www.nice.org.uk/process/pmg36/chapter/how-to-use-this-manual (Accessed July 2022).

32. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD*, et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *British Medical Journal* 2021;**372**
33. Sharifabadi AD, McInnes MDF, Bossuyt PMM. PRISMA-DTA: An Extension of PRISMA for Reporting of Diagnostic Test Accuracy Systematic Reviews. *Clinical Chemistry* 2018;**64**(6)
34. Cooper C, Dawson S, Peters J, Varley-Campbell J, Cockcroft E, Hendon J*, et al.* Revisiting the need for a literature search narrative: A brief methodological note. *Research Synthesis Methods* 2018;**9**(3)
35. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *Journal of Clinical Epidemiology* 2016;**75**
36. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I*, et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *British Medical Journal* 2019;**366**
37. ROBINS-E Development Group. *Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E)*. 2022. URL: https://www.riskofbias.info/welcome/robins-e-tool (Accessed September 2022).
38. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB*, et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine* 2011;**155**(8)
39. Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. *Network Meta-analysis for Comparative Effectiveness Research*. NJ: Wiley; 2018.
40. Langan D, Higgins JPT, Jackson D, Bowden J, Veroniki AA, Kontopantelis E*, et al.* A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. *Research Synthesis Methods* 2019;**10**(1)
41. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109)
42. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J*, et al.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**
43. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *Journal of Clinical Epidemiology* 2005;**58**(10)
44. Chu H, Cole SR. Bivariate meta-analysis of sensitivity and specificity with sparse data: a generalized linear mixed model approach (author reply). *Journal of Clinical Epidemiology* 2006;**59**(12)
45. Xia C, Zhang Z, He X, Liu J, Li X, Chang Q*, et al.* Correlation between CYP2C19 gene polymorphism and individualized medication in patients with ischemic stroke. [Chinese]. *Chinese Journal of Clinical Pharmacology and Therapeutics* 2021;**26(3)**
46. Lan H, Ying T, Xi-Hua S, Yi L. Anti-Platelet Therapy in Mild Cerebral Infarction Patients on the Basis of CYP2C19 Metabolizer Status. *Cell Transplantation* 2019;**28**(8)
47. Han SW, Kim YJ, Ahn SH, Seo WK, Yu S, Oh SH*, et al.* Effects of Triflusal and Clopidogrel on the Secondary Prevention of Stroke Based on Cytochrome P450 2C19 Genotyping. *Journal of Stroke* 2017;**19**(3)
48. Meschia JF, Walton RL, Farrugia LP, Ross OA, Ross OA, Elm JJ*, et al.* Efficacy of Clopidogrel for Prevention of Stroke Based on CYP2C19 Allele Status in the POINT Trial. *Stroke* 2020

49. Wang Y, Meng X, Wang A, Xie X, Pan Y, Johnston SC*, et al.* Ticagrelor versus Clopidogrel in CYP2C19 Loss-of-Function Carriers with Stroke or TIA. *New England Journal of Medicine* 2021;**385**(27)
50. Wu H, Song H, Dou L, Gao B, Pan Y, Dong M*, et al.* Effectiveness and safety of high dose clopidogrel plus aspirin in ischemic stroke patients with the single CYP2C19 loss-of-function allele: a randomized trial. *BMC Neurology* 2020;**20**(1)
51. Wang YL, Zhao XQ, Lin JX, Li H, Johnston SC, Lin Y*, et al.* Association Between CYP2C19 Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischemic Attack. *Journal of the American Medical Association* 2016;**316**(1)
52. Chen W, Lin Y, Meng X, Chen G, Wang Z, Wu J*, et al.* Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: Open label, blinded endpoint, randomised controlled phase II trial. *British Medical Journal* 2019;**365**
53. Yi X, Lin J, Zhou J, Wang Y, Huang R, Wang C. The secondary prevention of stroke according to cytochrome P450 2C19 genotype in patients with acute large-artery atherosclerosis stroke. *Oncotarget* 2018;**9**(25)
54. Xando Díaz Villamarín. *Polimorfismos cyp2c19 y abcb1 en el tratamiento antiagregante con clopidogrel en pacientes con enfermedad arterial periférica sometidos a angioplastia transluminal percutánea, ictus o accidente isquémico transitorio*: Universidad de Granada; 2018.
55. Fu H, Hu P, Ma C, Peng F, He Z. Association of clopidogrel high on-treatment reactivity with clinical outcomes and gene polymorphism in acute ischemic stroke patients: An observational study. *Medicine* 2020;**99**(15)
56. Fukuma K, Yamagami H, Ihara M, Tanaka T, Miyata T, Miyata S*, et al.* P2Y12 Reaction Units and Clinical Outcomes in Acute Large Artery Atherosclerotic Stroke: A Multicenter Prospective Study. *Journal of atherosclerosis and thrombosis* 2022;**05**
57. Hoh BL, Gong Y, McDonough CW, Waters MF, Royster AJ, Sheehan TO*, et al.* CYP2C19 and CES1 polymorphisms and efficacy of clopidogrel and aspirin dual antiplatelet therapy in patients with symptomatic intracranial atherosclerotic disease. *Journal of Neurosurgery* 2016;**124**(6)
58. Lin J, Mo Y, Cai, Mao D, Fu H, Wei D. CYP2C19 polymorphisms and clopidogrel efficacy in the secondary prevention of ischemic stroke: a retrospective observational study. *Annals of Palliative Medicine* 2021;**10**(12)
59. Liu G, Yang S, Chen S. The correlation between recurrent risk and CYP2C19 gene polymorphisms in patients with ischemic stroke treated with clopidogrel for prevention. *Medicine* 2020;**99**(11)
60. Lv H, Yang Z, Wu H, Liu M, Mao X, Liu X*, et al.* High On-Treatment Platelet Reactivity as Predictor of Long-term Clinical Outcomes in Stroke Patients with Antiplatelet Agents. *Translational Stroke Research* 2022;**13**(3)
61. McDonough CW, McClure LA, Mitchell BD, Gong Y, Horenstein RB, Lewis JP*, et al.* CYP2C19 metabolizer status and clopidogrel efficacy in the Secondary Prevention of Small Subcortical Strokes (SPS3) study. *Journal of the American Heart Association* 2015;**4**(6)
62. Ni G, Liang C, Liu K, Cao Y, Zhang H, Tian X*, et al.* The effects of CES1A2 and CYP2C19 polymorphisms on responsiveness to clopidogrel and clinical outcomes among Chinese patients with acute ischemic stroke. *International Journal of Clinical and Experimental Medicine* 2017;**10(2)**

63. Patel PD, Vimalathas P, Niu X, Shannon CN, Denny JC, Peterson JF*, et al.* CYP2C19 Loss-of-Function is Associated with Increased Risk of Ischemic Stroke after Transient Ischemic Attack in Intracranial Atherosclerotic Disease. *Journal of Stroke and Cerebrovascular Diseases* 2021;**30(2)**
64. Qiu LN, Sun Y, Wang L, Han RF, Xia XS, Liu J*, et al.* Influence of CYP2C19 polymorphisms on platelet reactivity and clinical outcomes in ischemic stroke patients treated with clopidogrel. *European Journal of Pharmacology* 2015;**747**
65. Sen HM, Silan F, Silan C, Degirmenci Y, Kamaran OHI. Effects of Cyp2c19 and P2y12 gene polymorphisms on clinical results of patients using clopidogrel after acute ischemic cerebrovascular disease. *Balkan Journal of Medical Genetics* 2014;**17(2)**
66. Spokoyny I, Barazangi N, Jaramillo V, Rose J, Chen C, Wong C*, et al.* Reduced clopidogrel metabolism in a multiethnic population: Prevalence and rates of recurrent cerebrovascular events. *Journal of Stroke and Cerebrovascular Diseases* 2014;**23(4)**
67. Sun W, Li Y, Li J, Zhang Z, Zhu W, Liu W*, et al.* Variant recurrent risk among stroke patients with different CYP2C19 phenotypes and treated with clopidogrel. *Platelets* 2015;**26**(6)
68. Tanaka T, Yamagami H, Ihara M, Miyata T, Miyata S, Hamasaki T*, et al.* Association of CYP2C19 Polymorphisms With Clopidogrel Reactivity and Clinical Outcomes in Chronic Ischemic Stroke. *Circulation Journal* 2019;**83**(6)
69. Tomek A, Mat'oska V, Frydmanova A, Magerova H, Sramek M, Paulasova-Schwabova J*, et al.* Impact of CYP2C19 Polymorphisms on Clinical Outcomes and Antiplatelet Potency of Clopidogrel in Caucasian Poststroke Survivors. *American Journal of Therapeutics* 2018;**25**(2)
70. Tornio A, Flynn R, Morant S, Velten E, Palmer CNA, MacDonald TM*, et al.* Investigating real-world clopidogrel pharmacogenetics in stroke using a bioresource linked to electronic medical records. *Clinical Therapeutics* 2017;**39**(1)
71. Wang Y, Cai H, Zhou G, Zhang Z, Liu X. Effect of CYP2C19*2 and *3 on clinical outcome in ischemic stroke patients treated with clopidogrel. *Journal of the Neurological Sciences* 2016;**369**
72. Yi X, Wang Y, Lin J, Cheng W, Zhou Q, Wang C. Interaction of CYP2C19, P2Y12, and GPIIIa Variants Associates with Efficacy of Clopidogrel and Adverse Events on Patients with Ischemic Stroke. *Clinical and Applied Thrombosis/Hemostasis* 2017;**23(7)**
73. Zhang J, Sun H, Ming T, Liu X, Cong Y, Li F*, et al.* Association between platelet function and recurrent ischemic vascular events after TIA and minor stroke. *International Journal of Clinical Pharmacology and Therapeutics* 2017;**55(10)**
74. Baudhuin LM, Train LJ, Goodman SG, Lane GE, Lennon RJ, Mathew V*, et al.* Point of care CYP2C19 genotyping after percutaneous coronary intervention. *Pharmacogenomics Journal* 2022;**22**
75. Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M*, et al.* Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. *Lancet* 2012;**379**(9827)
76. Spartan Bioscience Inc. 2020. Spartan Cube CYP2C19 Method Comparison Study. NCT04473586; URL: https://ClinicalTrials.gov/show/NCT04473586 (Accessed November 2022).
77. Spartan Bioscience Inc. 2020. Spartan Cube CYP2C19 Inter Laboratory Reproducibilty Study. NCT04473573; URL: https://ClinicalTrials.gov/show/NCT04473573 (Accessed November 2022).

78. Choi JL, Kim BR, Woo KS, Kim KH, Kim JM, Kim MH*, et al.* The diagnostic utility of the point-of-care CYP2C19 genotyping assay in patients with acute coronary syndrome dosing clopidogrel: Comparison with platelet function test and SNP genotyping. *Annals of Clinical and Laboratory Science* 2016;**46(5)**
79. Petrek M, Kocourkova L, Zizkova V, Nosek Z, Taborsky M, Petrkova J. Characterization of Three CYP2C19 Gene Variants by MassARRAY and Point of Care Techniques: Experience from a Czech Centre. *Archivum Immunologiae et Therapiae Experimentalis* 2016;**64**(Supplement 1)
80. So DYF, Wells GA, McPherson R, Labinaz M, Le May MR, Glover C*, et al.* A prospective randomized evaluation of a pharmacogenomic approach to antiplatelet therapy among patients with ST-elevation myocardial infarction: the RAPID STEMI study. *Pharmacogenomics Journal* 2016;**16**(1)
81. Wirth F, Zahra G, Xuereb RG, Barbara C, Fenech A, Azzopardi LM. Comparison of a rapid point-of-care and two laboratory-based CYP2C19*2 genotyping assays for personalisation of antiplatelet therapy. *International Journal of Clinical Pharmacy* 2016;**38(2)**
82. Spartan Bioscience Inc. 2022. Method Comparison Study of the Spartan FRX CYP2C19 Genotyping System Against Bi-directional Sequencing. NCT01718535; URL: https://ClinicalTrials.gov/show/NCT01718535 (Accessed November 2022).
83. Petrkova J, Paskova L, Zizkova V, Nosek Z, Taborsky M, Petrek M. POCT for determination of basic pharmacogenetic profile for individualization of antiplatelet therapy: Pilot study. *European Heart Journal* 2014;**1)**
84. Al-Rubaish AM, Al-Muhanna FA, Alshehri AM, Alsulaiman AA, Alabdulali MM, Alkhamis F*, et al.* Prevalence of CYP2C19*2 carriers in Saudi ischemic stroke patients and the suitability of using genotyping to guide antiplatelet therapy in a university hospital setup. *Drug Metabolism and Personalized Therapy* 2021;**37(1)**
85. Bergmeijer TO, Vos GJ, Claassens DM, Janssen PW, Harms R, der Heide RV*, et al.* Feasibility and implementation of CYP2C19 genotyping in patients using antiplatelet therapy. *Pharmacogenomics* 2018;**19**(7)
86. Cavallari LH, Franchi F, Rollini F, Been L, Rivas A, Agarwal M*, et al.* Clinical implementation of rapid CYP2C19 genotyping to guide antiplatelet therapy after percutaneous coronary intervention. *Journal of Translational Medicine* 2018;**16(1)**
87. Davis BH, DeFrank G, Limdi NA, Harada S. Validation of the Spartan RXCYP2C19 Genotyping Assay Utilizing Blood Samples. *Clinical and Translational Science* 2020;**13(2)**
88. Franchi F, Rollini F, Rivas J, Rivas A, Agarwal M, Briceno M*, et al.* Prasugrel Versus Ticagrelor in Patients With CYP2C19 Loss-of-Function Genotypes Results of a Randomized Pharmacodynamic Study in a Feasibility Investigation of Rapid Genetic Testing. *JACC - Basic to Translational Science* 2020;**5**(5)
89. Gurbel PA, Bell R, Bliden K, Yazdani S, Taheri H, Akbari M*, et al.* Bedside testing of CYP2C19 genotype to guide antiplatelet therapy: Implementation in the catheterization laboratory. *Journal of the American College of Cardiology Conference: 67th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC* 2018;**71**(Supplement 1)
90. Tomaniak M, Koltowski L, Kochman J, Huczek Z, Rdzanek A, Pietrasik A*, et al.* Can prasugrel decrease the extent of periprocedural myocardial injury during elective percutaneous coronary intervention? *Polish Archives of Internal Medicine-Polskie Archiwum Medycyny Wewnetrznej* 2017;**127**(11)

91. Zhou Y, Armstead AR, Coshatt GM, Limdi NA, Harada S. Comparison of two point-of-care cyp2c19 genotyping assays for genotype-guided antiplatelet therapy. *Annals of Clinical and Laboratory Science* 2017;**47(6)**
92. McDermott JH, Ainsworth S, Wright S, Sen D, Miele G, Smith CJ*, et al.* Development of a Point of Care Test for CYP2C19Allowing Genotype Guided Antiplatelet Prescribing to Prevent Recurrent Ischaemic Strokes. *European Journal of Human Genetics* 2020;**28(Supplement 1)**
93. Baudhuin L, Train L, Goodman S, Lane G, Lennon R, Mathew V*, et al.* Validation and performance of point-of-care rapid cyp2c19 genotyping in the tailor-pci multicenter international randomized clinical trial. *Journal of the American College of Cardiology* 2021;**77**(18)
94. Bergmeijer TO, Janssen PWA, Schipper JC, Qaderdan K, Ishak M, Ruitenbeek RS*, et al.* CYP2C19 genotype-guided antiplatelet therapy in ST-segment elevation myocardial infarction patients-Rationale and design of the Patient Outcome after primary PCI (POPular) Genetics study. *American Heart Journal* 2014;**168**(1)
95. Koltowski L, Tomaniak M, Aradi D, Huczek Z, Filipiak KJ, Kochman J*, et al.* Optimal antiplatelet pharmacotherapy guided by bedSIDE genetic or functional testing in elective PCI patients: A pilot study: ONSIDE TEST pilot. *Cardiology Journal* 2017;**24(3)**
96. Koltowski L, Aradi D, Huczek Z, Tomaniak M, Sibbing D, Filipiak KJ*, et al.* Study design and rationale for optimal antiplatelet pharmacotherapy guided by bedside genetic or functional TESTing in elective percutaneous coronary intervention patients (ONSIDE TEST): A prospective, open-label, randomised parallel-group multicentre trial (NCT01930773). *Kardiologia Polska* 2016;**74(4)**
97. Wirth F, Zahra G, Xuereb RG, Barbara C, Fenech A, Azzopardi LM. Comparison between a point-of-care and a laboratory-based CYP2C19 genotyping assay for pharmacist-led personalisation of antiplatelet therapy. *Pharmacotherapy* 2015;**35(11)**
98. Zhou Y, Armstead AR, Coshatt GM, Brott BC, Sankaranarayanan A, Limdi NA*, et al.* Rapid CYP2C19 genotype testing: Comparison between spartan RX CYP2C19 and verigene CYP2C19. *Journal of Molecular Diagnostics* 2015;**17(6)**
99. Office for National Statistics. *Ethnic group, England and Wales: Census 2021*. 2021. URL: https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/bulletins/ethnicgroupenglandandwales/census2021#:~:text=the%20%22Asian%2C%20or%20Asian%20British,was%2081.0%25%20(45.8%20million) (Accessed January 2023).
100. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd edn. Oxford: Oxford University Press; 2005.
101. Stuart J Wright. *Development of a point-of-care genetic test for effective treatment of patients with ischaemic stroke and transient ischaemic attacks: an early model-based cost-effectiveness analysis* 2022.)
102. Micieli A, Singh N, Jahn B, Siebert U, Menon BK, Demchuk AM. Cost effectiveness of testing for CYP2C19 loss-of-function carriers following transient ischemic attack/minor stroke: A Canadian perspective. *International journal of stroke* 2022
103. Narasimhalu K, Ang YK, Tan DSY, De Silva DA, Tan KB. Cost Effectiveness of Genotype-Guided Antiplatelet Therapy in Asian Ischemic Stroke Patients: Ticagrelor as an Alternative to Clopidogrel in Patients with CYP2C19 Loss of Function Mutations. *Clinical Drug Investigation* 2020;**40**(11)

104. Kremers F, Venema E, Cras T, Burke J, Roozenbeek B, Dippel D. Cost-effectiveness of cyp2c19 genotype-guided dual antiplatelet therapy for acute minor ischemic stroke or tia. *International Journal of Stroke* 2021;**16(2 SUPPL)**
105. The ACTIVE Writing Group on behalf of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *The Lancet* 2006;**367**(9526)
106. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Medical care* 2000;**38**(6)
107. Cai Z, Cai n, Wang R, Wang H, Yu Z, Gao F*, et al.* Cost-effectiveness of CYP2C19 genotyping to guide antiplatelet therapy for acute minor stroke and high-risk transient ischemic attack. *Scientific Reports* 2021;**11**(1)
108. Halkes PH, Gray LJ, Bath PM, Diener HC, Guiraud-Chaumeil B, Yatsu FM*, et al.* Dipyridamole plus aspirin versus aspirin alone in secondary prevention after TIA or stroke: a meta-analysis by risk. *Journal of Neurology, Neurosurgery, and Psychiatry* 2008;**79**(11)
109. Ministry of Health of the People's Republic of China. *China Statistics Yearbook*. 2012. URL: https://data.cnki.net/ValueSearch/ (Accessed November 2022).
110. Pan Y, Wang A, Liu G, Zhao X, Meng X, Zhao K*, et al.* Cost-effectiveness of clopidogrel-aspirin versus aspirin alone for acute transient ischemic attack and minor stroke. *Journal of the American Heart Association* 2014;**3**(3)
111. Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P*, et al.* Efficacy and safety of ticagrelor versus aspirin in acute stroke or transient ischaemic attack of atherosclerotic origin: a subgroup analysis of SOCRATES, a randomised, double-blind, controlled trial. *The Lancet Neurology* 2017;**16**(4)
112. National Registry of Diseases Office. *Singapore Stroke Registry Annual Report*. 2016. URL: https://www.nrdo.gov.sg/docs/librariesprovider3/Publications---Stroke/singapore-stroke-registry-annual-reprot-2016_upload_nrdo_website.pdf?sfvrsn=0 (Accessed Novemeber 2022).
113. Goh LL, Lim CW, Sim WC, Toh LX, Leong KP. Analysis of Genetic Variation in CYP450 Genes for Clinical Implementation. *PLoS ONE* 2017;**12**(1)
114. Guzauskas GF, Boudreau DM, Villa KF, Levine SR, Veenstra DL. The Cost-Effectiveness of Primary Stroke Centers for Acute Stroke Care. *Stroke* 2012;**43**(6)
115. Samsa GP, Reutter RA, Parmigiani G, Ancukiewicz M, Abrahamse P, Lipscomb J*, et al.* Performing Cost-Effectiveness Analysis by Integrating Randomized Trial Data with a Comprehensive Decision Model: Application to Treatment of Acute Ischemic Stroke. *Journal of Clinical Epidemiology* 1999;**52**(3)
116. Kremers F. Cost-effectiveness of cyp2c19 genotype-guided dual antiplatelet therapy for acute minor ischemic stroke or tia – updated abstract via correspondence with author 2022
117. Greenhalgh J, Bagust A, Boland A, Martin Saborido C, Oyee J, Blundell M*, et al.* Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of Technology Appraisal No. 90): a systematic review and economic analysis. *Health Technology Assessment* 2011;**15**(31)
118. Office for National Statistics. *Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland*. 2019. URL: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populat

ionestimates/bulletins/annualmidyearpopulationestimates/mid2018 (Accessed March 2022).
119. Zhou LW, Kraler L, de Havenon A, Lansberg MG. Cost-Effectiveness of Cilostazol Added to Aspirin or Clopidogrel for Secondary Prevention After Noncardioembolic Stroke. *Journal of the American Heart Association* 2022;**11**(11)
120. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;**348**(9038)
121. Baharoglu MI, Cordonnier C, Salman RA-S, de Gans K, Koopman MM, Brand A*, et al.* Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. *The Lancet* 2016;**387**(10038)
122. Cucchiara B, Elm J, Easton JD, Coutts SB, Willey JZ, Biros MH*, et al.* Disability After Minor Stroke and Transient Ischemic Attack in the POINT Trial. *Stroke* 2020;**51**(3)
123. Buskens E, Nederkoorn PJ, Woude TB-vd, Mali WPTM, Kappelle LJ, Eikelboom BC*, et al.* Imaging of Carotid Arteries in Symptomatic Patients: Cost-effectiveness of Diagnostic Strategies. *Radiology* 2004;**233**(1)
124. Ali M, MacIsaac R, Quinn TJ, Bath PM, Veenstra DL, Xu Y*, et al.* Dependency and health utilities in stroke: Data to inform cost-effectiveness analyses. *European Stroke Journal* 2016;**2**(1)
125. Diener H-C, Sacco RL, Yusuf S, Cotton D, Ôunpuu S, Lawton WA*, et al.* Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. *The Lancet Neurology* 2008;**7**(10)
126. Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006;**367**(9523)
127. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *Journal of the Neurological Sciences* 1996;**143**(1-2)
128. Boehringer Ingelheim. *Submission to NICE to support the review of health technology appraisal 90: clopidogrel and modified-release dipyridamole and aspirin for the prevention of occlusive vascular events*. Bracknell: Boehringer Ingelheim; 2009.)
129. Sanofi-aventis and Bristol-Myers Squibb. *The use of clopidogrel hydrogen sulphate (Plavix) in patients with atherosclerotic disease: manufacturer submission*. Montreal QC: Bristol-Myers Squibb; 2009.)
130. Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics* 2003;**21 Suppl 1**
131. Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). *Diabetic Medicine* 2003;**20**(6)
132. Schleinitz MD, Weiss JP, Owens DK. Clopidogrel versus aspirin for secondary prophylaxis of vascular events: a cost-effectiveness analysis. *The American Journal of Medicine* 2004;**116**(12)
133. O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. *Journal of the American Medical Association* 2005;**293**(6)

134. Jansen JP, Pellissier J, Choy EH, Ostor A, Nash JT, Bacon P*, et al.* Economic evaluation of etoricoxib versus non-selective NSAIDs in the treatment of ankylosing spondylitis in the UK. *Current Medical Research and Opinion* 2007;**23**(12)
135. Quinn RR, Naimark DM, Oliver MJ, Bayoumi AM. Should hemodialysis patients with atrial fibrillation undergo systemic anticoagulation? A cost-utility analysis. *American Journal of Kidney Diseases* 2007;**50**(3)
136. Malinina D, Zema C, Sander S, Serebruany V. Cost–effectiveness of antiplatelet therapy for secondary stroke prevention. *Expert Review of Pharmacoeconomics & Outcomes Research* 2007;**7**(4)
137. Johnson ES, Lanes SF, Wentworth CE, 3rd, Satterfield MH, Abebe BL, Dicker LW. A metaregression analysis of the dose-response effect of aspirin on stroke. *Archives of internal medicine* 1999;**159**(11)
138. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G*, et al.* Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke* 1999;**30**(4)
139. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke. The Oxfordshire Community Stroke Project. *Stroke* 1994;**25**(2)
140. Samsa GP, Bian J, Lipscomb J, Matchar DB. Epidemiology of recurrent cerebral infarction: a medicare claims-based comparison of first and recurrent strokes on 2-year survival and cost. *Stroke* 1999;**30**(2)
141. Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M*, et al.* Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation. *Health Technology Assessment* 2004;**8**(38)
142. Wolfe CD, Rudd AG, Howard R, Coshall C, Stewart J, Lawrence E*, et al.* Incidence and case fatality rates of stroke subtypes in a multiethnic population: the South London Stroke Register. *Journal of Neurology, Neurosurgery, and Psychiatry* 2002;**72**(2)
143. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**(7329)
144. Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J*, et al.* A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. *Health Technology Assessment* 2002;**6**(26)
145. PharmGKB. *Gene-specific Information Tables for CYP2C19*. URL: https://www.pharmgkb.org/page/cyp2c19RefMaterials (Accessed July 2022).
146. Amin AM, Sheau Chin L, Teh CH, Mostafa H, Mohamed Noor DA, Abdul Kader M*, et al.* Pharmacometabolomics analysis of plasma to phenotype clopidogrel high on treatment platelets reactivity in coronary artery disease patients. *European Journal of Pharmaceutical Sciences* 2018;**117**
147. Pilling LC, Turkmen D, Fullalove H, Atkins JL, Delgado J, Kuo CL*, et al.* Analysis of CYP2C19 genetic variants with ischaemic events in UK patients prescribed clopidogrel in primary care: a retrospective cohort study. *BMJ Open* 2021;**11**(12)
148. Ionova Y, Ashenhurst J, Zhan J, Nhan H, Kosinski C, Tamraz B*, et al.* CYP2C19 Allele Frequencies in Over 2.2 Million Direct-to-Consumer Genetics Research Participants and the

Potential Implication for Prescriptions in a Large Health System. *Clinical and Translational Science* 2020;**13**(6)
149. Mohan KM, Crichton SL, Grieve AP, Rudd AG, Wolfe CDA, Heuschmann PU. Frequency and predictors for the risk of stroke recurrence up to 10 years after stroke: the South London Stroke Register. *Journal of Neurology, Neurosurgery & Psychiatry* 2009;**80**(9)
150. Sentinel Stroke National Audit Programme (SSNAP). *SSNAP Annual Portfolio for April 2021-March 2022 admissions and discharges.*; 2021. URL: https://www.strokeaudit.org/results/Clinical-audit/National-Results.aspx (Accessed November 2022).
151. National Guideline Centre & SSNAP. *Sentinel Stroke National Audit Program. Cost and Cost-effectiveness analysis* 2016. URL: https://www.strokeaudit.org/SupportFiles/Documents/Health-Economics/Health-economic-report-2016.aspx (Accessed December 2022).
152. Lioutas V-A, Ivan CS, Himali JJ, Aparicio HJ, Leveille T, Romero JR*, et al.* Incidence of Transient Ischemic Attack and Association With Long-term Risk of Stroke. *Journal of the American Medical Association* 2021;**325**(4)
153. Office for National Statistics. *National Life Tables - life expectancy in the UK: 2018 to 2020*. 2021. URL: https://www.ons.gov.uk/releases/nationallifetableslifeexpectancyintheuk2018to2020 (Accessed January 2022).
154. Greving JP, Diener HC, Reitsma JB, Bath PM, Csiba L, Hacke W*, et al.* Antiplatelet Therapy After Noncardioembolic Stroke. *Stroke* 2019;**50**(7)
155. Del Giovane C, Boncoraglio GB, Bertu L, Banzi R, Tramacere I. Antiplatelet drugs for secondary prevention in patients with ischemic stroke or transient ischemic attack: a systematic review and network meta-analysis. *BMC Neurology* 2021;**21**(1)
156. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA*, et al.* Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *New England Journal of Medicine* 2008;**359**(12)
157. Swen JJ, van der Wouden CH, Manson LEN, Abdullah-Koolmees H, Blagec K, Blagus T*, et al.* A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. *The Lancet* 2023;**401**(10374)
158. Narasimhalu K, Ang YK, Tan D, De Silva D, Tan K. Cost effectiveness of CYP2C19 genetic testing in guiding antiplatelet choice in patients with ischemic stroke-an asian perspective. *International Journal of Stroke* 2020;**15(1 SUPPL)**
159. Haacke C, Althaus A, Spottke A, Siebert U, Back T, Dodel R. Long-Term Outcome After Stroke. *Stroke* 2006;**37**(1)
160. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. *Medical Decison Making* 2010;**30**(3)
161. Whynes DK, Sprigg N, Selby J, Berge E, Bath PM. Testing for Differential Item Functioning within the EQ-5D. *Medical Decision Making* 2012;**33**(2)
162. Wang YL, Pan YS, Zhao XQ, Wang D, Johnston SC, Liu LP*, et al.* Recurrent stroke was associated with poor quality of life in patients with transient ischemic attack or minor stroke: finding from the CHANCE trial. *CNS neuroscience & therapeutics* 2014;**20**(12)

163. Wang X, Moullaali TJ, Li Q, Berge E, Robinson TG, Lindley R*, et al.* Utility-Weighted Modified Rankin Scale Scores for the Assessment of Stroke Outcome: Pooled Analysis of 20 000+ Patients. *Stroke* 2020;**51**(8)
164. Patchwood E, Woodward-Nutt K, Rhodes SA, Batistatou E, Camacho E, Knowles S*, et al.* Organising Support for Carers of Stroke Survivors (OSCARSS): a cluster randomised controlled trial with economic evaluation. *BMJ Open* 2021;**11**(1)
165. Forster A, Dickerson J, Young J ea, editors. *A cluster randomised controlled trial and economic evaluation of a structured training programme for caregivers of inpatients after stroke: the TRACS trial*. Southampton; 2013.
166. NHS Employers. *Hourly pay scales 2021/22*. 2021. URL: https://www.nhsemployers.org/articles/hourly-pay-scales-202122 (Accessed January 2023).
167. Xu Z, Li Y, Dai S, Liu J, Pan J, Jiang Y. Comparison between MassARRAY and pyrosequencing for CYP2C19 and ABCB1 gene variants of clopidogrel efficiency genotyping. *Molecular Membrane Biology* 2019;**35(1)**
168. Svidnicki MCCC, Silva-Costa SM, Ramos PZ, dos Santos NZP, Martins FTA, Castilho AM*, et al.* Screening of genetic alterations related to non-syndromic hearing loss using MassARRAY iPLEX® technology. *BMC Medical Genetics* 2015;**16**(1)
169. Le Hellard S, Ballereau SJ, Visscher PM, Torrance HS, Pinson J, Morris SW*, et al.* SNP genotyping on pooled DNAs: comparison of genotyping technologies and a semi automated method for data storage and analysis. *Nucleic acids research* 2002;**30**(15)
170. Büyükkaramikli NC, Rutten-van Mölken MPMH, Severens JL, Al M. TECH-VER: A Verification Checklist to Reduce Errors in Models and Improve Their Credibility. *Pharmacoeconomics* 2019;**37**(11)
171. Public Health England. *Briefing document: First incidence of stroke. Estimates for England 2007 to 2016*. 2018. URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/678444/Stroke_incidence_briefing_document_2018.pdf (Accessed January 2023).
172. National Institute of Health and Care Excellence (NICE). *Clopidogrel genotype testing after ischaemic stroke or transient ischaemic attack (DAP 65): final protocol*. 2022. URL: https://www.nice.org.uk/guidance/gid-dg10054/documents/final-protocol (Accessed August 2022).
173. National Institute of Health and Care Excellence (NICE). *Clopidogrel genotype testing after ischaemic stroke (provisional title) Draft scope*. 2022 (Accessed Junly 2022).
174. Dahabreh Ij, Moorthy D., L. LJ, Chen M. L., Kent D. M., J. L. *Testing of CYP2C19 variants and platelet reactivity for guiding antiplatelet treatment*. Agency for Healthcare Research and Quality (AHRQ); 2013. URL: https://www.ncbi.nlm.nih.gov/books/NBK236984/ (Accessed July 2022).
175. McDermott JH, Leach M, Sen D, Smith CJ, Newman WG, Bath PM. The role of CYP2C19 genotyping to guide antiplatelet therapy following ischemic stroke or transient ischemic attack. *Expert review of clinical pharmacology* 2022;**01**
176. The national Institute for Health and Care Excellence (NICE). *Spartan RX point-of-care CYP2C19 test to guide treatment in acute coronary syndrome*. 2020. URL: https://www.nice.org.uk/advice/mib223).
177. Whiting PF, Rutjes AWS, Westwood ME, Mallett S. A systematic review classifies sources of bias and variation in diagnostic test accuracy studies. *Journal of Clinical Epidemiology* 2013;**66**(10)

178. Royal College of Physicians, British Pharmacological Society joint working party. *Personalised prescribing: using pharmacogenomics to improve paqtient outcomes*. 2022. URL: https://www.bps.ac.uk/getmedia/b43a3dca-1bbf-4bff-9379-20bef9349a8c/Personalised-prescribing-full-report.pdf.aspx (Accessed February 2023).
179. NHS East Genomics. *PROGRESS Programme - Pharmacogenomics Roll Out and gauging response to service*. URL: https://www.eastgenomics.nhs.uk/about-us/genomic-medicine-service-alliance/Transformation_Projects/progress-programme-pharmacogenomics-roll-out-and-gauging-response-to-service/ (Accessed February 2023).
180. Wang Y, Lin Y, Meng X, Chen W, Chen G, Wang Z*, et al.* Effect of ticagrelor with clopidogrel on high on-treatment platelet reactivity in acute stroke or transient ischemic attack (PRINCE) trial: Rationale and design. *International Journal of Stroke* 2017;**12**(3)
181. Zhou M, Chen W, Pan Y, Lin Y, Meng X, Zhao X*, et al.* Antiplatelet effect of ticagrelor with aspirin in acute minor stroke and transient ischemic attack stratified by CYP2C19 metabolizer status: subgroup analysis of the PRINCE trial. *Aging* 2020;**13**(3)
182. Gangnam Severance Hospital. 2015. Comparison of Triflusal and Clopidogrel in Secondary Prevention of Stroke Based on the Genotyping. NCT01174693; URL: https://ClinicalTrials.gov/show/NCT01174693 (Accessed September 2022).
183. Han SW, Kim YJ, Ahn SH, Seo WK, Yu S, Oh SH*, et al.* Protocol for the comparison of triflusal and clopidogrel in secondary prevention of stroke based on cytochrome P450 2C19 genotyping (MASETRO study): A multicenter, randomized, open-label, parallel-group trial. *International Journal of Stroke* 2016;**11**(4)
184. Han SW, Park JH. Prevalence of cyp2c19 alleles in the maestro study participants. *European Stroke Journal* 2017;**2(1 Supplement 1)**
185. Han SW, Park JH, Cheon KY, Lee KY. Verifynow P2Y12 assay with regard to cytochrome P450 2C19 polymorphisms and stroke recurrence. *Stroke Conference: american heart association/american stroke association 2018 international stroke conference and state-of-the-science stroke nursing symposium United states* 2018;**49**(Supplement 1)
186. Lee KY, Han SW, Kim YJ, Ahn SH, Seo WK, Yu S*, et al.* Effects of triflusal and clopidogrel in secondary prevention of stroke based on cytochrome P450 2C19 genotyping. *Stroke* 2017;**48**
187. Wang Y, Johnston C, Bath PM, Meng X, Jing J, Xie X*, et al.* Clopidogrel with aspirin in High-risk patients with Acute Non-disabling Cerebrovascular Events II (CHANCE-2): rationale and design of a multicentre randomised trial. *Stroke & Vascular Neurology* 2021;**6**(2)
188. Pan Y, Meng X, Jin A, Johnston SC, Li H, Bath PM*, et al.* Time Course for Benefit and Risk with Ticagrelor and Aspirin in Individuals with Acute Ischemic Stroke or Transient Ischemic Attack Who Carry CYP2C19 Loss-of-Function Alleles: a Secondary Analysis of the CHANCE-2 Randomized Clinical Trial. *JAMA Neurology* 2022
189. Joundi RA. In patients with stroke or TIA and CYP2C19 loss-of-function alleles, ticagrelor vs. clopidogrel reduced 90-d stroke. *Annals of Internal Medicine* 2022;**175**(3)
190. Wang A, Meng X, Tian X, Johnston SC, Li H, Bath PM*, et al.* Bleeding Risk of Dual Antiplatelet Therapy after Minor Stroke or Transient Ischemic Attack. *Annals of Neurology* 2022;**91(3)**
191. Beijing Tiantan Hospital. 2021. Clopidogrel With Aspirin in High-risk Patients With Acute Non-disabling Cerebrovascular Events II. NCT04078737; URL: https://ClinicalTrials.gov/show/NCT04078737 (Accessed September 2022).
192. Xu J, Wang A, Wangqin R, Mo J, Chen Z, Dai L*, et al.* Efficacy of clopidogrel for stroke depends on CYP2C19 genotype and risk profile. *Annals of Neurology* 2019;**86**(3)

193. Pan Y, Wangqin R, Li H, Meng X, Johnston SC, Simon T*, et al.* F2R Polymorphisms and Clopidogrel Efficacy and Safety in Patients With Minor Stroke or TIA. *Neurology* 2021;**96(1)**
194. Wu Y, Zhou Y, Pan Y, Zhao X, Liu L, Wang D*, et al.* Impact of CYP2C19 polymorphism in prognosis of minor stroke or TIA patients with declined eGFR on dual antiplatelet therapy: CHANCE substudy. *Pharmacogenomics Journal* 2018;**18**(6)
195. Davila-Fajardo CL, Diaz-Villamarin X, Blanquez-Martinez D, Caballero-Romero A, Antunez-Rodriguez A, Perez-Campos M*, et al.* Implementing CYP2C19 genotyping in our daily clinical practice. *International Journal of Clinical Pharmacy* 2018;**40(1)**
196. Diaz-Villamarin X, Davila-Fajardo CL, Blanquez-Martinez D, Fernandez-Gomez E, Antunez-Rodriguez A, Raquel AS. CYP2C19 SNP's influence on clopidogrel response in cerebrovascular disease patients: Final results. *European Journal of Hospital Pharmacy* 2019;**26(Supplement 1)**
197. Fukuma K, Yamagami H, Kamiyama K, Enomoto Y, Furui E, Manabe Y*, et al.* Association between CYP2C19 genetic polymorphisms and clinical outcome in acute atherothrombotic stroke: A sub-analysis of the praise study. *European Stroke Journal* 2017;**2(1 Supplement 1)**
198. Han Y, Lv H, Wu H, Liu M, Liu Q, Huo Y*, et al.* The value of platelet reactivity and genetic polymorphism in predicting long-term clinical outcomes in stroke patients. *Circulation Research* 2019;**125(12)**
199. Simpkins AN, McDonough CW, McClure LA, Mitchell BD, Shuldiner AR, Benavente OR*, et al.* Secondary stroke prevention with aspirin and clopidogrel in CYP2C19*17 carriers increases risk of major non-CNS bleeding. *Stroke Conference: American Heart Association/American Stroke Association* 2019;**50**(Supplement 1)
200. Spokoyny I, Barazangi N, Jaramillo V, Rose J, Chen C, Wong C*, et al.* Reduced CYP219 clopidogrel metabolism in a multiethnic population: Prevalance and associated rates of recurrent cerebrovascular events. *Neurology Conference: 65th American Academy of Neurology Annual Meeting San Diego, CA United States Conference Publication:* 2013;**80**(1)
201. National Cerebral and Cardiovascular Center. 2016. The Influence of CYP2C19 Polymorphism and Clinical Outcomes in Stroke Patients. NCT02711410; URL: https://ClinicalTrials.gov/show/NCT02711410 (Accessed September 2022).
202. Doney A, Palmer C, Morant S, Flynn R, MacDonald T. Impact of CYP2C19 genotype in ischaemic stroke patients treated with clopidogrel. *International Journal of Stroke* 2015;**5**
203. Wang J, Han M, Kuang J, Tu J, Starcevich K, Gao P*, et al.* Personalized antiplatelet therapy based on clopidogrel/aspirin resistance tests in acute ischemic stroke and transient ischemic attack: Study protocol of a multi-center, single-blinded and randomized controlled trial. *Contemporary Clinical Trials* 2021;**108**
204. Gangnam Severance Hospital. 2022. Clopidogrel Preventive Effect Based on CYP2C19 Genotype in Ischemic Stroke. NCT04072705; URL: https://ClinicalTrials.gov/show/NCT04072705 (Accessed September 2022).
205. Zhang XG, Zhu XQ, Xue J, Li ZZ, Jiang HY, Hu L*, et al.* Personalised antiplatelet therapy based on pharmacogenomics in acute ischaemic minor stroke and transient ischaemic attack: study protocol for a randomised controlled trial. *BMJ Open* 2019;**9**(5)
206. Zhao X, Lin J, Li H, Johnston SC, Lin Y, Pan Y*, et al.* Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. *Journal of the American Medical Association* 2016;**316(1)**

207. Tornio A, Flynn R, Morant S, Velten E, Palmer CNA, MacDonald TM*, et al.* Investigating Real-World Clopidogrel Pharmacogenetics in Stroke Using a Bioresource Linked to Electronic Medical Records. *Clinical Pharmacology and Therapeutics* 2018;**103(2)**
208. Matchar DB, Jacobson A, Dolor R, Edson R, Uyeda L, Phibbs CS*, et al.* Effect of home testing of international normalized ratio on clinical events. *New England Journal of Medicine* 2010;**363(17)**

Appendix 1: Literature search strategies

a. Effectiveness and accuracy searches

We used two searches: one for objectives 1 to 3 and a separate search for objectives 4 and 5. The searches were not limited by study design, date of publication, or language. This allowed us to use these searches to identify studies for our review of cost effectiveness.

Objectives 1, 2 and 3

Resource	N
MEDLINE	1330
Embase	2334
CENTRAL	379
CINAHL	82
CTG	115
ICTRP	45
ECONLit	2
HTA Library	3
NHS EED	4
Tufts CEA Register	44
Total	4328
- Duplicates	- 1414
To screen	2914

Database: MEDLINE (MEDALL)

Host: Ovid

Data parameters: 1946 to present

Date of search: 10 August 2022

#	Searches	Results
1	Clopidogrel/	9894
2	(clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2").ti,ab,kw,rn,tn,dq,dy,cn.	13992
3	1 or 2	15893
4	Cytochrome P-450 *CYP2C19*/	3314
5	(*CYP2C19** or cypiic19* or "Cytochrome P-450").ti,ab,kw,kf.	20356
6	4 or 5	20904
7	3 and 6	1330

Search narrative

Lines 1-2: search for Clopidogrel. Line 1 focuses on the controlled indexing term for Clopidogrel. The / indicates that this is a controlled indexing term. The free-text terms

search in the following fields: ti = title; ab = abstract; kw = author keyword; kf = key field; and; ot = original title. The structure in line 2 is the prevailing name of the intervention (clopidogrel), followed by alternate brand names or synonyms (e.g., duoplavin, plavix, zyllt) ATC codes or UNII code (A74586SNO7), and the CAS registry number ("113665-84-2").
Lines 4-5: search for *CYP2C19* Genotype. We have truncated *CYP2C19* (using the * marker) to identify *CYP2C19**2, *CYP2C19**3, and CYP2C9*17, and other alleles.
Line 7 combines the search: Line 3 – terms for Clopidogrel AND Line 6 – terms for *CYP2C19*

Database: Embase

Host: Ovid
Data parameters: 1974 to 2022 August 09
Date of search: 10 August 2022

#	Searches	Results
1	*clopidogrel/	12222
2	(clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2").ti,ab,kw,rn,tn,dq,dy,cn.	71596
3	1 or 2	71596
4	*cytochrome P450 2C19/	2197
5	(*CYP2C19** or cypiic19* or "Cytochrome P-450").ti,ab,kw,kf.	25516
6	4 or 5	25632
7	3 and 6	2324

Database: CENTRAL

Host: Wiley interface

Data parameters: Issue 7 of 12, July 2022

Date of search: 10 August 2022

ID	Query	Results
#1	[mh ^Clopidogrel]	2166
#2	(clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2"):ti,ab,kw	5907
#3	#1 or #2	5907
#4	MeSH descriptor: [Cytochrome P-450 *CYP2C19*] this term only	362
#5	(*CYP2C19** or cypiic19* or "Cytochrome P-450"):ti,ab,kw	362
#6	#4 or #5	2496
#7	#3 AND #6	379

Database: CINAHL

Host: Ovid

Data parameters: 1981 to present

Date of search: 10 August 2022

#	Query	Results
S1	TI ((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2")) OR AB ((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2"))	4,401
S2	TI ((*CYP2C19** or cypiic19* or "Cytochrome P-450")) OR AB ((*CYP2C19** or cypiic19* or "Cytochrome P-450"))	1,092
S3	S1 AND S2	273
S4	S1 AND S2	82

Notes: studies indexed in MEDLINE were removed at S4 using the server-side de-duplication feature.

Database: Clinical Trials.gov
Host: https://www.clinicaltrials.gov/ct2/results/refine?show_xprt=Y
Date of search: 10 August 2022

115 Studies found for: (clopidogrel OR clopidogrelum OR M-clopidogrel OR Nra-clopidogrel OR grepid OR iscover OR duoplavin OR plavi OR Plavix OR zyllt OR EXPAND[Concept] "R 130964" OR EXPAND[Concept] "R-130964" OR R130964 OR EXPAND[Concept] "SR 25990" OR EXPAND[Concept] "SR-25990" OR SR25990 OR A74586SNO7 OR EXPAND[Concept] "113665-84-2") AND (*CYP2C19* OR cypiic19 OR EXPAND[Concept] "Cytochrome P-450")

Database: WHO International Clinical Trials Registry Platform (ICTRP)
Host: https://trialsearch.who.int/Default.aspx
Date of search: 10 August 2022

(clopidogrel OR clopidogrelum OR M-clopidogrel OR Nra-clopidogrel OR grepid OR iscover OR duoplavin OR plavi OR Plavix OR zyllt OR "R 130964" OR "R-130964" OR R130964 OR "SR 25990" OR "SR-25990" OR SR25990 OR A74586SNO7 OR "113665-84-2") AND (*CYP2C19* OR cypiic19 OR "Cytochrome P-450")

Database: ECONLit
Host: EBSCOhost
Data parameters: 1886 to present
Date of search: 10 August 2022

#	Query	Results
S1	TI ((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2")) OR AB ((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2"))	8
S2	TI ((*CYP2C19** or cypiic19* or "Cytochrome P-450")) OR AB ((*CYP2C19** or cypiic19* or "Cytochrome P-450"))	2
S3	S1 AND S2	2

Database: HTA Library
Host: https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
Date of search: 10 August 2022

(((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or R 130964 or R-130964 or R130964 or SR 25990 or SR-25990 or SR25990 or A74586SNO7 or 113665-84-2)) AND ((*CYP2C19** or cypiic19* or Cytochrome P-450))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA

Database: NHS EED
Host: https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
Date of search: 10 August 2022

(((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or R 130964 or R-130964 or R130964 or SR 25990 or SR-25990 or SR25990 or A74586SNO7 or 113665-84-2)) AND ((*CYP2C19** or cypiic19* or Cytochrome P-450))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHS EED

Database: Tufts CEA Register
Host: https://cear.tuftsmedicalcenter.org/about
Date of search: 10 August 2022

Methods
Clopidogrel AND *CYP2C19* n=20

Ratios
Clopidogrel AND *CYP2C19* n=9

Utilities
Clopidogrel AND *CYP2C19* n=15

Objectives 4 and 5

Resource	N
MEDLINE	92
Embase	296
CENTRAL	51
CINAHL	8
CTG	93
ICTRP	13
ECONLit	0
HTA Library	2
NHS EED	0
Tufts CEA Register	0
Total	555
- Duplicates	-107
To screen	448

Database: MEDLINE (MEDALL)
Host: Ovid
Data parameters: 1946 to present
Date of search: 11 August 2022

#	Searches	Results
1	Point-of-Care Testing/	3652
2	((Point of Care adj2 test*) or POCT).ti,ab,kf,kw.	9296
3	(Genomadix* or Genedrive or Spartan).ti,ab,hw,kf,kw.	340
4	1 or 2 or 3	11544
5	Cytochrome P-450 *CYP2C19*/	3312
6	(*CYP2C19** or cypiic19* or "Cytochrome P-450").ti,ab,kw,kf.	20353
7	5 or 6	20901
8	Clopidogrel/	9890
9	(clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2").ti,ab,kw,kf.	13984
10	8 or 9	15885
11	4 and (7 or 10)	92

Search narrative

Line 1: focuses on the controlled indexing term for Point of Care Testing. The / indicates that this is a controlled indexing term. The free-text terms (Line 2 or Line 3) search in the

following fields: ti = title; ab = abstract; kw = author keyword; kf = key field; hw = heading word.

Lines 5-7: Terms for *CYP2C19*. The free-text terms are truncated using the * marker. Truncation ensures that the root word and other possible variations are identified and returned by the search. We have truncated *CYP2C19* (using the * marker again) to identify *CYP2C19**2, *CYP2C19**3, and CYP2C9*17, and other alleles.

Lines 8 or 9: Terms for Clopidogrel

Line 11: combines terms for Point of Care testing AND terms for *CYP2C19* OR terms for Clopidogrel.

Database: Embase

Host: Ovid

Data parameters: 1974 to 2022 August 10

Date of search: 11 August 2022

#	Searches	Results
1	*"point of care testing"/	6784
2	((Point of Care adj2 test*) or POCT).ti,ab,kf,kw.	12848
3	(Genomadix* or Genedrive or Spartan).ti,ab,kf,kw.	558
4	1 or 2 or 3	16726
5	*cytochrome P450 2C19/	2200
6	(*CYP2C19** or cypiic19* or "Cytochrome P-450").ti,ab,kw,kf.	25520
7	5 or 6	25636
8	*clopidogrel/	12224
9	(clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2").ti,ab,kw,rn,tn,dq,dy,cn.	71601
10	8 or 9	71601
11	4 and (7 or 10)	296

Database: CENTRAL

Host: Wiley interface

Data parameters: Issue 7 of 12, July 2022

Date of search: 11 August 2022

ID	Query	Results
#1	[mh ^Clopidogrel]	2166
#2	(clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2"):ti,ab,kw	5907
#3	#1 or #2	5907
#4	MeSH descriptor: [Cytochrome P-450 *CYP2C19*] this term only	362
#5	(*CYP2C19** or cypiic19* or "Cytochrome P-450"):ti,ab,kw	2496
#6	#4 or #5	2496
#7	#3 OR #6	8024
#8	MeSH descriptor: [Point-of-Care Testing] this term only	101
#9	((Point of Care NEAR/2 test*) or POCT):ti,ab,kw	949
#10	(Genomadix* or Genedrive or Spartan)	161
#11	#8 OR #9 OR #10	1103
#12	#7 AND #11	51

Database: CINAHL

Host: Ovid

Data parameters: 1981 to present

Date of search: 11 August 2022

#	Query	Results
S1	(MH "Point-of-Care Testing")	4,414
S2	TI (((Point of Care N2 test*) or POCT)) OR AB (((Point of Care N2 test*) or POCT))	3,304
S3	TI ((Genomadix* or Genedrive or Spartan)) OR AB ((Genomadix* or Genedrive or Spartan).)	98
S4	S1 OR S2 OR S3	6,432
S5	TI (TI ((*CYP2C19** or cypiic19* or "Cytochrome P-450")) OR AB ((*CYP2C19** or cypiic19* or "Cytochrome P-450"))) OR AB (TI ((*CYP2C19** or cypiic19* or "Cytochrome P-450")) OR AB ((*CYP2C19** or cypiic19* or "Cytochrome P-450")))	1,092
S6	TI (TI ((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2")) OR AB ((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R	4,402

	130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2"))) OR AB (TI ((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2")) OR AB ((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2")))	
S7	S5 OR S6	5,221
S8	S4 AND S7	28
S9	S4 AND S7	8

Notes: studies indexed in MEDLINE were removed at S9 using the server-side de-duplication feature.

Database: CTG
Host: https://www.clinicaltrials.gov/ct2/results/refine?show_xprt=Y
Date of search: 11 August 2022
Search a
((clopidogrel OR clopidogrelum OR M-clopidogrel OR Nra-clopidogrel OR grepid OR iscover OR duoplavin OR plavi OR Plavix OR zyllt OR "R 130964" OR "R-130964" OR R130964 OR "SR 25990" OR "SR-25990" OR SR25990 OR A74586SNO7 OR "113665-84-2") AND (Genomadix* OR Genedrive OR Spartan OR "point of care"))

Search b
((*CYP2C19* OR cypiic19 OR "Cytochrome P-450") AND (Genomadix* OR Genedrive OR Spartan OR "point of care"))

Database: ICTRP
Host: https://trialsearch.who.int/Default.aspx
Data parameters: 1946 to present
Date of search: 11 August 2022

Search a
((clopidogrel OR clopidogrelum OR M-clopidogrel OR Nra-clopidogrel OR grepid OR iscover OR duoplavin OR plavi OR Plavix OR zyllt OR "R 130964" OR "R-130964" OR R130964 OR "SR 25990" OR "SR-25990" OR SR25990 OR A74586SNO7 OR "113665-84-2") AND (Genomadix* OR Genedrive OR Spartan OR "point of care"))

Search b
((*CYP2C19* OR cypiic19 OR "Cytochrome P-450") AND (Genomadix* OR Genedrive OR Spartan OR "point of care")

Database: ECONLit
Host: EBSCOhost
Data parameters: 1886 to present
Date of search: 11 August 2022

#	Query	Results
S1	(MH "Point-of-Care Testing")	0
S2	TI (((Point of Care N2 test*) or POCT)) OR AB (((Point of Care N2 test*) or POCT))	5
S3	TI ((Genomadix* or Genedrive or Spartan)) OR AB ((Genomadix* or Genedrive or Spartan).)	10
S4	S1 OR S2 OR S3	15
S5	TI (TI ((*CYP2C19** or cypiic19* or "Cytochrome P-450")) OR AB ((*CYP2C19** or cypiic19* or "Cytochrome P-450"))) OR AB (TI ((*CYP2C19** or cypiic19* or "Cytochrome P-450")) OR AB ((*CYP2C19** or cypiic19* or "Cytochrome P-450")))	2
S6	TI (TI ((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2")) OR AB ((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2"))) OR AB (TI ((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2")) OR AB ((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or "R 130964" or "R-130964" or R130964 or "SR 25990" or "SR-25990" or SR25990 or A74586SNO7 or "113665-84-2")))	8
S7	S5 OR S6	8
S8	S4 AND S7	0
S9	S4 AND S7	0

Database: **HTA Library**
Host: https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
Date of search: 11 August 2022

Results for: ((((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or R 130964 or R-130964 or R130964 or SR 25990 or SR-25990 or SR25990 or A74586SNO7 or 113665-84-2) OR (*CYP2C19** or cypiic19* or Cytochrome P-450))) AND ((Genomadix* OR Genedrive OR Spartan OR Point of Care))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA

Database: **NHS EED**
Host: https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
Date of search: 11 August 2022

Results for: ((((clopidogrel* or clopidogrelum or M-clopidogrel or Nra-clopidogrel or grepid or iscover or duoplavin* or plavi* or Plavix* or zyllt* or R 130964 or R-130964 or R130964 or SR 25990 or SR-25990 or SR25990 or A74586SNO7 or 113665-84-2) OR (*CYP2C19** or cypiic19* or Cytochrome P-450))) AND ((Genomadix* OR Genedrive OR Spartan OR Point of Care))) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHS EED

Database: **Tufts CEA Register**
Host: https://cear.tuftsmedicalcenter.org/about
Date of search: 11 August 2022

Methods

1. (Genomadix* OR Genedrive OR Spartan) n=0
2. ((clopidogrel OR clopidogrelum OR M-clopidogrel OR Nra-clopidogrel OR grepid OR iscover OR duoplavin OR plavi OR Plavix OR zyllt OR "R 130964" OR "R-130964" OR R130964 OR "SR 25990" OR "SR-25990" OR SR25990 OR A74586SNO7 OR "113665-84-2") AND (Genomadix* OR Genedrive OR Spartan OR "point of care"))
3. ((*CYP2C19* OR cypiic19 OR "Cytochrome P-450") AND (Genomadix* OR Genedrive OR Spartan OR "point of care"))

Ratios

1. (Genomadix* OR Genedrive OR Spartan) n=0
2. ((clopidogrel OR clopidogrelum OR M-clopidogrel OR Nra-clopidogrel OR grepid OR iscover OR duoplavin OR plavi OR Plavix OR zyllt OR "R 130964" OR "R-130964" OR R130964 OR "SR 25990" OR "SR-25990" OR SR25990 OR A74586SNO7 OR "113665-84-2") AND (Genomadix* OR Genedrive OR Spartan OR "point of care"))
3. ((*CYP2C19* OR cypiic19 OR "Cytochrome P-450") AND (Genomadix* OR Genedrive OR Spartan OR "point of care"))

Utilities

1. (Genomadix* OR Genedrive OR Spartan) n=0
2. ((clopidogrel OR clopidogrelum OR M-clopidogrel OR Nra-clopidogrel OR grepid OR iscover OR duoplavin OR plavi OR Plavix OR zyllt OR "R 130964" OR "R-130964" OR R130964 OR "SR 25990" OR "SR-25990" OR SR25990 OR A74586SNO7 OR "113665-84-2") AND (Genomadix* OR Genedrive OR Spartan OR "point of care"))
3. ((*CYP2C19* OR cypiic19 OR "Cytochrome P-450") AND (Genomadix* OR Genedrive OR Spartan OR "point of care"))

b. Supplemental cost-effectiveness searches

Resource	N
MEDLINE	48
Embase	43
Econlit	2
Total	93
- duplicates	-34
Total to screen	59 to screen

Database: MEDLINE (MEDALL)
Host: Ovid
Data parameters: 1946 to present
Date of search: 17 Oct 2022

#	Searches	Results
1	*Ischemic Stroke/ and second*.ti,ab,kw,kf.	939
2	(second* adj2 (stroke or ischemic)).ti,ab,kw,kf.	4404
3	1 or 2	5198
4	*economics/ or exp *"costs and cost analysis"/	89042
5	((cost adj2 effectiveness) or (economic adj2 evaluation*)).ti,ab,kw,kf.	78596
6	4 or 5	155602
7	(2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022*).dt,dp,ed,ep,yr.	13653990
8	3 and 6 and 7	48

Database: Embase
Host: Ovid
Data parameters: 1980 to 2022 Week 41
Date of search: 17 Oct 2022

#	Searches	Results
1	*Ischemic Stroke/ and second*.ti,ab,kw,kf.	713
2	(second* adj2 (stroke or ischemic)).ti,ab,kw,kf.	7718
3	1 or 2	8275
4	*economics/ or *"cost effectiveness analysis"/	62335
5	((cost adj2 effectiveness) or (economic adj2 evaluation*)).ti,ab,kw,kf.	116387
6	4 or 5	147059
7	(2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020* or 2021* or 2022*).yr.	17134825
8	3 and 6 and 7	76
9	limit 8 to embase	43

Database: Econlit

Host: EbscoHost

Data parameters: 1981-Current

Date of search: 17 Oct 2022

#	Query	Results
1	AB ((second* N2 (stroke or ischemic))) OR TI ((second* N2 (stroke or ischemic)))	2

Appendix 2: Tables of included, on-going, or excluded studies

Studies included in the review showing primary and secondary reports

Primary reports are the primary publication for the study and are used to refer to that study throughout text and tables.

Objective 1

Study name	Primary Report	Secondary reports
NA	Lan H, Ying T, Xi-Hua S, Yi L. Anti-Platelet Therapy in Mild Cerebral Infarction Patients on the Basis of *CYP2C19* Metabolizer Status. Cell Transplantation 2019;28(8).[46]	None
NA	Xia C, Zhang Z, He X, Liu J, Li X, Chang Q, et al. Correlation between *CYP2C19* gene polymorphism and individualized medication in patients with ischemic stroke. [Chinese]. Chinese Journal of Clinical Pharmacology and Therapeutics 2021;26(3).[45]	None

Objective 2

Studies shaded blue were included for both objectives 2 and 3

Study name	Primary Report	Secondary reports
PRINCE	Chen W, Lin Y, Meng X, Chen G, Wang Z, Wu J, et al. Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: Open label, blinded endpoint, randomised controlled phase II trial. British Medical Journal 2019;365. [52]	Wang Y, Lin Y, Meng X, Chen W, Chen G, Wang Z, et al. Effect of ticagrelor with clopidogrel on high on-treatment platelet reactivity in acute stroke or transient ischemic attack (PRINCE) trial: Rationale and design. International Journal of Stroke 2017;12(3).[180] Zhou M, Chen W, Pan Y, Lin Y, Meng X, Zhao X, et al. Antiplatelet effect of ticagrelor with aspirin in acute minor stroke and transient ischemic attack stratified by *CYP2C19* metabolizer status: subgroup analysis of the PRINCE trial. Aging 2020;13(3).[181]
MASETRO	Han SW, Kim YJ, Ahn SH, Seo WK, Yu S, Oh SH, et al. Effects of Triflusal and Clopidogrel on the Secondary Prevention of Stroke Based on Cytochrome P450 2C19 Genotyping. Journal of Stroke 2017;19(3).[47]	Gangnam Severance Hospital. 2015. Comparison of Triflusal and Clopidogrel in Secondary Prevention of Stroke Based on the Genotyping. NCT01174693; URL: https://ClinicalTrials.gov/show/NCT01174693 (Accessed September 2022).[182] Han SW, Kim YJ, Ahn SH, Seo WK, Yu S, Oh SH, et al. Protocol for the comparison of triflusal and clopidogrel in secondary prevention of

Study name	Primary Report	Secondary reports
		stroke based on cytochrome P450 2C19 genotyping (MASETRO study): A multicenter, randomized, open-label, parallel-group trial. International Journal of Stroke 2016;11(4).[183] Han SW, Park JH. Prevalence of *CYP2C19* alleles in the maestro study participants. European Stroke Journal 2017;2(1 Supplement 1).[184] Han SW, Park JH, Cheon KY, Lee KY. Verifynow P2Y12 assay with regard to cytochrome P450 2C19 polymorphisms and stroke recurrence. Stroke Conference: american heart association/american stroke association 2018 international stroke conference and state-of-the-science stroke nursing symposium United states 2018;49(Supplement 1).[185] Lee KY, Han SW, Kim YJ, Ahn SH, Seo WK, Yu S, et al. Effects of triflusal and clopidogrel in secondary prevention of stroke based on cytochrome P450 2C19 genotyping. Stroke 2017;48.[186]
POINT	Meschia JF, Walton RL, Farrugia LP, Ross OA, Ross OA, Elm JJ, et al. Efficacy of Clopidogrel for Prevention of Stroke Based on *CYP2C19* Allele Status in the POINT Trial. Stroke 2020; 51 (7).[48]	None
NA	Wang Y, Meng X, Wang A, Xie X, Pan Y, Johnston SC, et al. Ticagrelor versus Clopidogrel in *CYP2C19* Loss-of-Function Carriers with Stroke or TIA. New England Journal of Medicine 2021;385(27).[49]	Wang Y, Johnston C, Bath PM, Meng X, Jing J, Xie X, et al. Clopidogrel with aspirin in High-risk patients with Acute Non-disabling Cerebrovascular Events II (CHANCE-2): rationale and design of a multicentre randomised trial. Stroke & Vascular Neurology 2021;6(2).[187] Pan Y, Meng X, Jin A, Johnston SC, Li H, Bath PM, et al. Time Course for Benefit and Risk with Ticagrelor and Aspirin in Individuals with Acute Ischemic Stroke or Transient Ischemic Attack Who Carry *CYP2C19* Loss-of-Function Alleles: a Secondary Analysis of the CHANCE-2 Randomized Clinical Trial. JAMA Neurology 2022.[188] Joundi RA. In patients with stroke or TIA and *CYP2C19* loss-of-function alleles, ticagrelor vs. clopidogrel reduced 90-d stroke. Annals of Internal Medicine 2022;175(3).[189]

Study name	Primary Report	Secondary reports
		Wang A, Meng X, Tian X, Johnston SC, Li H, Bath PM, et al. Bleeding Risk of Dual Antiplatelet Therapy after Minor Stroke or Transient Ischemic Attack. Annals of Neurology 2022;91(3).[190]
NA	Wu H, Song H, Dou L, Gao B, Pan Y, Dong M, et al. Effectiveness and safety of high dose clopidogrel plus aspirin in ischemic stroke patients with the single *CYP2C19* loss-of-function allele: a randomized trial. BMC Neurology 2020;20(1).[50]	None
NA	Yi X, Lin J, Zhou J, Wang Y, Huang R, Wang C. The secondary prevention of stroke according to cytochrome P450 2C19 genotype in patients with acute large-artery atherosclerosis stroke. Oncotarget 2018;9(25).[53]	None
CHANCE	Zhao X, Lin J, Li H, Johnston SC, Lin Y, Pan Y, et al. Association between *CYP2C19* loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. Journal of the American Medical Association 2016;316(1).[51]	Beijing Tiantan Hospital. 2021. Clopidogrel With Aspirin in High-risk Patients With Acute Non-disabling Cerebrovascular Events II. NCT04078737; URL: https://ClinicalTrials.gov/show/NCT04078737 (Accessed September 2022).[191] Xu J, Wang A, Wangqin R, Mo J, Chen Z, Dai L, et al. Efficacy of clopidogrel for stroke depends on *CYP2C19* genotype and risk profile. Annals of Neurology 2019;86(3).[192] Zhang J, Sun H, Ming T, Liu X, Cong Y, Li F, et al. Association between platelet function and recurrent ischemic vascular events after TIA and minor stroke. International Journal of Clinical Pharmacology and Therapeutics 2017;55(10).[73] Pan Y, Wangqin R, Li H, Meng X, Johnston SC, Simon T, et al. F2R Polymorphisms and Clopidogrel Efficacy and Safety in Patients With Minor Stroke or TIA. Neurology 2021;96(1).[193] Wu Y, Zhou Y, Pan Y, Zhao X, Liu L, Wang D, et al. Impact of *CYP2C19* polymorphism in prognosis of minor stroke or TIA patients with declined eGFR on dual antiplatelet therapy: CHANCE substudy. Pharmacogenomics Journal 2018;18(6).[194]

Objective 3

Studies shaded blue were included for both objectives 2 and 3

Study name	Primary Report*	Secondary reports
PRINCE	Chen W, Lin Y, Meng X, Chen G, Wang Z, Wu J, et al. Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: Open label, blinded endpoint, randomised controlled phase II trial. British Medical Journal 2019;365.[52]	Wang Y, Lin Y, Meng X, Chen W, Chen G, Wang Z, et al. Effect of ticagrelor with clopidogrel on high on-treatment platelet reactivity in acute stroke or transient ischemic attack (PRINCE) trial: Rationale and design. International Journal of Stroke 2017;12(3).[180] Zhou M, Chen W, Pan Y, Lin Y, Meng X, Zhao X, et al. Antiplatelet effect of ticagrelor with aspirin in acute minor stroke and transient ischemic attack stratified by *CYP2C19* metabolizer status: subgroup analysis of the PRINCE trial. Aging 2020;13(3).[181]
NA	Diaz-Villamarin X, Davila-Fajardo CL, Martinez-Gonzalez LJ, Rodriguez-Delgado A, Villegas-Rodriguez I, Cabeza-Barrera J. *CYP2C19**2, *3 polymorphisms in the response to clopidogrel after percutaneous transluminal angioplasty or stroke. International Journal of Clinical Pharmacy 2017;39(1).[195]	Diaz-Villamarin X, Davila-Fajardo CL, Blanquez-Martinez D, Fernandez-Gomez E, Antunez-Rodriguez A, Raquel AS. *CYP2C19* SNP's influence on clopidogrel response in cerebrovascular disease patients: Final results. European Journal of Hospital Pharmacy 2019;26(Supplement 1).[196]
NA	Fu H, Hu P, Ma C, Peng F, He Z. Association of clopidogrel high on-treatment reactivity with clinical outcomes and gene polymorphism in acute ischemic stroke patients: An observational study. Medicine 2020;99(15).[55]	None
NA	Fukuma K, Yamagami H, Ihara M, Tanaka T, Miyata T, Miyata S, et al. P2Y12 Reaction Units and Clinical Outcomes in Acute Large Artery Atherosclerotic Stroke: A Multicenter Prospective Study. Journal of atherosclerosis and thrombosis 2022;05.[197]	Fukuma K, Yamagami H, Kamiyama K, Enomoto Y, Furui E, Manabe Y, et al. Association between *CYP2C19* genetic polymorphisms and clinical outcome in acute atherothrombotic stroke: A sub-analysis of the praise study. European Stroke Journal 2017;2(1 Supplement 1).[197]
MAESTRO	Han SW, Kim YJ, Ahn SH, Seo WK, Yu S, Oh SH, et al. Effects of Triflusal and Clopidogrel on the Secondary Prevention of Stroke Based on Cytochrome P450 2C19 Genotyping. Journal of Stroke 2017;19(3).[47]	Gangnam Severance Hospital. 2015. Comparison of Triflusal and Clopidogrel in Secondary Prevention of Stroke Based on the Genotyping. NCT01174693; URL: https://ClinicalTrials.gov/show/NCT01174693 (Accessed September 2022).[182] Han SW, Kim YJ, Ahn SH, Seo WK, Yu S, Oh SH, et al. Protocol for the comparison of triflusal and clopidogrel in secondary prevention of stroke based on cytochrome P450 2C19 genotyping (MASETRO study): A multicenter, randomized, open-label,

Study name	Primary Report*	Secondary reports
		parallel-group trial. International Journal of Stroke 2016;11(4).[183] Han SW, Park JH. Prevalence of *CYP2C19* alleles in the maestro study participants. European Stroke Journal 2017;2(1 Supplement 1).[184] Han SW, Park JH, Cheon KY, Lee KY. Verifynow P2Y12 assay with regard to cytochrome P450 2C19 polymorphisms and stroke recurrence. Stroke Conference: american heart association/american stroke association 2018 international stroke conference and state-of-the-science stroke nursing symposium United states 2018;49(Supplement 1).[185] Lee KY, Han SW, Kim YJ, Ahn SH, Seo WK, Yu S, et al. Effects of triflusal and clopidogrel in secondary prevention of stroke based on cytochrome P450 2C19 genotyping. Stroke 2017;48.[186]
NA	Hoh BL, Gong Y, McDonough CW, Waters MF, Royster AJ, Sheehan TO, et al. *CYP2C19* and CES1 polymorphisms and efficacy of clopidogrel and aspirin dual antiplatelet therapy in patients with symptomatic intracranial atherosclerotic disease. Journal of Neurosurgery 2016;124(6).[57]	None
NA	Lin J, Mo Y, Cai, Mao D, Fu H, Wei D. *CYP2C19* polymorphisms and clopidogrel efficacy in the secondary prevention of ischemic stroke: a retrospective observational study. Annals of Palliative Medicine 2021;10(12).[58]	None
NA	Liu G, Yang S, Chen S. The correlation between recurrent risk and *CYP2C19* gene polymorphisms in patients with ischemic stroke treated with clopidogrel for prevention. Medicine 2020;99(11).[59]	None
NA	Lv H, Yang Z, Wu H, Liu M, Mao X, Liu X, et al. High On-Treatment Platelet Reactivity as Predictor of Long-term Clinical Outcomes in Stroke Patients with Antiplatelet Agents. Translational Stroke Research 2022;13(3).[60]	Han Y, Lv H, Wu H, Liu M, Liu Q, Huo Y, et al. The value of platelet reactivity and genetic polymorphism in predicting long-term clinical outcomes in stroke patients. Circulation Research 2019;125(12).[198]
NA	McDonough CW, McClure LA, Mitchell BD, Gong Y, Horenstein RB, Lewis JP, et al.	Simpkins AN, McDonough CW, McClure LA, Mitchell BD, Shuldiner AR, Benavente OR, et

Study name	Primary Report*	Secondary reports
	CYP2C19 metabolizer status and clopidogrel efficacy in the Secondary Prevention of Small Subcortical Strokes (SPS3) study. Journal of the American Heart Association 2015;4(6).[61]	al. Secondary stroke prevention with aspirin and clopidogrel in *CYP2C19**17 carriers increases risk of major non-CNS bleeding. Stroke Conference: American Heart Association/American Stroke Association 2019;50(Supplement 1).[199]
POINT	Meschia JF, Walton RL, Farrugia LP, Ross OA, Ross OA, Elm JJ, et al. Efficacy of Clopidogrel for Prevention of Stroke Based on *CYP2C19* Allele Status in the POINT Trial. Stroke 2020; 51 (7).[48]	None
NA	Ni G, Liang C, Liu K, Cao Y, Zhang H, Tian X, et al. The effects of CES1A2 and *CYP2C19* polymorphisms on responsiveness to clopidogrel and clinical outcomes among Chinese patients with acute ischemic stroke. International Journal of Clinical and Experimental Medicine 2017;10(2).[62]	None
NA	Patel PD, Vimalathas P, Niu X, Shannon CN, Denny JC, Peterson JF, et al. *CYP2C19* Loss-of-Function is Associated with Increased Risk of Ischemic Stroke after Transient Ischemic Attack in Intracranial Atherosclerotic Disease. Journal of Stroke and Cerebrovascular Diseases 2021;30(2).[63]	None
NA	Qiu LN, Sun Y, Wang L, Han RF, Xia XS, Liu J, et al. Influence of *CYP2C19* polymorphisms on platelet reactivity and clinical outcomes in ischemic stroke patients treated with clopidogrel. European Journal of Pharmacology 2015;747.[64]	None
NA	Sen HM, Silan F, Silan C, Degirmenci Y, Ozisik Kamaran HI. Effects of *CYP2C19* and P2Y12 Gene Polymorphisms on Clinical Results of Patients Using Clopidogrel after Acute Ischemic Cerebrovascular Disease. Balkan Journal of Medical Genetics 2014;17(2).[65]	None
NA	Spokoyny I, Barazangi N, Jaramillo V, Rose J, Chen C, Wong C, et al. Reduced clopidogrel metabolism in a multiethnic population: Prevalence and rates of recurrent cerebrovascular events. Journal of Stroke and Cerebrovascular Diseases 2014;23(4).[66]	Spokoyny I, Barazangi N, Jaramillo V, Rose J, Chen C, Wong C, et al. Reduced CYP219 clopidogrel metabolism in a multiethnic population: Prevalance and associated rates of recurrent cerebrovascular events. Neurology Conference: 65th American Academy of Neurology Annual Meeting San Diego, CA United States Conference Publication: 2013;80(1).[200]

Study name	Primary Report*	Secondary reports
	Sun W, Li Y, Li J, Zhang Z, Zhu W, Liu W, et al. Variant recurrent risk among stroke patients with different *CYP2C19* phenotypes and treated with clopidogrel. Platelets 2015;26(6).[67]	
NA	Tanaka T, Yamagami H, Ihara M, Miyata T, Miyata S, Hamasaki T, et al. Association of *CYP2C19* Polymorphisms With Clopidogrel Reactivity and Clinical Outcomes in Chronic Ischemic Stroke. Circulation Journal 2019;83(6).[68]	National Cerebral and Cardiovascular Center. 2016. The Influence of *CYP2C19* Polymorphism and Clinical Outcomes in Stroke Patients. NCT02711410; URL: https://ClinicalTrials.gov/show/NCT02711410 (Accessed September 2022).[201]
NA	Tomek A, Mat'oska V, Frydmanova A, Magerova H, Sramek M, Paulasova-Schwabova J, et al. Impact of *CYP2C19* Polymorphisms on Clinical Outcomes and Antiplatelet Potency of Clopidogrel in Caucasian Poststroke Survivors. American Journal of Therapeutics 2018;25(2).[69]	None
NA	Tornio A, Flynn R, Morant S, Velten E, Palmer CNA, MacDonald TM, et al. Investigating real-world clopidogrel pharmacogenetics in stroke using a bioresource linked to electronic medical records. Clinical Therapeutics 2017;39(8 Supplement 1).[70]	Doney A, Palmer C, Morant S, Flynn R, MacDonald T. Impact of *CYP2C19* genotype in ischaemic stroke patients treated with clopidogrel. International Journal of Stroke 2015;5.[202] Tornio A, Flynn R, Morant S, Velten E, Palmer CNA, MacDonald TM, et al. Investigating real-world clopidogrel pharmacogenetics in stroke using a bioresource linked to electronic medical records. Clinical Therapeutics 2017;39(1).[70]
NA	Wang Y, Cai H, Zhou G, Zhang Z, Liu X. Effect of *CYP2C19**2 and *3 on clinical outcome in ischemic stroke patients treated with clopidogrel. Journal of the Neurological Sciences 2016;369.[71]	None
NA	Yi X, Wang Y, Lin J, Cheng W, Zhou Q, Wang C. Interaction of *CYP2C19*, P2Y12, and GPIIIa Variants Associates with Efficacy of Clopidogrel and Adverse Events on Patients with Ischemic Stroke. Clinical and Applied Thrombosis/Hemostasis 2017;23(7).[72]	None
NA	Yi X, Lin J, Zhou J, Wang Y, Huang R, Wang C. The secondary prevention of stroke according to cytochrome P450 2C19 genotype in patients with acute large-artery atherosclerosis stroke. Oncotarget 2018;9(25).[53]	None
NA	Zhang J, Sun H, Ming T, Liu X, Cong Y, Li F, et al. Association between platelet	None

Study name	Primary Report*	Secondary reports
	function and recurrent ischemic vascular events after TIA and minor stroke. International Journal of Clinical Pharmacology and Therapeutics 2017;55(10).[73]	
CHANCE	Zhao X, Lin J, Li H, Johnston SC, Lin Y, Pan Y, et al. Association between *CYP2C19* loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. Journal of the American Medical Association 2016;316(1).[51]	Beijing Tiantan Hospital. 2021. Clopidogrel With Aspirin in High-risk Patients With Acute Non-disabling Cerebrovascular Events II. NCT04078737; URL: https://ClinicalTrials.gov/show/NCT04078737 (Accessed September 2022).[191] Xu J, Wang A, Wangqin R, Mo J, Chen Z, Dai L, et al. Efficacy of clopidogrel for stroke depends on *CYP2C19* genotype and risk profile. Annals of Neurology 2019;86(3).[192] Zhang J, Sun H, Ming T, Liu X, Cong Y, Li F, et al. Association between platelet function and recurrent ischemic vascular events after TIA and minor stroke. International Journal of Clinical Pharmacology and Therapeutics 2017;55(10).[73] Pan Y, Wangqin R, Li H, Meng X, Johnston SC, Simon T, et al. F2R Polymorphisms and Clopidogrel Efficacy and Safety in Patients With Minor Stroke or TIA. Neurology 2021;96(1).[193] Wu Y, Zhou Y, Pan Y, Zhao X, Liu L, Wang D, et al. Impact of *CYP2C19* polymorphism in prognosis of minor stroke or TIA patients with declined eGFR on dual antiplatelet therapy: CHANCE substudy. Pharmacogenomics Journal 2018;18(6).[194]

Objective 4

Studies shaded blue were included for both objectives 4 and 5

Study name	Primary Report	Secondary reports
TAILOR-PCI (pre-trial and main trial)	Baudhuin LM, Train LJ, Goodman SG, Lane GE, Lennon RJ, Mathew V, et al. Point of care CYP2C19 genotyping after percutaneous coronary intervention. Pharmacogenomics Journal 2022;22.[74]	Baudhuin L, Train L, Goodman S, Lane G, Lennon R, Mathew V, et al. Validation and performance of point-of-care rapid CYP2C19 genotyping in the tailor-pci multicenter international randomized clinical trial. Journal of the American College of Cardiology 2021;77(18).[93]
NA	Choi JL, Kim BR, Woo KS, Kim KH, Kim JM, Kim MH, et al. The diagnostic utility of the point-of-care CYP2C19 genotyping assay in patients with acute coronary syndrome dosing clopidogrel: Comparison with platelet function test and SNP genotyping. Annals of Clinical and Laboratory Science 2016;46(5).[78]	None
NA	Petrek M, Kocourkova L, Zizkova V, Nosek Z, Taborsky M, Petrkova J. Characterization of Three CYP2C19 Gene Variants by MassARRAY and Point of Care Techniques: Experience from a Czech Centre. Archivum Immunologiae et Therapiae Experimentalis 2016;64(Suppl 1).[79]	Petrkova J, Paskova L, Zizkova V, Nosek Z, Taborsky M, Petrek M. POCT for determination of basic pharmacogenetic profile for individualization of antiplatelet therapy: Pilot study. European Heart Journal 2014;1).[83]
NA	So DYF, Wells GA, McPherson R, Labinaz M, Le May MR, Glover C, et al. A prospective randomized evaluation of a pharmacogenomic approach to antiplatelet therapy among patients with ST-elevation myocardial infarction: the RAPID STEMI study. Pharmacogenomics Journal 2016;16(1).[80]	None
NA	Spartan Bioscience Inc. 2022. Method Comparison Study of the Spartan FRX *CYP2C19* Genotyping System Against Bi-directional Sequencing. NCT01718535; URL: https://ClinicalTrials.gov/show/NCT01718535 (Accessed November 2022).[82]	None
NA	Spartan Bioscience Inc. 2020. Spartan Cube CYP2C19 Inter Laboratory Reproducibilty Study. NCT04473573; URL: https://ClinicalTrials.gov/show/NCT04473573 (Accessed November 2022).[77]	None
NA	Spartan Bioscience Inc. 2020. Spartan Cube CYP2C19 Method Comparison Study. NCT04473586; URL: https://ClinicalTrials.gov/show/NCT04473586 (Accessed November 2022).[76]	None
NA	Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective,	None

Study name	Primary Report	Secondary reports
	randomised, proof-of-concept trial. Lancet 2012;379(9827).[75]	
NA	Wirth F, Zahra G, Xuereb RG, Barbara C, Fenech A, Azzopardi LM. Comparison of a rapid point-of-care and two laboratory-based CYP2C19*2 genotyping assays for personalisation of antiplatelet therapy. International Journal of Clinical Pharmacy 2016;38(2).[81]	Wirth F, Zahra G, Xuereb RG, Barbara C, Fenech A, Azzopardi LM. Comparison between a point-of-care and a laboratory-based CYP2C19 genotyping assay for pharmacist-led personalisation of antiplatelet therapy. Pharmacotherapy 2015;35(11).[97]

Objective 5

Study name	Primary Report	Secondary reports
NA	Al-Rubaish AM, Al-Muhanna FA, Alshehri AM, Alsulaiman AA, Alabdulali MM, Alkhamis F, et al. Prevalence of *CYP2C19**2 carriers in Saudi ischemic stroke patients and the suitability of using genotyping to guide antiplatelet therapy in a university hospital setup. Drug Metabolism and Personalized Therapy 2021;37(1).[84]	None
TAILOR-PCI	Baudhuin LM, Train LJ, Goodman SG, Lane GE, Lennon RJ, Mathew V, et al. Point of care *CYP2C19* genotyping after percutaneous coronary intervention. Pharmacogenomics Journal 2022;22.[74]	Baudhuin L, Train L, Goodman S, Lane G, Lennon R, Mathew V, et al. Validation and performance of point-of-care rapid *CYP2C19* genotyping in the tailor-pci multicenter international randomized clinical trial. Journal of the American College of Cardiology 2021;77(18).[93]
NA	Bergmeijer TO, Vos GJ, Claassens DM, Janssen PW, Harms R, der Heide RV, et al. Feasibility and implementation of *CYP2C19* genotyping in patients using antiplatelet therapy. Pharmacogenomics 2018;19(7).[85]	Bergmeijer TO, Janssen PWA, Schipper JC, Qaderdan K, Ishak M, Ruitenbeek RS, et al. *CYP2C19* genotype-guided antiplatelet therapy in ST-segment elevation myocardial infarction patients-Rationale and design of the Patient Outcome after primary PCI (POPular) Genetics study. American Heart Journal 2014;168(1).[94]
NA	Cavallari LH, Franchi F, Rollini F, Been L, Rivas A, Agarwal M, et al. Clinical implementation of rapid *CYP2C19* genotyping to guide antiplatelet therapy after percutaneous coronary intervention. Journal of Translational Medicine 2018;16(1).[86]	None
NA	Choi JL, Kim BR, Woo KS, Kim KH, Kim JM, Kim MH, et al. The diagnostic utility of the point-of-care *CYP2C19* genotyping assay in patients with acute coronary syndrome dosing clopidogrel: Comparison with platelet function test and SNP genotyping. Annals of Clinical and Laboratory Science 2016;46(5).[78]	None

Study name	Primary Report	Secondary reports
NA	Davis BH, DeFrank G, Limdi NA, Harada S. Validation of the Spartan RX*CYP2C19* Genotyping Assay Utilizing Blood Samples. Clinical and Translational Science 2020;13(2).[87]	None
NA	Franchi F, Rollini F, Rivas J, Rivas A, Agarwal M, Briceno M, et al. Prasugrel Versus Ticagrelor in Patients With *CYP2C19* Loss-of-Function Genotypes Results of a Randomized Pharmacodynamic Study in a Feasibility Investigation of Rapid Genetic Testing. JACC - Basic to Translational Science 2020;5(5).[88]	None
NA	Gurbel PA, Bell R, Bliden K, Yazdani S, Taheri H, Akbari M, et al. Bedside testing of *CYP2C19* genotype to guide antiplatelet therapy: Implementation in the catheterization laboratory. Journal of the American College of Cardiology Conference: 67th Annual Scientific Session of the American College of Cardiology and i2 Summit: Innovation in Intervention, ACC 2018;71(Supplement 1).[89]	None
NA	McDermott JH, Ainsworth S, Wright S, Sen D, Miele G, Smith CJ, et al. Development of a Point of Care Test for *CYP2C19*Allowing Genotype Guided Antiplatelet Prescribing to Prevent Recurrent Ischaemic Strokes. European Journal of Human Genetics 2020;28(Supplement 1).[92]	None
NA	Petrek M, Kocourkova L, Zizkova V, Nosek Z, Taborsky M, Petrkova J. Characterization of Three *CYP2C19* Gene Variants by MassARRAY and Point of Care Techniques: Experience from a Czech Centre. Archivum Immunologiae et Therapiae Experimentalis 2016;64(Supplement 1).[79]	Petrkova J, Paskova L, Zizkova V, Nosek Z, Taborsky M, Petrek M. POCT for determination of basic pharmacogenetic profile for individualization of antiplatelet therapy: Pilot study. European Heart Journal 2014;1).[83]
NA	Roberts JD, Wells GA, Le May MR, Labinaz M, Glover C, Froeschl M, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. Lancet 2012;379(9827).[75]	None
NA	So DYF, Wells GA, McPherson R, Labinaz M, Le May MR, Glover C, et al. A prospective randomized evaluation of a pharmacogenomic approach to antiplatelet therapy among patients with ST-elevation myocardial infarction: the RAPID STEMI study. Pharmacogenomics Journal 2016;16(1).[80]	None
NA	Spartan Bioscience Inc. 2020. Spartan Cube *CYP2C19* Method Comparison Study. NCT04473586; URL: https://ClinicalTrials.gov/show/NCT04473586 (Accessed November 2022).[76]	None
NA	Spartan Bioscience Inc. 2020. Spartan Cube *CYP2C19* Inter Laboratory Reproducibilty Study. NCT04473573; URL:	None

Study name	Primary Report	Secondary reports
	https://ClinicalTrials.gov/show/NCT04473573 (Accessed November 2022).[77]	
NA	Tomaniak M, Koltowski L, Kochman J, Huczek Z, Rdzanek A, Pietrasik A, et al. Can prasugrel decrease the extent of periprocedural myocardial injury during elective percutaneous coronary intervention? Polish Archives of Internal Medicine-Polskie Archiwum Medycyny Wewnetrznej 2017;127(11)	None
NA	Zhou Y, Armstead AR, Coshatt GM, Limdi NA, Harada S. Comparison of two point-of-care *CYP2C19* genotyping assays for genotype-guided antiplatelet therapy. *Annals of Clinical and Laboratory Science* 2017;**47(6)**.[91]	Zhou Y, Armstead AR, Coshatt GM, Brott BC, Sankaranarayanan A, Limdi NA, et al. Rapid *CYP2C19* genotype testing: Comparison between spartan RX *CYP2C19* and verigene *CYP2C19*. Journal of Molecular Diagnostics 2015;17(6).[98]

On-going studies

Objective	Report
1	Wang J, Han M, Kuang J, Tu J, Starcevich K, Gao P, et al. Personalized antiplatelet therapy based on clopidogrel/aspirin resistance tests in acute ischemic stroke and transient ischemic attack: Study protocol of a multi-center, single-blinded and randomized controlled trial. Contemporary Clinical Trials 2021;108[203]
3	Gangnam Severance Hospital. 2022. Clopidogrel Preventive Effect Based on *CYP2C19* Genotype in Ischemic Stroke. NCT04072705; URL: https://ClinicalTrials.gov/show/NCT04072705 (Accessed September 2022)[204]
3	Zhang XG, Zhu XQ, Xue J, Li ZZ, Jiang HY, Hu L, et al. Personalised antiplatelet therapy based on pharmacogenomics in acute ischaemic minor stroke and transient ischaemic attack: study protocol for a randomised controlled trial. BMJ Open 2019;9(5)[205]

Studies excluded at full-text screening (objective 1-3)

Reasons for exclusion align with the study selection protocol above.

Study Details	Reason for exclusion
1. Al-Rubaish AM, Al-Muhanna FA, Alshehri AM, Alsulaiman AA, Alabdulali MM, Alkhamis F, et al. Prevalence of *CYP2C19**2 carriers in Saudi ischemic stroke patients and the suitability of using genotyping to guide antiplatelet therapy in a university hospital setup. Drug Metabolism and Personalized Therapy 2022;37(1).	Intervention: no intervention listed in the protocol (obj1/2) or presence of *2 or *3 LOF alleles)
2. Alakbarzade V, Huang X, Drury S, Chis Ster I, McEntagert M, Pereira AC. High on-clopidogrel platelet reactivity in stroke: A systematic review and meta-analysis. European Stroke Journal 2019;4(Supplement 1).	Publication type: Systematic review
3. Alakbarzade V, Huang X, Ster IC, McEntagart M, Pereira AC. High on-clopidogrel platelet reactivity in ischaemic stroke or transient ischaemic attack: Systematic review and meta-analysis. Journal of Stroke and Cerebrovascular Diseases 2020;29(7)	Publication type: Systematic review
4. Ali Z, Elewa H. The Effect of *CYP2C19* and Nongenetic Factors on Clopidogrel Responsiveness in the MENA Region: A Systematic Review. Clinical and Applied Thrombosis/Hemostasis 2019;25	Publication type: Systematic review
5. Alkattan A, Almutairi Y, Alsalameen E, Alkhalifah A, Alghanim F. The *CYP2C19* genotypes and its effect on clopidogrel as an anti-platelet drug among the Arab population. Indian Journal of Pharmacology 2021;53(1).	Publication type: Commentary
6. Alkattan A, Alsalameen E. Polymorphisms of genes related to phase-I metabolic enzymes affecting the clinical efficacy and safety of clopidogrel treatment. Expert Opinion on Drug Metabolism and Toxicology 2021;17(6).	Publication type: Review
7. Alrajeh KY, Roman YM. The frequency of major *CYP2C19* genetic polymorphisms in women of Asian, Native Hawaiian and Pacific Islander subgroups. Personalized Medicine 2022;19(4).	Outcomes: did not report on any outcomes specified in the inclusion criteria.
8. Bauer T, Bouman HJ, Van Werkum JW, Ford NF, Ten Berg JM, Taubert D. Impact of *CYP2C19* variant genotypes on clinical efficacy of antiplatelet treatment with clopidogrel: Systematic review and meta-analysis. British Medical Journal 2011;343(7819) (no pagination).	Publication type: Systematic review
9. Bhopalwala AM, Hong RA, Khan ZR, Valentin MR, Badawi RA. Routine screening for *CYP2C19* polymorphisms for patients being treated with clopidogrel is not recommended. Hawai'i Journal of Medicine & Public Health : A Journal of Asia Pacific Medicine & Public Health 2015;74(1).	Publication type: Review
10. Bo H, De-Jun C, Ying R, Bin H, Da-Ping Y, Xun Z. Effect of cytochrome P450 2C19*17 allelic variant on cardiovascular and cerebrovascular outcomes in clopidogrel-treated patients: A systematic review and meta-analysis. Journal of Research in Medical Sciences 2017;22.	Publication type: Systematic review
11. Borchard-Tuch C. Transient ischemic attacks/stroke: *CYP2C19* variations induce reduced effectiveness of clopidogrel. Medizinische Monatsschrift fur Pharmazeuten 2017;40(6).	Publication type: Commentary

Study Details	Reason for exclusion
12 Calcagno S, Di Pietro R, Biondi-Zoccai G, Versaci F. Do We Really Need Routine *CYP2C19* Genotyping? JACC: Cardiovascular Interventions 2020;13(9).	Publication type: Letter
13. Castrichini M, Luzum JA, Pereira N. Pharmacogenetics of Antiplatelet Therapy. Annual review of pharmacology and toxicology 2022;01.	Publication type: Review
14. Chen YB, Zhou ZY, Li GM, Xiao CX, Yu WB, Zhong SL, et al. Influences of an NR1I2 polymorphism on heterogeneous antiplatelet reactivity responses to clopidogrel and clinical outcomes in acute ischemic stroke patients. Acta Pharmacologica Sinica 2019;40(6).	Intervention: no intervention listed in the protocol (obj1/2)
15. Chi NF, Wang SJ. *CYP2C19* loss-of-function alleles: A common but overlooked problem associated with clopidogrel resistance. Journal of the Chinese Medical Association 2019;82(10).	Publication type: Editorial
16. Department of Neurology, Zhujiang Hospital of Southern Medical University. 2018. The efficacy of Clopidogrel on patients of different *CYP2C19* genotypes under the guidance of thromboelastogram. ChiCTR1800015314; URL: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01898880/full (Accessed September 2022).	Outcomes: did not report on any outcomes specified in the inclusion criteria.
17. Dong Y, Cheng X, Dong Q. Letter by Dong et al regarding article, "*CYP2C19* polymorphisms and antiplatelet effects of clopidogrel in acute ischemic stroke in China". Stroke 2013;44(9).	Publication type: Letter
18. Ellithi M, Baye J, Wilke RA. *CYP2C19* genotype-guided antiplatelet therapy: promises and pitfalls. Pharmacogenomics 2020;21(12).	Publication type: Review
19. Fang L, Zhao Y, Wang N, Yang Z, Huang H, Lin M. Association of *CYP2C19* gene polymorphisms with long-term recurrent risk of ischemic stroke among ethnic Han Chinese from Fujian. [Chinese]. Zhonghua yi xue yi chuan xue za zhi = Zhonghua yixue yichuanxue zazhi = Chinese journal of medical genetics 2015;32(6).	Unretrievable
20. Geisler T, Bigalke B, Schwab M. *CYP2C19* genotype and outcomes of clopidogrel treatment [1]. New England Journal of Medicine 2011;364(5).	Publication type: Letter
21. Han SW, Park JH, Kim K, Lee KY. Influence of smoking on the effect of clopidogrel may be dependent on *CYP2C19* polymorphisms. International Journal of Stroke 2018;13(2 Supplement 1).	Intervention : not the right test and there is no report of LOF alleles
22. Han Y, Lv HH, Liu X, Dong Q, Yang XL, Li SX, et al. Influence of Genetic Polymorphisms on Clopidogrel Response and Clinical Outcomes in Patients with Acute Ischemic Stroke *CYP2C19* Genotype on Clopidogrel Response. CNS Neuroscience and Therapeutics 2015;21(9).	Outcomes: did not report on any outcomes specified in the inclusion criteria.
23. Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP. *CYP2C19* genotype, clopidogrel metabolism, platelet function, and cardiovascular events: A systematic review and meta-analysis. Journal of the American Medical Association 2011;306(24).	Publication type: Systematic review
24. Hulot JS, Collet JP, Silvain J, Pena A, Bellemain-Appaix A, Barthelemy O, et al. Cardiovascular Risk in Clopidogrel-Treated Patients According to Cytochrome P450 2C19*2 Loss-of-Function	Publication type: Systematic review

Study Details	Reason for exclusion
Allele or Proton Pump Inhibitor Coadministration. A Systematic Meta-Analysis. Journal of the American College of Cardiology 2010;56(2).	
25. Jeong TD, Kim SM, Kim HJ, Lee W, Kwon SU, Min WK, et al. *CYP2C19* genotype and early ischemic lesion recurrence in stroke patients treated with clopidogrel. Journal of Stroke and Cerebrovascular Diseases 2015;24(2).	Outcomes: did not report on any outcomes specified in the inclusion criteria.
26. Jia DM, Chen ZB, Zhang MJ, Yang WJ, Jin JL, Xia YQ, et al. *CYP2C19* polymorphisms and antiplatelet effects of clopidogrel in acute ischemic stroke in China. Stroke 2013;44(6).	Outcomes: did not report on any outcomes specified in the inclusion criteria.
27. Joob B, Wiwanitkit V. *CYP2C19**2 polymorphism and clopidogrel resistance. Archivos de Cardiologia de Mexico 2020;90(4).	Publication type: Letter
28. Kitazono T, Ikeda Y, Nishikawa M, Yoshiba S, Abe K, Ogawa A. Influence of cytochrome P450 polymorphisms on the antiplatelet effects of prasugrel in patients with non-cardioembolic stroke previously treated with clopidogrel. Journal of Thrombosis and Thrombolysis 2018;46(4).	Outcomes – Did no report on any relevant outcomes for comparison of interest specified in the inclusion criteria by genotype
29. Kremers F, Van Den Biggelaar J, Lingsma H, Roozenbeek B, Dippel D. Effect of clopidogrel in *CYP2C19* polymorphisms for prevention of vascular events in patients with cardiovascular disease or recent tia or minor ischemic stroke. European Stroke Journal 2021;6(1 SUPPL).	Publication type: Systematic review
30. Kreutzkamp B. Secondary prevention with clopidogrel: *CYP2C19**2 gene variant as a common cause of treatment failure. [German]. Arzneimitteltherapie 2009;27(9).	Publication type: Commentary
31. Lan H, Ying T, Xi-Hua S, Yi L. Anti-Platelet Therapy in Mild Cerebral Infarction Patients on the Basis of *CYP2C19* Metabolizer Status. Cell Transplantation 2019;28(8).	Intervention: no intervention listed in the protocol (obj1/2) and presence of *2 or *3 LOF alleles)
32. Lee BC, Oh MS, Yu KH, Kwon KH, Kim BS. *CYP2C19* variants do not associated with clinical efficacy of clopidogrel in Korean stroke survivors. Cerebrovascular Diseases 2012;2.	Unretrievable
33. Li C, Jia W, Li J, Li F, Ma J, Zhou L. Association with *CYP2C19* polymorphisms and Clopidogrel in treatment of elderly stroke patients. BMC Neurology 2021;21(1).	Intervention: no relevant comparisons of interest
34. Lin J, Han Z, Wang C, Yi X, Chai Z, Zhou Q, et al. Dual therapy with clopidogrel and aspirin prevents early neurological deterioration in ischemic stroke patients carrying *CYP2C19**2 reduced-function alleles. European Journal of Clinical Pharmacology 2018;74(9).	Outcomes: did not report on any outcomes specified in the inclusion criteria.
35. Lin YJ, Li JW, Zhang MJ, Qian L, Yang WJ, Zhang CL, et al. The association between *CYP2C19* genotype and of in-stent restenosis among patients with vertebral artery stent treatment. CNS Neuroscience and Therapeutics 2014;20(2).	Outcomes: did not report on any outcomes specified in the inclusion criteria.
36. Liu YP, Hao PP, Zhang MX, Zhang C, Gao F, Zhang Y, et al. Association of genetic variants in *CYP2C19* and adverse clinical outcomes after treatment with clopidogrel: an updated meta-analysis. Thrombosis Research 2011;128(6).	Publication type: Letter
37. Lun R, Zitikyte G, Roy DC, Dhaliwal S, Hutton B, Dowlatshahi D. Ticagrelor and Aspirin Vs Clopidogrel and Aspirin in Patients with Minor Ischemic Stroke or Transient Ischemic Attack (Tia) - an	Publication type: Systematic review

Study Details	Reason for exclusion
Updated Network Meta-Analysis. European Stroke Journal 2022;7(1 SUPPL).	
38. Lyu SQ, Yang YM, Zhu J, Wang J, Wu S, Zhang H, et al. The efficacy and safety of *CYP2C19* genotype-guided antiplatelet therapy compared with conventional antiplatelet therapy in patients with acute coronary syndrome or undergoing percutaneous coronary intervention: A meta-analysis of randomized controlled trials. Platelets 2020;31(8).	Publication type: Systematic review
39. Maeda A. Different influences of *CYP2C19* gene polymorphisms on the antiplatelet effect of clopidogrel and ticlopidine. [Japanese]. Japanese Journal of Clinical Pharmacology and Therapeutics 2011;42(3).	Outcomes: did not report on any outcomes specified in the inclusion criteria.
40. Malik AH, Gupta R, Chakraborty S, Mahajan P, Bandyopadhyay D, Yandrapalli S, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. Cardiovascular Revascularization Medicine 2022;41.	Publication type: Systematic review
41. Mao L, Jian C, Changzhi L, Dan H, Suihua H, Wenyi T, et al. Cytochrome *CYP2C19* polymorphism and risk of adverse clinical events in clopidogrel-treated patients: a meta-analysis based on 23,035 subjects. Archives of cardiovascular diseases 2013;106(10).	Publication type: Systematic review
42. McDermott JH, Leach M, Sen D, Smith CJ, Newman WG, Bath PM. The role of *CYP2C19* genotyping to guide antiplatelet therapy following ischemic stroke or transient ischemic attack. Expert review of clinical pharmacology 2022;01.	Publication type: Literature review
43. Medco Health Solutions Inc. 2012. Genotype Guided Comparison of Clopidogrel and Prasugrel Outcomes Study (GeCCO). NCT00995514; URL: https://ClinicalTrials.gov/show/NCT00995514 (Accessed September 2022).	Population: no report of stroke or TIA
44. Minderhoud C, Otten LS, Hilkens PHE, van den Broek MPH, Harmsze AM. Increased frequency of *CYP2C19* loss-of-function alleles in clopidogrel-treated patients with recurrent cerebral ischemia. British Journal of Clinical Pharmacology 2022;88(7).	Study design: not an RCT or cohort study
47. Niu X, Mao L, Huang Y, Baral S, Li JY, Gao Y, et al. *CYP2C19* polymorphism and clinical outcomes among patients of different races treated with clopidogrel: A systematic review and meta-analysis. Journal of Huazhong University of Science and Technology Medical Sciences 2015;35(2).	Publication type: Systematic review
48. Pan Y, Chen W, Xu Y, Yi X, Han Y, Yang Q, et al. Genetic polymorphisms and clopidogrel efficacy for acute ischemic stroke or transient ischemic attack. Circulation 2017;135(1).	Publication type: Systematic review
49. Pilling LC, Turkmen D, Fullalove H, Atkins JL, Delgado J, Kuo CL, et al. Analysis of *CYP2C19* genetic variants with ischaemic events in UK patients prescribed clopidogrel in primary care: a retrospective cohort study. BMJ Open 2021;11(12).	Population – not exclusively stroke/TIA population and data not reported separately for subset that were.
50. Siasos G, Tousoulis D, Stefanadis C. *CYP2C19* genotype and outcomes of clopidogrel treatment [2]. New England Journal of Medicine 2011;364(5).	Publication type: Letter

Study Details	Reason for exclusion
51. Sienkiewicz-Oleszkiewicz B, Wiela-Hojenska A. *CYP2C19* polymorphism in relation to the pharmacotherapy optimization of commonly used drugs. Pharmazie 2018;73(11).	Publication type: Literature review
52. Singh A, Coy K, Schmidtman D, Stys A, Stys T. Impact of clopidogrel metabolizer status on incidence of gastrointestinal bleed. Circulation Conference: American Hearts Association's 2021;144(SUPPL 1).	Population: no report of stroke or TIA
53. Sofi F, Giusti B, Gori A, Marcucci R, Abbate R, Gensini G. Cytochrome P450 2C19 polymorphism and cardiovascular recurrences in patients under clopidogrel treatment: A meta-analysis. Journal of Thrombosis and Haemostasis 2009;7(S2). (The review was reported in publication: Sofi, F., Giusti, B., Marcucci, R. et al. Cytochrome P450 2C19*2 polymorphism and cardiovascular recurrences in patients taking clopidogrel: a meta-analysis. Pharmacogenomics J 11)	Publication type: Systematic review
54. Sofi F, Giusti B, Gori AM, Cesari F, Marcucci R, Abbate R, et al. Cytochrome P450 2c19 polymorphism and cardiovascular recurrences in patients under clopidogrel treatment: A meta-analysis. European Journal of Cardiovascular Prevention and Rehabilitation 2010;2).	Publication type: Systematic review
55. Song TJ, Kim J, Han SW, Kim YD, Lee JY, Ahn SH, et al. Clopidogrel preventive effect based on cytochrome P450 2C19 genotype in ischaemic stroke: protocol for multicentre observational study. BMJ Open 2020;10(8).	Publication type: Protocol
56. Sorich MJ, Polasek TM, Wiese MD. Systematic review and meta-analysis of the association between cytochrome P450 2C19 genotype and bleeding. Thrombosis and Haemostasis 2012;108(1).	Publication type: Letter
57. Stanley A, Beoris M, Austria A, Baca AA, Amos Wilson J, Garces JA, et al. Clopidogrel utilization in a U.S. population: A pharmacogenetic and metabolic overview of patient eligibility. Journal of Molecular Diagnostics 2015;17(6).	Outcomes: did not report on any outcomes specified in the inclusion criteria.
58. University of Puerto Rico. 2022. A Genomic Approach for Clopidogrel in Caribbean Hispanics. NCT03419325; URL: https://ClinicalTrials.gov/show/NCT03419325 (Accessed September 2022).	Population: no report of stroke or TIA.
59. Wang D, Li L, Jiang J, Zhang Q, Liu M, Liu Y, et al. Age-dependent association of *CYP2C19* polymorphisms with clinical outcome of clopidogrel therapy in minor stroke patients with large-artery atherosclerosis. European Journal of Clinical Pharmacology 2020;76(9).	Outcomes: did not report on any outcomes specified in the inclusion criteria.
60. Xie Q, Xiang Q, Liu Z, Mu G, Zhou S, Zhang Z, et al. Effect of *CYP2C19* genetic polymorphism on the pharmacodynamics and clinical outcomes for patients treated with ticagrelor: a systematic review with qualitative and quantitative meta-analysis. BMC Cardiovascular Disorders 2022;22(1).	Publication type: Systematic review
61. Xu H, Xu B, Zu Q, Zhao Y, Gao P, Yu Y. Effects of *CYP2C19* gene polymorphism on the clinical prognosis of clopidogrel in elderly patients with acute cerebral infarction. [Chinese]. Chinese Journal of Clinical Pharmacology and Therapeutics 2020;25(9).	Unretrievable

Study Details	Reason for exclusion
62. Yamaguchi Y, Abe T, Sato Y, Matsubara Y, Moriki T, Murata M. Effects of VerifyNow P2Y12 test and *CYP2C19**2 testing on clinical outcomes of patients with cardiovascular disease: A systematic review and meta-analysis. Platelets 2013;24(5).	Publication type: Systematic review
63. Yang L, Xie J, Liu Y, Hu X. Correlation between the genetic polymorphism of *CYP2C19**2, *3 and the clinical efficacy of clopidogrel: Asystematic review. [Chinese]. Chinese Journal of Evidence-Based Medicine 2012;12(9).	Unretrievable
64. Yang Y, Chen W, Pan Y, Yan H, Meng X, Liu L, et al. Ticagrelor Is Superior to Clopidogrel in Inhibiting Platelet Reactivity in Patients With Minor Stroke or TIA. Frontiers in Neurology 2020;11 (no pagination).	Outcomes: did not report on any outcomes specified in the inclusion criteria by genotype.
65. Yi X, Zhou Q, Wang C, Lin J, Chai Z. Aspirin plus clopidogrel may reduce the risk of early neurologic deterioration in ischemic stroke patients carrying *CYP2C19**2 reduced-function alleles. Journal of Neurology 2018;265(10).	Outcomes: did not report on any outcomes specified in the inclusion criteria by genotype.
66. New Zealand University Hospital. 2017. Clopidogrel Response and *CYP2C19* Genotype in Ischemic Stroke Patients (CLOGIS). NCT03385538; URL: https://ClinicalTrials.gov/show/NCT03385538 (Accessed September 2022).	Outcomes: did not report on any outcomes specified in the inclusion criteria.
67. Zhang H, Xiang Q, Liu Z, Mu G, Xie Q, Zhou S, et al. Genotype-guided antiplatelet treatment versus conventional therapy: A systematic review and meta-analysis. British Journal of Clinical Pharmacology 2021;87(5).	Publication type: Systematic review
68. Zhang S, Lai X, Li W, Xiong Z, Xu A, Xu A, et al. VASP phosphorylation and genetic polymorphism for clopidogrel resistance in Chinese patients with non-cardioembolic ischemic stroke. Thrombosis Research 2014;134(6).	Publication type: Systematic review
69. Zhang X, Jing J, Zhao X, Liu L, Wang A, Pan Y, et al. No rebound effect after a course of clopidogrel in patients with acute TIA or minor stroke. Neurological Research 2022.	Exposure: compares patients who continued treatment vs. patients who stopped treatment.
70. Zheng L, Yang C, Xiang L, Hao Z. Genotype-guided antiplatelet therapy compared with conventional therapy for patients with acute coronary syndromes: a systematic review and meta-analysis. Biomarkers 2019;24(6).	Publication type: Systematic review
71. Zhu Y, Moriarty JP, Swanson KM, Takahashi PY, Bielinski SJ, Weinshilboum R, et al. PCV10 A MODEL-Based Cost-Effectiveness Analysis of Pharmacogenomic Panel Testing in Cardiovascular Disease Management: Preemptive, Reactive or NONE? Value in Health Regional Issues 2020;22(Supplement).	Study design: Cost-effectiveness study

Studies excluded at full-text screening (objective 4-5)

Study Details	Reason for exclusion
Biswas M. Global distribution of *CYP2C19* risk phenotypes affecting safety and effectiveness of medications. Pharmacogenomics. 2021;21(2):190-199.	Not a primary study: secondary reanalysis of a data set
Capodanno D, Angiolillo DJ, Lennon RJ, Goodman SG, Kim SW, O'Cochlain F, et al. ABCD-GENE Score and Clinical Outcomes Following Percutaneous Coronary Intervention: Insights from the TAILOR-PCI Trial. Journal of the American Heart Association 2022;11(4).	Used Genomadix Cube but did not report an evaluation of the test or outcomes of interest
Chen X, Xu J, Chen S, Dong Q, Dong Y. Dual antiplatelet therapy with ticagrelor may increase the risk of all bleeding events in patients with minor strokes or high risk TIAs: a meta- analysis [published online ahead of print, 2022 Mar 3]. Stroke and Vascular Neurology 2022;	Publication type: Systematic review
Claassens DMF, Bergmeijer TO, Vos GJA, Hermanides RS, t Hof A, van der Harst P, et al. Clopidogrel Versus Ticagrelor or Prasugrel After Primary Percutaneous Coronary Intervention According to *CYP2C19* Genotype A POPular Genetics Subanalysis. Circulation-Cardiovascular Interventions 2021;14(4).	Used Genomadix Cube but did not report an evaluation of the test or outcomes of interest
Claassens DMF, Gimbel ME, Bergmeijer TO, Vos GJA, Hermanides RS, van der Harst P, et al. Clopidogrel in noncarriers of *CYP2C19* loss-of-function alleles versus ticagrelor in elderly patients with acute coronary syndrome: A pre-specified sub analysis from the POPular Genetics and POPular Age trials *CYP2C19* alleles in elderly patients. International Journal of Cardiology 2021;334.	Used Genomadix Cube but did not report an evaluation of the test or outcomes of interest
Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P, et al. A Genotype-Guided Strategy for Oral P2Y(12) Inhibitors in Primary PCI. New England Journal of Medicine 2019;381(17).	Used Genomadix Cube but did not report an evaluation of the test or outcomes of interest
Collet JP, Kerneis M, Hulot JS, O'Connor SA, Silvain J, Mansencal N, et al. Point-of-care genetic profiling and/or platelet function testing in acute coronary syndrome. Thrombosis and Haemostasis 2016;115(2).	Test: POCT out of scope (Verigene test)
Dawson J, Merwick A, Webb A, Dennis M, Ferrari J, Fonseca AC, et al. European Stroke Organisation expedited recommendation for the use of short-term dual antiplatelet therapy early after minor stroke and high-risk TIA. European stroke journal 2021;6(2):VI.	Not a primary study: guideline
Erlinge D, James S, Duvvuru S, Jakubowski J, Wanger H, Varenhorst C, et al. Point-of-care genetic testing of eleven *CYP2C19* single nucleotide polymorphisms identifies extensive and reduced metabolizers of clopidogrel with high accuracy in patients with coronary artery disease. Journal of the American College of Cardiology 2012;17.	Test: POCT out of scope (Verigene test)
Franchi F, Rollini F. Genotype-Guided Antiplatelet Therapy in Patients With Coronary Artery Disease. JACC-Cardiovascular Interventions 2021;14(7).	Publication type: Editorial
Gurbel PA, Bliden KP, Antonino M, Verma A, Jeong YH, Tantry US. First validation of point-of-care *CYP2C19* genetic testing in patients undergoing coronary angiography with the Verigene nucleic acid assay. Journal of the American College of Cardiology 2011;1.	Test: POCT out of scope (Verigene test)

Study Details	Reason for exclusion
Hao Q, Tampi M, O'Donnell M, Foroutan F, Siemieniuk RA, Guyatt G. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. British Medical Journal 2018;363:k5108.	Publication type: Systematic review
Hulot JS, Chevalier B, Belle L, Cayla G, Khalife K, Funck F, et al. Routine *CYP2C19* Genotyping to Adjust Thienopyridine Treatment After Primary PCI for STEMI Results of the GIANT Study. JACC-Cardiovascular Interventions 2020;13(5).	Test: No POCT used
Hulot JS, Collet JP, Cayla G, Silvain J, Allanic F, Bellemain-Appaix A, et al. *CYP2C19* But Not PON1 Genetic Variants Influence Clopidogrel Pharmacokinetics, Pharmacodynamics, and Clinical Efficacy in Post-Myocardial Infarction Patients. Circulation-Cardiovascular Interventions 2011;4(5).	Test: No POCT used
Imam Abdulrahman Bin Faisal University. 2016. Bedside Testing of *CYP2C19* Gene for Treatment of Patients With PCI With Antiplatelet Therapy. NCT01823185; URL: https://ClinicalTrials.gov/show/NCT01823185 (Accessed November 2022).	Test: Used Genomadix Cube but did not report an evaluation of the test or outcomes of interest
Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, et al. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. New England journal of medicine 2016;375(1):35-43.	Test: No POCT used
Kim HK, Sibbing D, Jeong YH. Effect of genotype-guided strategy in East Asian vs. Caucasian patients after percutaneous coronary intervention: insight from the TAILOR-PCI trial. Journal of Thoracic Disease 2020;12(12).	Not a primary study
Koltowski L, Aradi D, Huczek Z, Tomaniak M, Sibbing D, Filipiak KJ, et al. Study design and rationale for Optimal aNtiplatelet pharmacotherapy guided by bedSIDE genetic or functional TESTing in elective percutaneous coronary intervention patients (ONSIDE TEST): a prospective, open-label, randomised parallel-group multicentre trial. Kardiologia Polska 2016;74(4).	Not a primary study
Lee CR, Luzum JA, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2C19* Genotype and Clopidogrel Therapy: 2022 Update [published online ahead of print, 2022 Jan 16]. *Clinical Pharmacology & Therapeutics*. 2022;10.1002/cpt.2526.	Not a primary study
Li YJ, Chen X, Tao LN, Hu XY, Wang XL, Song YQ. Association between *CYP2C19* polymorphisms and clinical outcomes in patients undergoing stent procedure for cerebral artery stenosis. Sci Rep. 2021;11(1):5974. Published 2021 Mar 16.	Test: No POCT used
Li Y-J, Chen X, Tao L-N, Hu X-Y, Wang X-L, Song Y-Q. Association between *CYP2C19* polymorphisms and clinical outcomes in patients undergoing stent procedure for cerebral artery stenosis. *Scientific Reports* 2021;**11**(1):5974	Test: No POCT used
Luengo-Fernandez R, Violato M, Candio P, Leal J. Economic burden of stroke across Europe: A population-based cost analysis. Eur Stroke J. 2020;5(1):17-25.	Test: Not an evaluation of a POCT (cost-analysis)

Study Details	Reason for exclusion
Madan M, Abbott JD, Lennon R, So DYF, MacDougall AM, McLaughlin MA, et al. Sex-Specific Differences in Clinical Outcomes After Percutaneous Coronary Intervention: Insights from the TAILOR-PCI Trial. Journal of the American Heart Association 2022;11(12).	Test: Used Genomadix Cube but did not report an evaluation of the test or outcomes of interest
Marziliano N, Notarangelo MF, Cereda M, Caporale V, Coppini L, Demola MA, et al. Rapid and portable, lab-on-chip, point-of-care genotyping for evaluating clopidogrel metabolism. International journal of clinical chemistry 2015;Part B. 451.	Population: not our cohort of interest
Meng X, Wang A, Zhang G, Niu S, Li W, Han S, et al. Analytical validation of GMEX rapid point-of-care *CYP2C19* genotyping system for the CHANCE-2 trial. Stroke and Vascular Neurology 2021;6(2).	Test: POCT out of scope (GMEX system)
Anita Patel, Vladislav Berdunov, Derek King, Zahidul Quayyum, Raphael Wittenberg, Martin Knapp. *Current, future and avoidable costs of stroke in the UK*. London: Centre for Primary Care & Public Health, Queen Mary University of London, and the Personal Social Services Research Unit,; 2017. (Accessed November 2022) https://www.stroke.org.uk/sites/default/files/costs_of_stroke_in_the_uk_summary_report_0.pdf:	Not a primary study: Published report
Pereira NL, Avram R, So DY, Iturriaga E, Byrne J, Lennon RJ*, et al.* Rationale and design of the TAILOR-PCI digital study: Transitioning a randomized controlled trial to a digital registry. American Heart Journal 2021;**232**	Not a primary study: paper describing the TAILOR-PCI study
Pereira NL, Rihal CS, So DYF, Rosenberg Y, Lennon RJ, Mathew V, et al. Clopidogrel Pharmacogenetics State-of-the-Art Review and the TAILOR-PCI Study. Circulation-Cardiovascular Interventions 2019;12(4).	Not a primary study: Literature review
Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V*, et al.* Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: the TAILOR-PCI Randomized Clinical Trial. Journal of the American Medical Association 2020;**324**(8).	Population: no extra data on cohort of interest
Pilling LC, Türkmen D, Fullalove H, et al. Analysis of *CYP2C19* genetic variants with ischaemic events in UK patients prescribed clopidogrel in primary care: a retrospective cohort study. BMJ Open. 2021;11(12):e053905. Published 2021 Dec 13.	Test: No POCT used
Stimpfle F, Karathanos A, Droppa M, et al. Impact of point-of-care testing for *CYP2C19* on platelet inhibition in patients with acute coronary syndrome and early dual antiplatelet therapy in the emergency setting. Thrombosis Research. 2014;134(1):105-110.	Used Genomadix Cube but did not report an evaluation of the test or outcomes of interest
Spartan Bioscience Inc. Spartan FRX Project Reproducibility Study. NCT01676298; URL: https://ClinicalTrials.gov/show/NCT01676298 (Accessed November 2022).	Study design: Analytical validity study
Uchino K. Guideline: Starting dual antiplatelet therapy ≤ 24 h after high-risk TIA or minor ischemic stroke is recommended. Annals of Internal Medicine. 2019 Apr 16;170(8):JC38.	Not a primary study: guideline
Wafa HA, Wolfe CDA, Emmett E, Roth GA, Johnson CO, Wang Y. Burden of Stroke in Europe: Thirty-Year Projections of Incidence, Prevalence, Deaths, and Disability-Adjusted Life Years. Stroke. 2020	Not a primary study: review of prevenance

Study Details	Reason for exclusion
Aug;51(8):2418-2427. doi: 10.1161/STROKEAHA.120.029606. Epub 2020 Jul 10.	
Wang YJ, Meng X, Wang AX, Xie XW, Pan YS, Johnston SC, et al. Ticagrelor versus Clopidogrel in *CYP2C19* Loss-of-Function Carriers with Stroke or TIA. New England Journal of Medicine 2021;385(27).	Test: POCT out of scope (GMEX system)
Wang YL, Zhao XQ, Lin JX, Li H, Johnston SC, Lin Y, et al. Association Between *CYP2C19* Loss-of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients With Minor Stroke or Transient Ischemic Attack. Journal of the American Medical Association 2016;316(1).	Test: No POCT used
Zhang LC, Ma XW, You GL, Zhang XQ, Fu QH. A Novel Multiplex HRM Assay to Detect Clopidogrel Resistance. Scientific Reports 2017;7.	Test: Test out of scope (Multiplex HRM Assay)

Studies included in manufacturers' submissions

Below we tabulate how studies reported in submissions were handled. These tables/studies apply to the review of test accuracy (objectives 4 or 5).

Genedrive

No studies were included in the manufacturers submission.

Genomadix

Study Details	Decision	Reason for exclusion
Al-Rubaish AM, Al-Muhanna FA, et al. Prevalence of *CYP2C19**2 carriers in Saudi ischemic stroke patients and the suitability of using genotyping to guide antiplatelet therapy in a university hospital setup. Drug Metabolism and Personalized Therapy. 2021 Jul 8;37(1).	Included	N/A
Baudhuin LM, Train LJ, *et al.* Point of care *CYP2C19* genotyping after percutaneous coronary intervention. Pharmacogenomics. 2022 Apr 21.	Included	N/A
Roberts JD, Wells GA, Le May MR, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. Lancet. 2012;379(9827).	Included	N/A
Zhou Y, Armstead AR, Coshatt GM, Limdi NA, Harada S. Comparison of Two Point-of- Care *CYP2C19* Genotyping Assays for Genotype-Guided Antiplatelet Therapy. Ann Clin Lab Sci. 2017 Nov;47(6):738-743.	Included	N/A
Biswas M. Global distribution of *CYP2C19* risk phenotypes affecting safety and effectiveness of medications. Pharmacogenomics. 2021;21(2).	Excluded	Not a primary study: prevalence study (no data).
Chen X, Xu J, Chen S, Dong Q, Dong Y. Dual antiplatelet therapy with ticagrelor may increase the risk of all bleeding events in patients with minor strokes or high risk TIAs: a meta- analysis [published online ahead of print, 2022 Mar 3]. Stroke and vascular neurology. 2022;	Excluded	Publication type: Meta-analysis

Study Details	Decision	Reason for exclusion
Claassens DMF, Vos GJA, Ten Berg JM et al. A Genotype-Guided Strategy for Oral P2Y12 Inhibitors in Primary PCI. New England Journal of Medicine. 2019 Oct 24;381(17).	Excluded	Outcomes: no outcome data for Genomadix.
Dawson J, Merwick Á, Webb A, et al. European Stroke Organisation expedited recommendation for the use of short-term dual antiplatelet therapy early after minor stroke and high- risk TIA. European Stroke Journal. 2021;6(2).	Excluded	Not a primary study: guideline.
Hao Q, Tampi M, O'Donnell M, Foroutan F, Siemieniuk RA, Guyatt G. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. British Medical Journal. 2018;363.	Excluded	Publication type: Systematic review
Johnston SC, Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Jonasson J, Minematsu K, Molina CA, Wang Y, Wong KS; SOCRATES Steering Committee and Investigators. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. New England Journal of Medicine. 2016 Jul 7;375(1).	Excluded	Test: no reported *CYP2C19* genotyping
Lee CR, Luzum JA, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for *CYP2C19* Genotype and Clopidogrel Therapy: 2022 Update [published online ahead of print, 2022 Jan 16]. Clinical Pharmacology & Therapeutic.	Excluded	Not a primary study: guideline.
Li C, Jia W, Li J, Li F, Ma J, Zhou L. Association with *CYP2C19* polymorphisms and Clopidogrel in treatment of elderly stroke patients. BMC Neurology. 2021;21(1):104.	Excluded	Test: no reported *CYP2C19* genotyping
Li YJ, Chen X, Tao LN, Hu XY, Wang XL, Song YQ. Association between *CYP2C19* polymorphisms and clinical outcomes in patients undergoing stent procedure for cerebral artery stenosis. Scientific Reports . 2021;11(1).	Excluded	Test: Study did not report an evaluation of POCT in scope
Luengo-Fernandez R, Violato M, Candio P, Leal J. Economic burden of stroke across Europe: A population-based cost analysis. European Stroke Journal. 2020;5(1).	Excluded	Test/ Outcomes: no reported *CYP2C19* genotyping and study reports cost outcomes.
Anita Patel, Vladislav Berdunov, Derek King, Zahidul Quayyum, Raphael Wittenberg, Martin Knapp. *Current, future and avoidable costs of stroke in the UK*. London: Centre for Primary Care & Public Health, Queen Mary University of London, and the Personal Social Services Research Unit,; 2017. (Accessed November 2022) https://www.stroke.org.uk/sites/default/files/ costs_of_stroke_in_the_uk_summary_report_0.pdf:	Excluded	Not a primary study: report.
Pereira NL, Farkouh ME, So D, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. Journal of the American Medical Association. 2020;324(8).	Excluded	Population: study cohort not of interest.
Pilling LC, Türkmen D, Fullalove H, et al. Analysis of *CYP2C19* genetic variants with ischaemic events in UK patients prescribed clopidogrel in primary care: a retrospective cohort study. *BMJ Open*. 2021;11(12).	Excluded	Test: no reported *CYP2C19* genotyping

Study Details	Decision	Reason for exclusion
Stimpfle F, Karathanos A, Droppa M, et al. Impact of point-of-care testing for *CYP2C19* on platelet inhibition in patients with acute coronary syndrome and early dual antiplatelet therapy in the emergency setting. Thrombosis Research. 2014;134(1)	Excluded	Outcomes: no outcome data for Genomadix.
Uchino K. Guideline: Starting dual antiplatelet therapy ≤ 24 h after high-risk TIA or minor ischemic stroke is recommended. Annanls of Internal Medicine. 2019 Apr 16;170(8).	Excluded	Not a primary study: guideline.
Wafa HA, Wolfe CDA, Emmett E, Roth GA, Johnson CO, Wang Y. Burden of Stroke in Europe: Thirty-Year Projections of Incidence, Prevalence, Deaths, and Disability-Adjusted Life Years. Stroke. 2020 Aug;51(8).	Excluded	Not a primary study: modelling study.
Wang Y, Meng X, Wang A, et al. Ticagrelor vs Clopidogrel in *CYP2C19* Loss-of-Function Carriers with Stroke or TIA. NEJM 385; 2520-2530. Published October 28, 2021.	Excluded	Test: Study did not report an evaluation of POCT in scope

Studies excluded at full-text screening (Review of Cost-effectiveness)

Study Details	Reason for exclusion
Bereza BG, Coyle D, So DY, Kadziola Z, Wells G, Grootendorst P, et al. Stated preferences for attributes of a *CYP2C19* pharmacogenetic test among the general population presented with a hypothetical acute coronary syndrome scenario. ClinicoEconomics and Outcomes Research 2020;12	Population/Study type: Population is ACS and study is not a cost effectiveness analysis.
Dong OM, Friede KA, Chanfreau-Coffinier C, Voora D. Cost-effectiveness of *CYP2C19*-guided P2Y(12) inhibitors in Veterans undergoing percutaneous coronary intervention for acute coronary syndromes. European Heart Journal-Quality of Care and Clinical Outcomes; 10	Population: PCI
Drain PK, Hyle EP, Noubary F, Freedberg KA, Wilson D, Bishai WR, et al. Diagnostic point-of-care tests in resource-limited settings. Lancet Infectious Diseases 2014;14(3)	Study type: not a cost effectiveness analysis.
Jiang M, You JHS. Cost-effectiveness analysis of personalized antiplatelet therapy in patients with acute coronary syndrome. Pharmacogenomics 2016;17(7)	Population: ACS
Kim K, Touchette DR, Cavallari LH, Ardati AK, DiDomenico RJ. Cost-Effectiveness of Strategies to Personalize the Selection of P2Y(12) Inhibitors in Patients with Acute Coronary Syndrome. Cardiovascular Drugs and Therapy 2019;33(5)	Population: ACS
Lala A, Berger JS, Sharma G, Hochman JS, Scott Braithwaite R, Ladapo JA. Genetic testing in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A cost-effectiveness analysis. Journal of Thrombosis and Haemostasis 2013;11(1)	Population: ACS
Pourdjabbar A, Hibbert B, Chong AY, Le May MR, Labinaz M, Simard T, et al. A randomised study for optimising crossover from ticagrelor to clopidogrel in patients with acute coronary syndrome The CAPITAL OPTI-CROSS Study. Thrombosis and Haemostasis 2017;117(2)	Population/Study type: Population is ACS and study is not a cost effectiveness analysis.

Appendix 4: Data extraction tables

Objective 1

Baseline Details

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Lan et al. (2019)[46] **Country** China **Study Design** Controlled trial **Funding** Non industry **Setting** China	**Condition:** Stroke **Inclusion Criteria:** 45–80 years Patients diagnosed with acute cerebral infarction within 24 h after symptom onset. National Institutes of Health Stroke Scale(NIHSS) score ≤ 5 Non-cardiogenic cerebral infarction confirmed by imaging examinations in all patients **Exclusion Criteria:** Patients with cerebral haemorrhage and massive infarction Heart, liver, kidney, or any other important organ failure Active bleeding Platelet count < 100x10^9 L Allergy to ticagrelor, aspirin or clopidogrel **Number of eligible patients (enrolled):** 180 **Omeprazole use:** NR **Age – Mean (SD):** Only reported by study arm: group A: 69 (3.4), group B: 68.9 (3.7) **Sex - % female:** 37.7% **Ethnicities included:** Not reported but likely Chinese	***CYP2C19* test:** Gene chip image analysis software (Affymetrix) **Poor metaboliser (PM) definition:** Two LOF alleles (*2/*2, *3/*3, *2/*3) **Intermediate metaboliser (IM) definition:** One LOF allele (*1/*2, *1/*3) **Extensive metabolisers (EM):** (*1/*1) **Ultra-fast (UF) metabolism: at least one LOF allele** (*1/*17, *17/*17)	**Genetic testing + individualized treatment** **Regimen:** Acute phase: Clopidogrel loading dose of 300 mg, and thereafter at 75 mg/day + aspirin 100 mg/day) for 21 days. Long term: EM and UF: clopidogrel 75 mg/day for 1 year IM and PM: aspirin 100 mg/day for 1 year	**Genetic testing but all given standard treatment** **Regimen:** Acute phase: Clopidogrel loading dose of 300 mg, and thereafter at 75 mg/day + aspirin 100 mg/day) for 21 days. Long term: Clopidogrel 75 mg/day for 1 year

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Xia et al. (2021)[45] **Country** China **Study Design** Non-randomised study of an intervention **Funding** NR **Setting** Hospital in China	**Condition:** Stroke **Inclusion Criteria:** **-** Patients with diagnosis of stroke by computed tompgraphy (CT) or magnetic resonance imaging (MRI) scan **Exclusion Criteria:** - Patients with cerebral haemorrhage and massive infarction - Heart, liver, kidney, or any other important organ failure - Active bleeding - Platelet count < 100x10^9 L - Allergy to ticagrelor, aspirin or clopidogrel **Number of eligible patients (enrolled):** 80 **Omeprazole use:** NR **Age – Mean (SD):** 69.6 (12.4) **Sex - % female:** 37.5% **Ethnicities included:** Not reported but likely Chinese	***CYP2C19* test:** NR **Poor metaboliser definition:** Two LOF alleles (*2/*2, *3/*3, *2/*3) **Intermediate metaboliser definition:** One LOF allele (*1/*2, *1/*3) **Fast metabolism:** (*1/*1) **Ultra-fast metabolism: at least one GOF allele** (*1/*17, *17/*17)	**Genetic testing + individualized treatment** **Regimen:** Slow metabolism: ticagrelor 90 mg twice daily or aspirin 100 mg daily Intermediate metabolism: clopidogrel 150 mg once a day Fast and ultra-fast metabolism: clopidogrel 75 mg daily	**Control group – no testing** **Regimen:** Clopidogrel 75 mg once daily

Risk of bias assessment

Study Details	Lan (2019)[46]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	N
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	N
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**High**
Rationale for judgement: Allocation was based on genetic profile but unclear how equal numbers were allocated to each group	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	PY
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Y
Risk of bias judgement	**High**
Rationale for judgement: Participants and carers probably aware of intervention, no data on potential deviations from intended interventions, no information on type of statistical analysis	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	N
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Y
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Y
Risk of bias judgement	**High**
Rationale for judgement: 12/90 and 13/90 patients were lost to follow-up, which could be associated with the outcomes	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
4.3 Were outcome assessors aware of the intervention received by study participants?	NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**Low**
Rationale for judgement: objective, clinical outcomes taken from clinical records and follow-up visits	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NI
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	NI
Risk of bias judgement	**Some concerns**
Rationale for judgement: protocol not available	

OVERALL RISK OF BIAS	**High**
Rationale for judgement: Participants and carers probably aware of intervention, no data on potential deviations from intended interventions, no information on type of statistical analysis High proportion loss to follow-up, which could be associated with presence of events	

PY: Probably yes; PN: Probably No; NI: No information

Study Details	Xia(2021)[45]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**High**
Rationale for judgement: There was no indication about randomisation of allocation	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	PY
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Y
Risk of bias judgement	**High**
Rationale for judgement: Participants and carers probably aware of intervention, no data on potential deviations from intended interventions, no information on type of statistical analysis	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**Low**
Rationale for judgement:	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
4.3 Were outcome assessors aware of the intervention received by study participants?	NI
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**Low**

Rationale for judgement: objective, clinical outcomes taken from clinical records and follow-up visits

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	NI
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	NI
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	NI
Risk of bias judgement	**Some concerns**
Rationale for judgement: There is no indication about randomisation of allocation, No information on statistical analysis methodology, statistical analysis protocol not available	

OVERALL RISK OF BIAS	**High**
Rationale for judgement: There is no indication about randomisation of allocation, protocol not available	

Results

Study details				Standard treatment		Test + Personalised treatment		Effect Estimate			
Study details	Type of outcome	Outcome	Follow-up Time (days)	No. patients	No. Events	No. patients	No. Events	HR	LCI	UCI	p-value
Lan (2019)[46]	Incidence of secondary vascular occlusive events	Ischaemic stroke	365	90	3	90	1	0.33	0.03	3.2	>0.05
	Incidence of secondary vascular occlusive events	Haemorrhagic stroke	365	90	1	90	0	0.33	0.01	8.17	>0.05
	Incidence of secondary vascular occlusive events	Myocardial infarction	365	90	0	90	1	3.00	0.12	73.74	>0.05
	Incidence of secondary vascular occlusive events	Composite outcome	365	90	4	90	2	0.50	0.09	2.74	NR
Xia (2021)[45]	Incidence of secondary vascular occlusive events	Composite outcome	90	40	17	40	9	0.53	0.24	1.18	0.033
	Incidence of secondary vascular occlusive events	Ischaemic stroke	90	40	12	40	5	0.42	0.15	1.18	NR
	Incidence of secondary vascular occlusive events	TIA	90	40	2	40	1	0.50	0.05	5.53	NR
	Incidence of secondary vascular occlusive events	Myocardial infarction	90	40	3	40	3	1.00	0.2	4.95	NR
	Incidence of secondary vascular occlusive events	Vascular death	90	40	3	40	3	1.00	0.2	4.95	NR

HR: hazard ratio; LCI: Low confidence interval; UCI: Upper confidence interval

Objective 2

Baseline Details

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Chen et al. (2019)[52, 180, 181] **Country** China **Study Design** Sub-analysis RCT **Funding** Non-industry **Setting** 26 hospitals in China	**Condition:** Stroke & TIA **Inclusion Criteria** • Age≥ 40 years and <80 years. • Acute non-disabling ischemic stroke (NIHSS≤ 3) or TIA (ABCD2 score ≥4) **Exclusion Criteria** • Other pathology on baseline head CT or MRI • Isolated or pure sensory symptoms (e.g., numbness), visual changes, or dizziness/vertigo without evidence of acute infarction on baseline head CT or MRI. • Modified Rankin Scale Score > 2 at randomization • Contraindication to ticagrelor, clopidogrel or aspirin • Severe renal or hepatic insufficiency, cardiac failure • Major surgery <30 days. • Low white blood cell, platelet count or hematocrit (Hct) • Clear indication for anticoagulation • Continuous use of ticagrelor or clopidogrel >5 days before randomization • Current treatment with heparin or anti coagulation therapy • Receipt of intravenous/ intra-arterial thrombolysis or mechanical thrombectomy < 24 hours prior to randomization. • Diagnosis or of acute coronary syndrome. • Anticipated requirement for long-term (>7 days) non-study anti-platelet drugs, or NSAIDs (nonsteroidal anti-inflammatory drugs) affecting platelet function. • Qualifying TIA or minor stroke induced by angiography or surgery. • Planned or likely revascularization < 3 months. • Scheduled for surgery or interventional treatment requiring study drug cessation. • Severe non-cardiovascular comorbidity with life expectancy < 3 months. **Eligible (total study):** 5644 **Enrolled (total study):** 675 **Enrolled (our cohort of interest):** 374 **Age – Mean (SD):** 60.8 (8.7); **Sex - % female:** 26.8%; **Ethnicities:** Not reported - likely most patients asian (chinese)	***CYP2C19* test:** Sequenom MassARRAY iPLEX platform **Poor metaboliser definition:** one or more *CYP2C19* *2 or *3 alleles	**Antiplatelet drug:** Clopidogrel + aspirin for first 21 days **Regimen:** 75 mg clopidogrel (loading dose of 300mg followed by **75 mg daily till day 90**) combined with aspirin (loading dose of 100-300mg followed by **100 mg once daily till day 21**)	**Antiplatelet drug:** Ticagrelor + aspirin for first 21 days **Regimen:** 90 mg ticagrelor (loading dose of 180 mg followed **by 90 mg twice daily till day 90**) combined with aspirin (loading dose of 100-300mg followed by **100 mg once daily till day 21**)

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Han et al. (2017)[47, 182-186] **Country** South Korea **Study Design** Sub-analysis of RCT **Funding** Industry **Setting** 18 tertiary-care hospitals in South Korea	**Condition:** Stroke **Inclusion Criteria** • non-cardiogenic ischemic stroke of TOAST classification < 30 days prior to screening • ≥ 20 years of age • Written informed consent **Exclusion Criteria** • History of bleeding tendency or recent major bleeding within 2 weeks • Chronic liver disease or renal dysfunction • Thrombocytopenia • Contraindication to antiplatelet agents • Severe congestive heart failure • Need to take anticoagulants ≥2 antiplatelet agents • Severe concomitant disease with expected survival < 2 years **Number of Participants** **Eligible (total study):** 795 **Enrolled (total study):** 784 **Enrolled (our cohort of interest):** 484 **Omeprazole use:** Proton pump inhibitor use prohibited **Age Mean (SD)** Reported by study arm: Triflusal: 61.6 (10.5); Clopidogrel: 61.2 (11.1) **Sex - % female:** Reported by study arm: Triflusal: 32%: Clopidogrel: 35% **Ethnicities included:** Not reported - likely most patients asian (South Korean)	***CYP2C19* test:** Seeplex *CYP2C19* ACE genotyping system and Real-Q *CYP2C19* genotyping kit **Poor metaboliser definition:** one or more *CYP2C19* *2 or *3 alleles	**Antiplatelet drug:** Clopidogrel **Regimen:** 75 mg clopidogrel once daily	**Antiplatelet drug:** Trifusal **Regimen:** 300 mg triflusal twice per day (600 mg/day)

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2

Author (Year)
Meschia et al. (2020)[48]
 	
Country
NR
 	
Study name:
POINT
 	
Study Design
Sub-analysis of RCT
 	
Funding
Non-industry
 	
Setting
International
	Condition
	Stroke & TIA
	
	Inclusion Criteria
	• Neurologic deficit attributed to focal brain ischemia and EITHER:
	  • High risk TIA: resolution of deficit prior to randomization AND ABCD2 score >4; or
	  • Minor ischemic stroke: residual deficit with NIHSS <3
	• Ability to randomize <12 hours of symptom onset.
	• Head CT or MRI ruling out hemorrhage or other pathology
	
	Exclusion Criteria
	• Age <18 years
	• Symptoms of TIA limited to isolated numbness, visual changes, or dizziness/vertigo.
	• Candidate for thrombolysis or endovascular interventior or received <1 week prior to index event
	• Gastrointestinal bleed or major surgery <3 months
	• History of nontraumatic intracranial hemorrhage.
	• Known internal carotid artery stenosis >50%
	• Clear indication for anticoagulation anticipated during study period
	• Qualifying ischemic event induced by angiography or surgery.
	• Comorbidity with life expectancy <3 months.
	• Contraindication to clopidogrel or aspirin.
	• Anticipated requirement for long-term non-study antiplatelet drugs or NSAIDs affecting platelet function
	
	Number of Participants
	Eligible (total study): 4881
	Enrolled (total study): 4881
	Enrolled (our cohort of interest): 667
	
	Omeprazole use:
	PPI and other drugs that may affect clopidogrel metabolism will be avoided, with others substituted.
	
	Age – Mean (Interquartile Range (IQR)): 63 (53-72)
	
	Sex - % female: 44.5%
	
	Ethnicity: White: 175 (67%), black: 65 (24.5%), other: 25 (9.4%)
		***CYP2C19* test:**
		Drug Metabolism Enzyme TaqMan Allelic Discrimination Assay
		
		Poor metaboliser definition:
		one or more *CYP2C19* *2 or *3 alleles
			Antiplatelet drug:
			Clopidogrel + Aspirin
			
			Regimen:
			Clopidogrel at a loading dose of 600 mg on day 1, followed by 75 mg per day, plus aspirin at a dose of 50 to 325 mg per day
				Antiplatelet drug:
				Aspirin
				
				Regimen:
				Aspirin at a dose of 50 to 325 mg per day

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Wang et al. (2016a)[51, 73, 191-194] **Study name** CHANCE **Country** China **Study Design** Sub-analysis of RCT **Funding** Non-industry **Setting** 73 among 114 sites from CHANCE (China)	**Condition** Stroke & TIA **Inclusion Criteria** • Age ≥ 40 years • Acute non-disabling ischemic stroke (NIHSS≤3 at the time of randomization) or TIA with moderate/high risk of recurrence that can be treated with study drug <24 hours of symptoms onset. **Exclusion Criteria** • Diagnosis of haemorrhage or other pathology on baseline head CT or MRI. • Isolated or pure sensory symptoms without acute infarction on baseline head CT/MRI • Modified Rankin Scale Score > 2 at randomization • Clear indication for anticoagulation • Contraindication to clopidogrel or aspirin. • History of intracranial haemorrhage. • Anticipated requirement for long-term non-study antiplatelet drugs or NSAIDs affecting platelet function. • Current treatment with heparin therapy or oral anticoagulation. • Gastrointestinal bleed or major surgery <3 months. • Planned or likely revascularization <next 3 months • Scheduled for surgery or interventional treatment requiring study drug cessation. • Qualifying TIA or minor stroke induced by angiography or surgery. • Severe non-cardiovascular comorbidity with life expectancy < 3 months. **Eligible (total study):** 3010 **Enrolled (total study):** 2933 **Enrolled (our cohort of interest):** 1726 **Omeprazole use:** PPI will be avoided, with others substituted. PPI use: 10 patients within the carrier group and 10 within the non carrier group (20 out of 2933) **Age – Median (IQR):** 62.3 (54.5-71.2) **Sex - % female:** 32.6% **Ethnicities:** Not reported - likely most patients asian (chinese)	***CYP2C19* test:** Sequenom MassARRAY iPLEX platform (Sequenom). **Poor metaboliser definition:** one or more *CYP2C19* *2 or *3 alleles	**Antiplatelet drug:** Clopidogrel + aspirin for first 21 days **Regimen:** • Day 1: four tablets of clopidogrel 75 mg and open label aspirin (75 mg - 300 mg) • D2 to D21±2 days: one tablet of clopidogrel 75mg and one tablet of aspirin 75 mg per day • D22±2 days visit to D90±7 days: one tablet of clopidogrel 75mg and one tablet of placebo aspirin 75 mg per day	**Antiplatelet drug:** Aspirin **Regimen:** • Day 1: four tablets of placebo clopidogrel 75 mg and open label aspirin (75 mg - 300 mg) • D2 to D21±2 days: one tablet of placebo clopidogrel 75mg and one tablet of aspirin 75 mg per day • D22±2 days visit to D90±7 days: one tablet placebo of clopidogrel 75mg and one tablet of ASA 75 mg per day

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Wang et al. (2021)[49, 187-190] **Country** China **Study Design** RCT **Funding** Mixed - Drugs and tests were supplied by industry at no cost and with no restrictions **Setting** 202 centers in China	**Condition:** Stroke and TIA **Inclusion Criteria** • Age ≥40 years • Acute non-disabling ischemic stroke (NIHSS≤), or TIA with moderate-to-high risk of stroke (ABCD2 score ≥4), treated with study drug within 24 hours of symptoms onset • *CYP2C19* loss-of-function allele carrier. **Exclusion Criteria** • Other major non-ischemic brain disease on baseline head CT or MRI. • Symptoms without evidence of acute infarction on baseline head CT or MRI. • Iatrogenic causes. • Modified Rankin scale [mRS] score 3-5 • Contraindication to clopidogrel, ticagrelor or aspirin • Increased risk of bleeding • History of severe renal or hepatic insufficiency or cardiac failure • Low white blood cell, platelet count or haematocrit • Clear indication for anticoagulation • Requirement for long-term (>7 days) non-steroidal anti-inflammatory drugs (NSAIDs) • Planned or likely revascularization <3 months • Severe non-cardiovascular comorbidity with life expectancy < 3 months • Dual antiplatelet treatment < 72 hours before randomization • Current treatment with heparin therapy or oral anticoagulation • Intravenous thrombolytic therapy or mechanical thrombectomy < 24 hours prior to randomization • Gastrointestinal bleed within 3 months or major surgery within 30 days **Number of Participants** **Eligible (total study):** 6412 **Enrolled (total study):** 6412 **Enrolled (our cohort of interest):** 6412 **Omeprazole use:** strong *CYP2C19* inhibitors prohibited, including some PPI. **Age - Mean (SD):** 64.8 (NR) **Sex - % female:** 33.8% **Ethnicity:** Han Chinese ethnic group 98%; others not reported	***CYP2C19* test:** GMEX point-of-care genotyping system **Poor metaboliser definition:** one or more *CYP2C19* *2 or *3 alleles	Clopidogrel + aspirin for first 21 days **Regimen:** Placebo ticagrelor plus a 300-mg loading dose of clopidogrel on day 1, followed by **75 mg daily on days 2 through 90**, plus aspirin at a loading dose of 75 to 300 mg, **followed by 75 mg daily for 21 days.**	Ticagrelor + aspirin for first 21 days **Regimen:** 90 mg twice daily Placebo clopidogrel plus a 180-mg loading dose of ticagrelor on day 1, followed **by 90 mg twice daily on days 2 through 90**, plus aspirin at a loading dose of 75 to 300 mg, **followed by 75 mg daily for 21 days.**

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Wu et al. (2020)[50] **Country** China **Study Design** RCT **Funding** Non-industry **Setting** Single centre - China	**Condition:** Stroke **Inclusion Criteria** Acute ischaemic stroke; continuously hospitalised Aged ≥40 years and ≤ 75 years Moderate to severe cerebral artery stenosis < 7 days of ischaemic stroke onset Access to the study drug within 24 h of admission National Institutes of Health Stroke Scale (NIHSS) score ≤ 5 **Exclusion Criteria** Attack confirmed as non cerebrovascular attack Significant signs of anticoagulation Bleeding from the gastrointestinal tract <1 year Positive faecal occult blood on admission to hospital History of intracranial haemorrhage Severe heart failure, asthma, liver, or kidney insufficiency History of coagulation abnormalities or systemic bleeding disorders History of hemocytopenia, leukopoenia, or thrombocytopenia; Given aspirin combined with clopidogrel therapy at randomisation **Eligible (total study):** 162 **Enrolled (total study):** 131 **Enrolled (our cohort of interest):** 131 **Omeprazole use:** All patients administered pantoprazole during dual antiplatelet therapy **Age - Median (IQR):** Reported by study arm: High dose group: 60± 10.4, Normal dose group: 63.2 ±9.3 **Sex - % female:** Reported by study arm: High dose group: 20.97%, Normal dose group: 27.54 **Ethnicities included:** Not reported - likely most patients asian (chinese)	***CYP2C19* test:** Not reported **Poor metaboliser definition:** one or more *CYP2C19* *2 or *3 alleles	**Antiplatelet drug:** Clopidogrel + aspirin for 21 days followed by aspirin alone **Regimen:** Day 1: 300 mg clopidogrel Day 2-21: 75mg clopidogrel + 100 mg aspirin Day 21-90: 100 mg aspirin	**Antiplatelet drug:** High dose clopidogrel + aspirin for 21 days followed by aspirin alone **Regimen:** Day 1: 300 mg clopidogrel Day 1: 300 mg clopidogrel Day 2-21: 150mg clopidogrel + 100 mg aspirin Day 21-90: 100 mg aspirin

Study Details	Participants	*CYP2C19* testing	Group 1	Group 2
Author (Year) Yi et al. (2018)[53] **Country** China **Study Design** Sub-analysis of RCT **Funding** Non-industry **Setting** Hospitals in China	**Condition** Stroke **Inclusion Criteria** • ≥ 18 years • Diagnosis of ischemic stroke by cranial computed tomography and magnetic resonance imaging scanning **Exclusion Criteria** • No previous carotid endarterectomy or carotid stent therapy, or during treatment. **Number of eligible patients (randomised):** **Eligible (total study):** 570 **Enrolled (total study):** 570 **Enrolled (our cohort of interest):** 257 **Omeprazole use:** NR **Age – Mean (SD)** NR (For our cohort) **Sex - % female** NR (For our cohort) **Ethnicities included:** Not reported - likely most patients asian (chinese)	***CYP2C19* test:** NR **Poor metaboliser definition:** One or more *CYP2C19**2 alelles	**Antiplatelet drug:** Clopidogrel + aspirin for first 30 days **Regimen:** Aspirin plus clopidogrel (200 mg aspirin and 75 mg clopidogrel) for 30 days, and 75 mg/d clopidogrel thereafter	**Antiplatelet drug:** Aspirin **Regimen:** 200 mg/d for 30 days and 100 mg/d thereafter

Risk of bias assessment

Study Details	Chen (2019)[52]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No major issues observed regarding allocation and randomisation	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Participants and carers aware of intervention (ope-label trial) but no significant deviations and appropriate analysis	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: no significant missing data on outcome	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N
4.3 Were outcome assessors aware of the intervention received by study participants?	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant issues on outcome assessment	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Pre-specified and registered protocol	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No significant concerns on any domain	

Study Details	Han (2017)[47]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Allocation sequence is random and assigned through a secure web-based registration system.	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	Y
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: although there was no masking, there's no evidence suggesting deviations because of the trial context	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PN
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	Y
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Potentially significant missing data, but per-protocol (PP) analysis was consistent with intention to treat (ITT) analysis	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N
4.3 Were outcome assessors aware of the intervention received by study participants?	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: measuring methods appropriate	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Data analysed in accordance with a pre-specified plan	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No significant concerns on any domain	

Study Details	Meschia (2020)[48]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Even though we are assessing a subanalysis, the intervention was randomised in the subgroup and baseline characteristics are adequately balanced	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No issues with blinding and intervention deviations	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	NI
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	PY
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	PY
Risk of bias judgement	**HIGH**
Rationale for judgement: No clear data on loss to follow up, and it could potentially be related to the outcomes	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N
4.3 Were outcome assessors aware of the intervention received by study participants?	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Outcomes definitions are clear and objective, assessed by blinded staff	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: Data analysis was defined and published before outcome data was available	

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: No clear data on loss to follow up, and it could potentially be related to the outcomes	

Study Details	Wang et al (2016a)[206]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No information on allocation concealment, but no baseline differences.	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No data on blinding, no information on statistical analysis	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**LOW**
Rationale for judgement:	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N
4.3 Were outcome assessors aware of the intervention received by study participants?	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant issues with outcome measurement	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Study Details	Wang (2021)[49]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N
4.3 Were outcome assessors aware of the intervention received by study participants?	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No issues with outcome measurement	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: NO major issues on any domain	

Study Details	Wu (2020)[50]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: No concerns	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No data on blinding, but no evidence of deviations	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
4.3 Were outcome assessors aware of the intervention received by study participants?	NI

4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No information on assessors awareness of intervention, but not likely to influence assessment.	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No evidence of pre-specified protocol, but outcomes similar to similar studies	

OVERALL RISK OF BIAS	
Rationale for judgement:	

Study Details	Yi (2018)[53]

Domain 1: Bias arising from the randomization process	
1.1 Was the allocation sequence random?	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: No information on allocation concealment, but no baseline differences.	

DOMAIN 2: Bias due to deviations from intended interventions	
2.1. Were participants aware of their assigned intervention during the trial?	NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	NI
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	PN
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NI
Risk of bias judgement	**HIGH**
Rationale for judgement: No data on blinding, no information on statistical analysis	

DOMAIN 3: Bias due to missing outcome data	
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y
3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA
Risk of bias judgement	**LOW**
Rationale for judgement:	

DOMAIN 4: Bias in measurement of the outcome	
4.1 Was the method of measuring the outcome inappropriate?	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN
4.3 Were outcome assessors aware of the intervention received by study participants?	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant issues with outcome measurement	

DOMAIN 5: Bias in selection of the reported result	
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	PN
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No concerns	

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: No information on allocation concealment, no data on blinding, no information on statistical analysis	

Results

Study details					Clopidogrel group		Alternative group		Effect Estimates		
Study	**Ethnicity**	**Comparison**	**FU time (days)**	**Outcome**	**No. patients**	**No. Events**	**No. patients**	**No. Events**	**HR**	**logHR**	**SElogHR**
Chen (2019)[52]	Asian	Ticagrelor + Aspirin (short-term) vs. Clopidogrel + Aspirin (short-term)	90	Any bleeding	190	30	184	29	1.01	0.01	0.26
				Any stroke	190	22	184	15	0.69	-0.37	0.34
				Composite events	190	24	184	16	0.68	-0.39	0.32
				Haemorrhagic stroke	190	2	184	1	0.52	-0.65	1.21
				Ischaemic stroke	190	20	184	14	0.71	-0.34	0.35
				TIA	190	2	184	1	0.52	-0.65	1.21
				Myocardial infarction	190	1	184	0	0.34	-1.07	1.63
				Vascular death	190	2	184	0	0.21	-1.58	1.55
Han (2017)[47]	Asian	Triflusal vs. Clopidogrel	985.5	Any stroke	244	14	240	16	1.23	0.21	0.41
				Any bleeding	244	14	240	12	0.97	-0.03	0.39
				Haemorrhagic stroke	244	3	240	2	0.74	-0.30	0.92
				Ischaemic stroke	244	11	240	14	1.37	0.31	0.40
				Myocardial infarction	244	1	240	1	1.11	0.10	1.41
				Mortality	244	3	240	3	1.11	0.10	0.82
				Any stroke	244	14	240	16	1.23	0.21	0.41
Meschia (2020)[48]	Mixed	Aspirin vs. Clopidogrel + Aspirin	90	Mild bleeding	131	2	134	2	1.00	0.00	1.00
				Any stroke	131	3	134	9	3.03	1.11	0.66
				major ischaemic events	131	3	134	9	3.03	1.11	0.66
				Ischaemic stroke	131	3	134	9	3.03	1.11	0.66
Wang (2016a)[51]	Asian	Aspirin vs. Clopidogrel + Aspirin (short-term)	90	Any bleeding	854	20	872	12	0.61	-0.50	0.37
				Mild bleeding	854	8	872	2	0.25	-1.40	0.79
				Severe or Moderate bleeding	854	3	872	0	0.14	-1.97	1.51
				Any stroke	854	80	872	94	1.08	0.07	0.15
				Composite event	854	80	872	95	1.09	0.08	0.15
				Ischaemic stroke	854	78	872	93	1.18	0.16	0.15

Study details					Clopidogrel group		Alternative group		Effect Estimates		
Study	**Ethnicity**	**Comparison**	**FU time (days)**	**Outcome**	**No. patients**	**No. Events**	**No. patients**	**No. Events**	**HR**	**logHR**	**SElogHR**
Wang (2021)[49]	Asian	Ticagrelor + Aspirin (short-term) vs. Clopidogrel + Aspirin (short-term)	90	Any bleeding	3207	80	3205	170	2.18	0.78	0.14
				Severe or moderate bleeding	3207	11	3205	9	0.82	-0.20	0.45
				Any stroke	3207	243	3205	191	0.77	-0.26	0.10
				vascular event	3207	293	3205	229	0.77	-0.26	0.09
				Ischaemic stroke	3207	238	3205	189	0.78	-0.25	0.10
				Mortality	3207	18	3205	9	0.50	-0.69	0.41
Yi (2018)[53]	Asian	Aspirin vs. Clopidogrel + Aspirin	1825	Composite outcome	128	29	129	27	0.91	-0.09	0.27

Objective 3

Baseline Details

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Chen et al. (2019)[52, 180, 181] **Study Name** PRINCE **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** 26 hospitals in China	**Condition** Stroke & TIA **Inclusion Criteria** • ≥ 40 years and <80 years • Acute non-disabling ischemic stroke (NIHSS≤ 3) or TIA with ABCD2 score ≥ 4 treated with study drug within 24 hours of onset **Exclusion Criteria** • Diagnosis of intracranial haemorrhage or other pathology • Symptoms without evidence of acute infarction on head CT or MRI • Modified Rankin Scale Score > 2 • Contraindication to ticagrelor, clopidogrel or aspirin • Indication for anticoagulation • Intravenous/ intra-arterial thrombolysis or mechanical thrombectomy < 24 hours prior to randomization, or likely within 3 months • History of intracranial haemorrhage, cerebral artery amyloidosis or aneurysm • Indication for non-study anti-platelet drugs, or NSAIDs • Previous significant bleeding • Primary event induced by angiography or surgery • Life expectancy < 3 months • Hematocrit (Hct) < 30% **Number of Participants** **Eligible (total study):** 675 **Enrolled (total study):** 675 **Enrolled (our cohort of interest):** 329 **Omeprazole use:** 22.7% **Age** 61.7 (8.5) **Sex - % female** 28.8% **Ethnicities included:** Not reported - likely most patients asian (chinese)	**Antiplatelet** Clopidogrel **Dose** 75 mg **Regimen** clopidogrel (loading dose of 300mg followed by 75 mg daily until day 90) combined with aspirin (loading dose of 100-300mg followed by 100 mg once daily until day 21)	***CYP2C19* test:** Sequenom MassARRAY iPLEX platform **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** Unknown metabolisers

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Diaz-Villamarin et al. (2018)[54, 196] **Country** Spain **Study Design** Retrospective Cohort **Funding** Not stated **Setting** San Cecilio University Hospital	**Condition** Stroke & TIA **Inclusion Criteria** • >18 years old • Stroke/TIA • Treatment with clopidogrel 75 mg from diagnosis to hospital discharge and at least for a month. **Exclusion Criteria** • Contraindication to clopidogrel. • Indication for anticoagulants • Impossibility to access clinical records during the treatment period **Number of Participants** **Eligible (total study):** 114 **Enrolled (total study):** 67 **Enrolled (our cohort of interest):** 67 **Omeprazole use:** PPI: total: 30/67 (44.78%), *CYP2C19* LOF 10/18 (55.56%), CPY2C19 no LOF: 20 (40.82%) **Age - Mean (SD):** 68.2 (9.8) **Sex - % female** 35.8% **Ethnicities included:** White 100% (Caucasian)	**Antiplatelet** Clopidogrel **Regimen** 75 mg daily	***CYP2C19* test:** TaqMan genotyping assays technology. **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Poor metaboliser if accompanied by a LOF allele, extensive metaboliser if not.

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Fu et al. (2020)[55] **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • Patients diagnosed with acute ischemic stroke and treated with clopidogrel • ≥18 years • Computed tomography (CT) or magnetic resonance imaging (MRI) evidence of stroke • Baseline (NIHSS) score ≤22. **Exclusion Criteria** • Recent cerebral or gastrointestinal haemorrhage, any bleeding disorder or significant coagulopathy • History of tumours or other terminal medical comorbidities • Allergic or intolerant to clopidogrel • Platelet count <100 x10^12/L or >450x10^12/L. **Number of Participants** **Eligible (total study):** 175 **Enrolled (total study):** 131 **Enrolled (our cohort of interest):** 131 **Omeprazole use:** NR **Age** **Mean (SD):** 61.4 (10.9) **Sex - % female** 21% **Ethnicities included:** Asian: All the patients are Chinese-Han origins	**Antiplatelet** Clopidogrel **Dose** 75 mg **Regimen** Clopidogrel 75mg/d without loading dose	***CYP2C19* test:** (PCR-RFLP) **Alleles tested for:** *1, *2, and *3 **Poor metaboliser definition:** At least 1 LOF **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Fukuma et al. (2022)[56, 197] **Study Name** PRAISE **Country** Japan **Study Design** Prospective Cohort **Funding** Non-industry **Setting** Japan	**Condition** Stroke & TIA **Inclusion Criteria** • Acute ischameic stroke (IS)/TIA with symptomatic atherosclerotic stenosis (≥ 50%) or occlusion of ipsilateral intracranial or extracranial arteries • < 7 days after onset and treated with clopidogrel • ≥20 years • NIHSS score of 0 to 20 before treatment **Exclusion Criteria** • Modified Rankin Scale score >3 • Cardio-embolic source • Contraindication to MRI scanning • Treatment with ozagrel • Intracranial or severe systemic haemorrhage. **Number of Participants** **Eligible (total study): 230** **Enrolled (total study): 230** **Enrolled (our cohort of interest): 194** **Omeprazole use:** 21.33% (For 230 patients enrolled) **Age Mean (SD)** 72.1 **Sex - % female** 28 **Ethnicities included:** Not reported - likely most patients asian (japanese)	**Antiplatelet** Clopidogrel **Dose** Clopidogrel 75 mg **Regimen** • Clopidogrel (i) continued at 75 mg/day standard dose used before admission, (ii) newly administered at 75 mg/day standard dose, or (iii) newly administered at 300 mg loading and followed by 75 mg/day standard dose • With or without other antiplatelet agents (including aspirin at 200 mg/day and cilostazol at 200 mg/day), anticoagulant agents (including argatroban injection)	***CYP2C19* test:** TaqMan **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** Excluded from analysis

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Han et al (2017)[47, 182-186] **Study Name** MAESTRO **Country** South Korea **Study Design** Prospective Cohort **Funding** Industry - test manufacturer **Setting** 18 tertiary- care hospitals in South Korea	**Condition** Stroke **Inclusion Criteria** • Non-cardiogenic ischemic stroke of TOAST classification <30 days prior to screening • ≥ 20 years of age • Written informed consent **Exclusion Criteria** • History of bleeding tendency or recent major bleeding within 2 weeks • Chronic liver disease or renal dysfunction • Thrombocytopenia • Contraindication of antiplatelet agent • Severe congestive heart failure • Need to take anticoagulants or >= antiplatelet agents • Severe concomitant disease with expected survival < 2 years **Number of Participants** **Eligible (total study): 795** **Enrolled (total study): 795** **Enrolled (our cohort of interest): 393** **Omeprazole use:** Proton pump inhibitor use was prohibited **Age - Mean (SD):** 61 **Sex - % female:** 32 **Ethnicities included:** Not reported - likely most patients asian (South Korean)	**Antiplatelet** Clopidogrel **Regimen** 75 mg clopidogrel once daily	***CYP2C19* test:** Seeplex *CYP2C19* ACE genotyping system and Real-Q *CYP2C19* genotyping kit **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele (including *17) **How were 17* alleles handled?** Intermediate metaboliser if accompanied by a LOF allele, extensive metaboliser if not.

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Hoh et al. (2016)[57] **Country** US **Study Design** Retrospective Cohort **Funding** Non-industry **Setting** 3 US centres	**Condition** Stroke & TIA **Inclusion Criteria** • ≥18 years • Stroke or transient ischemic attack (TIA) attributable to 50% or greater stenosis of a major intracranial artery • Treatment with aspirin and clopidogrel for ≥3 months. **Exclusion Criteria** • Patients with moyamoya disease **Number of Participants** **Eligible (total study): NR** **Enrolled (total study): 188** **Enrolled (our cohort of interest): 188** **Omeprazole use:** 58% **Age** Mean (SD): 67 (NR) **Sex - % female** 36.7 **Ethnicities included:** Mixed: White: 84.6%, Black: 12.8%, Other: 2.7%	**Antiplatelet** Clopidogrel + aspirin **Regimen** NR	***CYP2C19* test:** Sequenom (Qiagen) and TaqMan Assay **Alleles tested for:** *1, *2, *3, *8 and *17 **Poor metaboliser definition:** 2 copies of LOF alleles **Intermediate metaboliser definition:** One copy of LOF allele **How were 17* alleles handled?** NR

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Lin et al. (2021)[58] **Country** China **Study Design** Retrospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • Clinical diagnosis of IS confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) • ≥18 years • Clopidogrel for 5 days or longer **Exclusion Criteria** • Recurrence or sequelae of stroke • Clopidogrel contraindicated • Platelet count >450×109/L or <150×109/L • Other anticoagulation drugs Recent history of active bleeding • Severe kidney or liver diseases • Major surgery within 1 month of the study. **Number of Participants** **Eligible (total study): 122** **Enrolled (total study): 122** **Enrolled (our cohort of interest): 89** **Omeprazole use:** 20.22 **Age - Mean (SD)** Only reported by study arm: non-carriers of LOF 65.1 (14.1), carriers of LoG 65.1 (12.3) **Sex - % female** Only reported by study arm: non-carriers 39.5%, carriers 53.3% **Ethnicities included:** Asian: Not reported - likely most patients asian (chinese)	**Antiplatelet** Clopidogrel **Regimen** NR	***CYP2C19* test:** NR **Alleles tested for:** *1, *2 and, *3 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Liu et al. (2020)[59] **Country** China **Study Design** Prospective Cohort **Funding** Not stated **Setting** First Affiliated Hospital of Shantou University Medical College, China	**Condition** Stroke **Inclusion Criteria** • Acute IS confirmed by computed tomography or magnetic resonance imaging within 1 week of onset. • Patient suitable for clopidogrel treatment. **Exclusion Criteria** • Clotting or other blood disorders. • Serious heart, liver, and kidney diseases • Patients received proton pump inhibitors. • IS caused by cardio embolism. **Number of Participants** **Eligible (total study):** 289 **Enrolled (total study):** 289 **Enrolled (our cohort of interest):** 289 **Omeprazole use:** Patients receiving PPI excluded **Age - Mean (SD)** 66.6 (10.90) **Sex - % female** 41.9 **Ethnicities included:** Not reported - likely most patients asian (chinese)	**Antiplatelet** Clopidogrel **Regimen** 75mg clopidogrel after the onset of symptoms daily.	***CYP2C19* test:** *CYP2C19* genotyping kit **Alleles tested for:** *1, *2 and, *3 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Lv et al. (2022)[60, 198] **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • ≥35 years • Acute ischemic stroke within 14 days, diagnosed by computer tomography (CT) or magnetic resonance imaging (MRI) • Informed consent **Exclusion Criteria** • cardiogenic cerebral embolism. • Ischemic stroke caused by other causes. • Under dual antiplatelet therapy • Allergy or contraindication to clopidogrel or aspirin • Active bleeding or bleeding tendency. • Severe liver or renal failure • Usage of *CYP2C19* inhibitors, NSAIDS, anticoagulants, and other antiplatelet drugs **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 485 **Enrolled (our cohort of interest):** 314 **Omeprazole use:** patients taking PPI excluded **Age Mean (SD)** NR **Sex - % female:** NR **Ethnicities included:** Not reported - likely most patients asian (chinese)	**Antiplatelet** Clopidogrel **Regimen** 75 mg daily	***CYP2C19* test:** Sequenom MassARRAY iPLEX platform **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled:** those with two GoF alleles (*17) or one functional allele (*1) and one GoF allele (*17) were classified as ultrarapid metabolizers

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) McDonough et al. (2015)[61, 199] **Study Name** SPS3 study **Country** International **Study Design** Prospective Cohort **Funding** Non-industry	**Condition** Stroke & TIA **Inclusion Criteria** • ≥30 years-old • Small subcortical ischemic stroke or subcortical TIA. • Lacunar stroke clinical syndrome lasting > 24 hrs within the past 6 months • Absence of signs or symptoms of cortical dysfunction. • No ipsilateral cervical carotid stenosis (≥50%) • No major-risk cardioembolic sources requiring anticoagulation or other specific therapy. **Exclusion Criteria** • Modified Rankin Scale ≤4 • Previous intracranial haemorrhage (excluding traumatic) or hemorrhagic stroke • High risk of bleeding • Prior cortical stroke or prior cortical or retinal TIA • Prior ipsilateral carotid endarterectomy • eGFR <40 • Intolerance or contraindications to aspirin or clopidogrel. • Folstein Mini Mental Status Examination < 24 **Number of Participants** **Eligible (total study): NR** **Enrolled (total study): 3020** **Enrolled (our cohort of interest): 522** **Omeprazole use:** No data **Age – Mean (SD) :** 62.5 (10.5) **Sex - % female:** 28% **Ethnicities included:** Mixed: Hispanic (244/46.7%), white (176/33.71%), and black (73/13.98%), NR: 29/5.6%	**Antiplatelet** Clopidogrel + aspirin **Regimen** 325 mg aspirin plus 75 mg clopidogrel daily	***CYP2C19* test:** TaqMan assays **Alleles tested for:** *1 and *2 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Meschia et al (2020)[48] **Study Name** POINT Trial **Country** US **Study Design** Prospective Cohort **Funding** Non-industry **Setting** International	**Condition** Stroke & TIA **Inclusion Criteria** • Neurologic deficit attributed to focal brain ischemia and EITHER: - High-risk TIA: Complete resolution of the deficit prior to randomization AND ABCD2 score >4, OR - Minor ischemic stroke: residual deficit with NIHSS <3 • Ability to randomize within 12 hours of symptom onset. • Head CT or MRI ruling out haemorrhage or other pathology **Exclusion Criteria** • Age <18 years • Candidate for intravenous or intra-arterial thrombolysis, or done within 1 week prior to index event. • Gastrointestinal bleed or major surgery < 3 months • History of nontraumatic intracranial haemorrhage. • Internal carotid artery stenosis >50%. • Indication for anticoagulation. • Primary event induced by angiography or surgery. • Life expectancy <3 months. • Contraindication to clopidogrel or aspirin. • Indication for nonstudy antiplatelet drugs or NSAIDs affecting platelet function. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** NR **Enrolled (our cohort of interest):** 457 **Omeprazole use:** Proton pump inhibitors will be switched when possible and new prescriptions will be avoided. **Age - Mean (SD):** only reported by study arm and as median (IQR): LOF carriers: 61 (51-71), Non-carriers: 64 (54-72) **Sex - % female:** Reported by study arm: LOF carriers: 34.3, non-carriers: 42.9 **Ethnicities included:** White: 175 (66.7%), black: 65 (24.5%), other: 25 (9.4%)	**Antiplatelet** Clopidogrel **Dose** 75 mg **Regimen** Clopidogrel at a loading dose of 600 mg on day 1, followed by **75 mg per day**, plus aspirin at a dose of 50 to 325 mg per day	***CYP2C19* test:** Drug Metabolism Enzyme TaqMan Allelic Discrimination Assay **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** Unknown

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Ni et al.(2017)[62] **Study Name** Nanjing Stroke Registry Program **Country** China **Study Design** Prospective Cohort **Funding** Not stated **Setting** Nanjing Stroke Registry Program (NSRP) Feb 2012 to Feb 2014	**Condition** Stroke **Inclusion Criteria** • Clinical diagnosis of acute cerebral infarction within 7 days after stroke onset - ≥ 35 years or older • Head magnetic resonance imaging or computerized tomography scan • Chinese Han ethnicity • Treated with clopidogrel at enrollment. **Exclusion Criteria** • Thienopyridine or glycoprotein IIb/IIIa inhibitor within one week • Allergy to clopidogrel • Atrial fibrillation • Oral anticoagulation therapy • NIHSS) score was > 15 • Serious kidney or liver disordersIncreased risk of bleeding • Major bleeding or intracranial hemorrhage within 3 months • Autoimmune disease • Platelet count < 100×109/L or > 500×109/L • Hemorrhage transformation after cerebral infarction. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 191 **Enrolled (our cohort of interest):** 191 **Omeprazole use:** 5.2% using PPI **Age mean (SD)** 61.5 (10.5) **Sex - % female:** 33% **Ethnicities included:** Asian: chinese han ethnicity	**Antiplatelet** Clopidogrel **Regimen** NR	***CYP2C19* test:** improved Multiple Ligase Detection Reaction (iMlDR) **Alleles tested for:** NR **Poor metaboliser definition:** At least 1 LOF **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Unknown

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Patel et al. (2021)[63] **Country** US **Study Design** Retrospective Cohort **Funding** Mixed **Setting** US	**Condition** TIA **Inclusion Criteria** • ICAD diagnostic code • *CYP2C19* genotyping data available. • Clopidogrel exposure (two separate mentions of clopidogrel as identified by MedEx natural language processing software) • Established prior patient care (at least one visit between 1 year and 1 month prior to study start). **Exclusion Criteria** • Acute ischemic stroke up to 2 weeks following study start • Previous diagnosis of intracranial aneurysm or arteriovenous malformation. • Last mention of clopidogrel occurring < 1 month after study start. **Number of Participants** **Eligible (total study):** 337 **Enrolled (total study):** 337 **Enrolled (our cohort of interest):** 161 **Omeprazole use:** NR **Age - Mean (IQR)** 70 (61.0,77.0) **Sex - % female** 29.1 **Ethnicities included:** Mixed: White: 89.4%, African American 10.6%	**Antiplatelet** Clopidogrel **Regimen** Patients undergoing dual antiplatelet therapy were not excluded. Dosing of medications was performed by the treating physician and was not standardized or mandated.	***CYP2C19* test:** TaqMan and Illumina BeadExpress microarrays, or the Infinium Expanded Multi-Ethnic Genotyping Array. **Alleles tested for:** *1, *2, *3, *4, *5, *6, *7, *8. and *17 **Poor metaboliser definition:** At least one LoF allele (*2, *3, *4, *5, *6, *7, or *8). **Intermediate metaboliser definition:** No intermediate **How were 17* alleles handled?** GoF were *1/*17 or *17/*17. Lof allele/*17 not defined.

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Qiu et al. (2015)[64] **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** Second Hospital of Tianjin Medical University	**Condition** Stroke **Inclusion Criteria** • Patients admitted to hospital within a week after symptoms onset, diagnosed as acute ischemic stroke by a neurologist **Exclusion Criteria** • Treatment with anticoagulants, thrombolytic agents and other antiplatelet drugs within 2 weeks. • Cranial bleeding or active haemorrhage. • Trauma, surgery, deep vein or arterial thrombosis within the preceding 3 months • Severe hepatic or renal dysfunction • Malignant diseases • Chronic inflammatory diseases • Infectious conditions at study entry. **Number of Participants** **Eligible (total study):** 211 **Enrolled (total study):** 211 **Enrolled (our cohort of interest):** 211 **Omeprazole use:** Usage of PPI: Noncarriers 29/82 (35.4%), carriers 56/129 (44.1%) **Age Mean (SD)** Reported only by study arm: non-carriers 67.4 (13.6), carriers: 66.7 (11.5) **Sex - % female** Reported only by study arm: non-carriers 41.5 carriers: 47.3 **Ethnicities included:** Not reported - likely most patients asian (chinese)	**Antiplatelet** Clopidogrel **Regimen** patients enrolled were given clopidogrel (75 mg once daily)	***CYP2C19* test:** Cwbiotech **Alleles tested for:** *1, *2 and, *3 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Sen et al. (2014)[65] **Country** Turkey **Study Design** Prospective Cohort **Funding** Not stated **Setting** Neurology Outpatient Clinic at Çanakkale Onsekiz Mart Üniversity Research Hospital, Çanakkale, Turkey.	**Condition** Stroke **Inclusion Criteria** • Patients who started clopidogrel 75 mg/day as a result of acute ICVD in the previous 2 years, and who were monitored for at least 1 year. **Exclusion Criteria** • Patients who stopped attending the clinic, or who did not take their medication regularly. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 51 **Enrolled (our cohort of interest):** 51 **Omeprazole use:** NR **Age Mean (SD)** 66.4 (9.6) **Sex - % female** 58.83 **Ethnicities included:** NR	**Antiplatelet** Clopidogrel **Regimen** Clopidogrel 75 mg daily	***CYP2C19* test:** Lightmix **Alleles tested for:** *1, *2 and, *3 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Spokoyny et al. (2014)[66, 200] **Country** US **Study Design** Retrospective Cohort **Funding** Not stated **Setting** US	**Condition** TIA & Stroke **Inclusion Criteria** Patients tested for the clopidogrel *CYP2C19* genotype between April 2010 and February 2012, and had suffered at least 1 stroke or TIA. **Exclusion Criteria** NR **Number of Participants** **Eligible (total study):** 53 **Enrolled (total study):** 53 **Enrolled (our cohort of interest):** 43 **Omeprazole use:** There were 9 patients concurrently taking a PPI and Clopidogrel. **Age Mean (SD)** 69.6 (NR) **Sex - % female** 46.6 **Ethnicities included:** Mixed: White: 70%, Middle eastern: 2%, Asian 11%, hispanic 7%, African American 4%, Filipino 4%, Indian: 2% [this is for full population of 53 people]	**Antiplatelet** Clopidogrel **Regimen** NR	***CYP2C19* test:** NR **Alleles tested for:** NR **Poor metaboliser definition:** NR **How were 17* alleles handled?** NR

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Sun et al. (2015)[67] **Study Name** Nanjing Stroke Registry Program (NSRP) - May 2008 to April 2010 **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • First-ever ischemic stroke evaluated by a neurologist < 7 days from stroke onset. • Computerized tomography (CT) or magnetic resonance imaging (MRI) scan. • Chinese Han ethnicity. • ≥18 years. • Treated with clopidogrel at time of enrollment. **Exclusion Criteria** • Hemodynamic instability • Oral anticoagulation therapy • Antiplatelets other than clopidogrel • Contraindications to clopidogrel treatment • Atrial fibrillation, malignancies, severe kidney, liver, or heart diseases. • Platelet count < 80x10^9 l^-1; • Active bleeding or bleeding diathesis • Intracranial haemorrhage < 3 months. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 625 **Enrolled (our cohort of interest):** 625 **Omeprazole use:** PPIs avoided when possible. If a PPI was warranted, pantoprazole was prescribed. **Age Mean (SD):** 61.6 (12.2) **Sex - % female:** 25.6 **Ethnicities included:** Asian: Cohort of chinese patients	**Antiplatelet** Clopidogrel The patients were given a standard clopidogrel dose of 75 mg daily.	***CYP2C19* test:** Improved Multiple Ligase Detection Reaction (iMLDR) **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Unknown

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Tanaka et al. (2019)[68, 201] **Country** Japan **Study Design** Prospective Cohort **Funding** NR **Setting** Stroke institutions, Japan	**Condition** Stroke & TIA **Inclusion Criteria** • ≥20 years or older. • Ischemic stroke or transient ischemic attack (TIA) (excluding cardiogenic embolism) in the 3 years prior but not in the past month. • Long-term clopidogrel therapy (75 mg once a day) for secondary prevention of stroke (for at least 1 month). **Exclusion Criteria** • Malignancies • Congenital bleeding tendency • Atrial fibrillation • Use of anticoagulant agent • Platelet count <100×10^9/L or >450×10^9/L within 3 months of enrollment • Modified Rankin Score >4. **Number of Participants** **Eligible (total study):** 518 **Enrolled (total study):** 518 **Enrolled (our cohort of interest):** 501 **Omeprazole use:** 99 (19.8%) **Age Mean (SD):** 68 (61-74) **Sex - % female** 27.3% **Ethnicities included:** Asian: 100% Japanese	**Antiplatelet** Clopidogrel **Regimen** 75 mg once a day	***CYP2C19* test:** TaqMan **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** Excluded

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Tomak et al (2018)[69] **Country** Czech Republic **Study Design** Retrospective Cohort **Funding** Not stated **Setting** Stroke center, Czech Republic	**Condition** Stroke **Inclusion Criteria** • Clopidogrel monotherapy after recent non-cardioembolic ischemic stroke. • Availability of complete clinical and laboratory dataset. • ≥18 years • Czech origin **Exclusion Criteria** • Homozygotes *CYP2C19**2/*2 were excluded. **Number of Participants** **Eligible (total study):** 130 **Enrolled (total study):** 130 **Enrolled (our cohort of interest):** 130 **Omeprazole use:** Used by 20.8% of patients **Age Mean (SD):** 64.5 (13.81) **Sex - % female** 40% **Ethnicities included:** White: (100% czech)	**Antiplatelet** Clopidogrel **Regimen** 75 mg daily	***CYP2C19* test:** LightScanner system **Alleles tested for:** *1, *2, and *17 **Poor metaboliser definition:** *1/*2 **Intermediate metaboliser definition:** 1 LOF allele **How were 17* alleles handled?** *2/*17 analysed on the LOF carrier group

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Tornio et al. (2018)[70, 202, 207] **Study Name** GoDARTS **Country** Scotland **Study Design** Retrospective Cohort **Funding** Non-industry **Setting** GoDARTS bioresource	**Condition** Stroke **Inclusion Criteria** Individuals in GoDARTS, genotyped for *CYP2C19**2 polymorphism and who had also redeemed at least one prescription for clopidogrel up to 21 days following hospitalization for arterial thrombo-occlusive events **Exclusion Criteria** NR **Number of Participants** **Eligible (total study):** 651 **Enrolled (total study):** 651 **Enrolled (our cohort of interest):** 94 **Omeprazole use:** NR **Age Mean (SD)** 74 **Sex - % female** 38% **Ethnicities included:** White: Ethnicity not reported but implies mostly caucasian	**Antiplatelet** Clopidogrel **Regimen** NR	***CYP2C19* test:** NR **Alleles tested for:** *1 and *2 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Wang et al. (2016a)[51, 73, 191-194] **Study Name** CHANCE **Country** China **Study Design** Prospective cohort **Funding** Non-industry **Setting** 73 among 114 sites from CHANCE (China)	**Condition** Stroke & TIA **Inclusion Criteria** • ≥ 40 years • Acute non-disabling ischemic stroke (NIHSS≤3) or TIA with ABCD2 score ≥ 4, treated with study drug < 24 hours after onset. **Exclusion Criteria** • Diagnosis of haemorrhage or other pathology. • Symptoms without evidence of acute infarction on baseline head CT or MRI. • Modified Rankin Scale Score > 2 • Indication for anticoagulation • Contraindication to clopidogrel or ASA • History of intracranial haemorrhage • Indication for long-term non-study antiplatelet drugs, or NSAIDs affecting platelet function • Gastrointestinal bleed or major surgery <3 months • Planned or likely revascularization within the next 3 month • Primary event induced by angiography or surgery • Life expectancy < 3 months. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 3010 **Enrolled (our cohort of interest):** 1463 **Omeprazole use:** Proton pump inhibitors will be switched when possible and new prescriptions will be avoided. (10 patients within the carrier group and 10 within the non carrier group (20 out of 2933)) **Age Mean (SD):** Carrier 62.2 (54.4-71.2), non-carrier: 63.1 (55.5-71.5) **Sex - % female:** Reported by study arm: Carrier 31.4, non-carrier: 34.8 **Ethnicities included:** Not reported - likely most patients asian (chinese)	**Antiplatelet** Clopidogrel **Regimen** *Day 1*: four tablets of clopidogrel 75 mg and open label ASA (75 mg -300 mg) *From D2 to D21±2 days*: one tablet of clopidogrel 75mg and one tablet of ASA 75 mg per day *From D22±2 days visit to D90±7 days*: one tablet of clopidogrel 75mg and one tablet of placebo ASA 75 mg per day	***CYP2C19* test:** Sequenom MassARRAY iPLEX platform (Sequenom). **Alleles tested for:** *1, *2, *3, and *17 **Poor metaboliser definition:** 2 LOF alleles **Intermediate metaboliser definition:** At least 1 LOF allele **How were 17* alleles handled?** (*2/*17 or *3/*17) were classified as unknown metabolizers.

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Wang et al. (2016b)[71] **Study Name** Nanjing Stroke Registry Program (NSRP) – April 2009 – March 2011 **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • Patients with ischemic stroke registered in Nanjing Stroke Registry Program (NSRP) between April 2009 and March 2011, confirmed by computer tomography or magnetic resonance imaging • ≥18 years • Treated with clopidogrel ≥3 months **Exclusion Criteria** • Other oral anticoagulation drugs. • Moyamoya diseases • Severe kidney or liver diseases. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 321 **Enrolled (our cohort of interest): 321** **Omeprazole use:** PPI: 10 (5.2%) **Age categories included** Only reported by study arm: non-carriers of LOF 62 (53-69), carriers of LOF: 62 (53-70) **Sex - % female** Only reported by study arm: non-carriers of LOF: 20.3%, carriers of LOF: 28.8% **Ethnicities included:** Not reported - likely most patients asian (chinese)	**Antiplatelet** Clopidogrel **Regimen** NR	***CYP2C19* test:** improved Multiple Ligase Detection Reaction (iMlDR) **Alleles tested for:** *1, *2 and, *3 **Poor metaboliser definition:** At least 1 LOF **Intermediate metaboliser definition:** No intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Yi et al.(2018)[53] **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • ≥18 years • Diagnosis of ischemic stroke by cranial computed tomography and magnetic resonance imaging scanning. • Cause of stroke: large-artery atherosclerosis • No carotid endarterectomy or carotid stent therapy at enrollment and during the 30 days of treatment **Exclusion Criteria** • Coma or NIHSS score ≥ 13 • Clinically relevant arrhythmia on admission • Major concurrent illness including renal failure and malignancies - Any relevant hemodynamic compromise on admission • Use of ticlopidine, dipyridamole, other nonsteroidal anti-inflammatory drugs, or other aspirin-containing drugs previously or at the time of the index stroke • Administration of heparin or low-molecular-weight heparin within 24 hours before their enrollment in the study • Major surgical procedure within 1 week before enrollment • Increased risk of bleeding **Number of Participants** **Eligible (total study):** 570 **Enrolled (total study):** 570 **Enrolled (our cohort of interest):** 284 **Omeprazole use:** NR **Age Mean (SD):** 69.2 (10.1) **Sex - % female:** 45.1% **Ethnicities included:** Not reported - likely most patients asian (chinese)	**Antiplatelet** Clopidogrel + aspirin **Regimen** aspirin plus clopidogrel (200 mg aspirin and 75 mg clopidogrel for 30 days, and 75 mg/d clopidogrel thereafter.	***CYP2C19* test:** NR **Alleles tested for:** *2 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not genotyped

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Yi et al. (2017)[72] **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke **Inclusion Criteria** • ≥ 40 years of age • IS-related atherothrombotic or small artery disease. • Not taking clopidogrel for at least 7 days before admission • NIHSS score <15. **Exclusion Criteria** • Allergy to clopidogrel • Cardiac cerebral embolism or any other determined or undetermined aetiology • Thrombolytic or anticoagulation therapy with warfarin or heparin within 7 days • Patients who received a proton pump inhibitor before or during hospital admission • Hemorrhagic stroke • Hematological, autoimmune, or other severe concomitant diseases • Platelet count < 1 x 10^11/L or > 4.5 x 10^11/L. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 375 **Enrolled (our cohort of interest):** 375 **Omeprazole use:** Proton pump inhibitors usage is exclusion criteria **Age Mean (SD)** Reported by study arm: clopidogrel resistant: 69.97 (11.23), clopidogrel sensitive: 67.04 (12.16) **Sex - % female** Reported by study arm: clopidogrel resistant: 35.14, clopidogrel sensitive: 35.58 **Ethnicities included:** Not reported - likely most patients asian (chinese)	**Antiplatelet** Clopidogrel + aspirin **Dose** 75 mg **Regimen** 75 mg clopidogrel once daily or clopidogrel (75 mg, once daily) plus aspirin (200 mg, once daily), for the initial 2 weeks, followed by treatment with clopidogrel alone (75 mg, once daily) for at least 6 months.	***CYP2C19* test:** Mass ARRAY RT software **Alleles tested for:** *1 and *2 **Poor metaboliser definition:** At least 1 LOF allele **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** Not meassured

Study Details	Participants	Intervention	*CYP2C19* testing & exposure group
Author (Year) Zhang et al. (2017)[73] **Country** China **Study Design** Prospective Cohort **Funding** Non-industry **Setting** China	**Condition** Stroke % TIA **Inclusion Criteria** • High risk acute TIA or acute minor stroke (ABCD2 score ≥ 4 or NIHSS score ≤ 3) • Diagnosis confirmed by CT and MRI. • $\geq$ 40 years • Able to receive treatment $\leq$ 24 hours after the onset of event. **Exclusion Criteria** • Haemorrhage or other major non-ischemic brain disease • Fever, hypoxia, unconsciousness, or hemodynamic disorder at admission • Modified Rankin scale >2 • Drugs within 1 week of the stroke that would affect platelet aggregation function • Platelet count > 450 × 10^9/L or < 100 × 10^9/L • Severe liver or renal insufficiency, tumours, or disease of the immune or respiratory systems • Gastrointestinal bleeding, severe trauma, or surgery within three months of the stroke. **Number of Participants** **Eligible (total study):** NR **Enrolled (total study):** 417 **Enrolled (our cohort of interest):** 417 **Omeprazole use:** 0.6% **Age Mean (SD)** Reported by study arm: LOF carriers: 64.31 (8.87), non-carriers: 63.18 (9.63). **Sex - % female** Reported by study arm: LOF carriers: 40.9, non-carriers: 35.5 **Ethnicities included:** Not reported - likely most patients asian (chinese)	**Antiplatelet** Clopidogrel **Regimen** Loading dose of 300 mg of clopidogrel on day 1, followed by 75 mg of clopidogrel per day for 6 months, plus 100 mg of aspirin per day for the first 21 days).	***CYP2C19* test:** Perkin Elmer Gene Amp PCR Systems 9600, **Alleles tested for:** *1, *2, *3 and *17 **Poor metaboliser definition:** At least 1 LOF **Intermediate metaboliser definition:** No Intermediate **How were 17* alleles handled?** included

*Number of participants randomised to our cohort of interest = everyone genotyped and receiving clopidogrel alone or in combination with another antiplatelet
Age/sex/ ethnicity is extracted for our cohort of interest (as above)

Risk of bias assessment

Review Level considerations	
List potential confounders	Ethnicity

Study Details	Chen et al. (2019)[52]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a majorly Asian setting	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	N
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA

3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant missing data	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	PN

6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Objective and well-defined outcomes, no information on outcome assessors' awareness of study participants' *CYP2C19* status, they do mention platelet data blinded, so likely included there	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	NA
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	N
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	N
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Results come from a RCT with a pre-specified analysis plan	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure, so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Diaz-Villamarin et al. (2018)[54]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a majorly Asian setting	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	N
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**

Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant missing data	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**

Rationale for judgement: Objective and well-defined outcomes, no information on outcome assessors' awareness of study participants' *CYP2C19* status, they do mention platelet data blinded, so likely included there	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	N
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	N
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	N
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different subgroups?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No information on pre-specified protocol but definitions of exposures and outcomes similar to similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure, so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Fu et al. (2020)[55]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No missing data reported	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: outcomes assessed by phone call or clinical visits, which could be open to bias, however the outcome definitions are objective	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	N
Risk of bias judgement	**LOW**
Rationale for judgement: No information on pre-specified protocol but this is a secondary outcome that was not "statistically significant", so not likely to have been selected based on desirability	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	SOME CONCERNS
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Fukuma et al. (2022)[56]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	N
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**

Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No missing data reported	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Objective outcome - exposure blinded to outcome assessors	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	PY
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: The paper mentions an approved protocol, but it's not available. Primary outcome is secondary stroke, and it's the only reported one considering different exposures.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Han et al (2017)[47]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a majorly Asian setting	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	N
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	N
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant missing data	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Genotype status blinded for investigators	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	Y

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	NA
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	N
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	N
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	N
Risk of bias judgement	**LOW**
Rationale for judgement: registered trial with pre-published protocol	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Hoh et al. (2016)[57]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	PY
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Estimates adjusted for race, which is likely to be measured accurately	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No missing data reported	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcomes (stroke, death, MI, TIA) are likely to be accurately characterised	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	*N*

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: Paper mentions study approval by institutional reviews, so likely it had a pre-specified protocol, but it's not available. Results against the study hypothesis, and primary outcome clearly defined, so it's likely it wasn't selected	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Lin et al. (2014)[58]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**Some concerns**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No missing data reported	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: NO information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcomes (stroke, death, MI, TIA) are likely to be accurately characterised	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on specified protocol, but results not likely to be selected	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Liu et al. (2020)[59]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**

Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No missing data reported	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcomes (stroke, death, MI, TIA) are likely to be accurately characterised	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on specified protocol, but results not likely to be selected	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Lv et al. (2022)[60]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a majorly Asian setting	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**

Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	N
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	Y
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	SY
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	N
Risk of bias judgement	**VERY HIGH**
Rationale for judgement: from 345 eligible patients, 314 were genotyped and included in the analysis. From the 345, authors report follow-up up for 54 months for a total of 270 patients (no data on how many genotyped patients).	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA

Risk of bias judgement	**LOW**
Rationale for judgement: Genotype status blinded for investigators	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No mention or a pre-specified protocol and analysis plan, but selected result it's very typical primary outcome for similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**VERY HIGH**
Rationale for judgement: Outcome data not available for a significant proportion of the population, missing data likely related with the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	McDonough et al. (2015)[61]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	PY
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors controlled for ethnicity on overall result and stratified by ethnicity too	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	PN
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	NI
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	Y
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	WY
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	N
Risk of bias judgement	**HIGH**
Rationale for judgement: No data on loss to follow-up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: "All primary events, the primary safety outcome, and most secondary outcomes were adjudicated by a blinded events-adjudication committee"	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	PY
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: This is a sub analysis of a pre-registered clinical trial, protocol not available. Exposure definitions and primary and secondary outcomes as in similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: NO data on loss to follow-up, potential missing data likely related to outcome. Lifetime exposure so follow-up does not begin at the start of the exposure window	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	Meschia et al (2020)[48]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with an homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	N
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	N
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant missing data	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Genotype status blinded for investigators	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	NA
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	N
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	N
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	N
Risk of bias judgement	**LOW**
Rationale for judgement: registered trial with pre-published protocol	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Ni et al.(2017)[62]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on Chinese Han patients only.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	PN
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	NI
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	Y
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	WY
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	N
Risk of bias judgement	**HIGH**
Rationale for judgement: No data on loss to follow up. Potential missing data likely to be related with the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Assessors were blinded to genotype	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: a study protocol is mentioned but not available -Exposure definitions and primary and secondary outcomes as in similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: No data on loss to follow up. Potential missing data likely to be related with the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	Patel et al. (2021)[63]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a mostly Caucasian population	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	PN
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	PN
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	PY
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: retrospective study so probably negligible loss to follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: outcome assessment by clinical records, based on diagnostic codes	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No mention of pre-specified protocol. Exposure definitions and primary and secondary outcomes as in similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Qiu et al. (2015)[64]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on Chinese Han patients only	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	NA
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: no reported loss of follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	Y
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: Data collection and follow-up were completed by another independent group and were unaware of the genotypic and platelet function information.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g. statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No info on predetermined analysis plan, but this was not reported as primary outcome, exposure and outcomes similar to other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	SOME CONCERNS
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Sen et al. (2014)[65]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	NI
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NI
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NI
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**HIGH**
Rationale for judgement: population likely not ethnically homogeneous, no info on ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	PY
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	PY
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: retrospective study so probably negligible loss to follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	PN
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcomes (are likely to be accurately characterised	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No info on predetermined analysis plan, but exposure and outcomes similar to other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: population likely not ethnically homogeneous, no info on ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	Spokoyny et al. (2014)[66]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	SN
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	NA
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**HIGH**
Rationale for judgement: ethnicity is a common cause of CYP219 variations and recurrent events - mixed population, results probably not adjusted by ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	PY
2.2 Was the exposure likely to be measured with error, or misclassified?	PN
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	PY
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	PY
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: retrospective study so probably negligible loss to follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcome is likely to be accurately characterised	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No info on predetermined analysis plan, but exposure and outcomes like other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: ethnicity is a common cause of CYP219 variations and recurrent events - mixed population, results probably not adjusted by ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	Sun et al. (2015)[67]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	PY
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on Chinese Han patients only	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	PN
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	PY
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: no reported loss of follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: NO information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcome is likely to be accurately characterised	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No info on predetermined analysis plan, but exposure and outcomes like other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Tanaka et al. (2019)[68]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on Japanese patients only	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**

Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	PY
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: no reported loss of follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	PN
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: outcome assessors not aware of exposure	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	NA
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: Registered and pre specified protocol. Primary outcome definitions like other studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Tomak et al (2018)[69]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	PY
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	PY
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: retrospective study so probably negligible loss to follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Outcomes assessed separately.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: NO info on predetermined analysis plan, but exposure and outcomes like other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Tornio et al. (2018)[70]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PY
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	PN
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	SN
Risk of bias judgement	**HIGH**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is dependent on hospitalization for arterial thrombo-occlusive events and redemption of at least one prescription for clopidogrel up to 21 days following hospitalization.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	PY
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	PY
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Study done on patients on GoDarts cohort by medical record linkage - potential for missing data, but ATO events likely to be accurately reflected on clinical records	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No information on how outcomes were assessed, no information on outcomes assessors' awareness of participant's exposure. However, outcome is likely to be accurately characterised	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result

7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No info on predetermined analysis plan, but exposure and outcomes like other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is dependent on hospitalization for arterial thrombo-occlusive events and redemption of at least one prescription for clopidogrel up to 21 days following hospitalization.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	Wang et al.(2016a)[51]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	NA
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	PY
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	N
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: No significant missing data	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Genotype status blinded for investigators	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	Y
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	NA
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	N
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	N
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	N
Risk of bias judgement	**LOW**
Rationale for judgement: registered trial with pre-published protocol	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Wang et al. (2016b)[71]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	N
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	Y
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	SY
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NI
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	PN
Risk of bias judgement	**HIGH**
Rationale for judgement: loss of follow: 14/321 patients, likely associated with outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: The adjudication of these events was blinded to genotype data.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No info on predetermined analysis plan, but exposure and outcomes like other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**HIGH**
Rationale for judgement: Significant loss to follow-up, likely associated with outcome	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	NI

Study Details	Yi et al.(2018)[53]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	Y
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Among the 284 patients, 7 patients in the clopidogrel group were lost to follow-up, 12 patients (2.1%) discontinued the study medication before the end of the study, 5 patients underwent carotid stent therapy during the follow-up period.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	N
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Genotype was blinded to outcome assessors.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	PY
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: The paper mentions a preapproved study protocol but it's not available, however exposure and outcomes like other similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Yi et al. (2017)[72]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	NA
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	N
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	NA
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	NA
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: out of 375 patients, 363 (96.8%) completed 6 months of follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	PN
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: no information on outcomes assessors' awareness of participant's exposure. However, outcome is likely to be accurately characterised	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: The paper mentions a pre-approved protocol, but it's not available. However, outcomes similar to similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: *Rationale for judgement:* Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Study Details	Zhang et al. (2017)[73]

Domain 1: Risk of bias due to confounding (Variant A)	
1.1 Did the authors control for all the important confounding factors for which this was necessary?	Y
1.2 If Y/PY/WN to 1.1: Were confounding factors that were controlled for (and for which control was necessary) measured validly and reliably by the variables available in this study?	Y
1.3 If Y/PY/WN to 1.1: Did the authors control for any variables after the start of the exposure period being studied that could have been affected by the exposure?	N
1.4 Did the use of negative controls, or other considerations, suggest serious uncontrolled confounding?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Authors did not need to control for ethnicity, because the study was conducted on a population with a homogeneous ethnicity	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 2: Risk of bias arising from measurement of the exposure (Variant A)	
2.1 Does the measured exposure well characterize the exposure metric specified to be of interest in this study?	Y
2.2 Was the exposure likely to be measured with error, or misclassified?	N
2.3 If SY/WY to 2.2: Could mismeasurement or misclassification of exposure have been differential (i.e., related to the outcome or risk of the outcome)?	N
2.4 If SY/WY to 2.2 and N/PN/WY to 2.3: Is non-differential measurement error likely to bias the estimated effect of exposure on outcome?	N
Risk of bias judgement	**LOW**
Rationale for judgement: Exposure can be objectively and accurately measured	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 3: Domain 3: Risk of bias in selection of participants into the study (or into the analysis) (Variant A)	
3.1 Did follow-up begin at (or close to) the start of the exposure window for most participants?	N
3.2 If N/PN to 3.1: Is the effect of exposure likely to be constant over the period of follow up analysed?	Y
3.3 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of the exposure window being studied?	Y
3.4 If Y/PY to 3.3: Were these characteristics likely to be influenced by exposure or a cause of exposure?	PN
3.5 If Y/PY to 3.4: Were these characteristics likely to be influenced by the outcome or a cause of the outcome?	PN
3.6 If N/PN to 3.2 or Y/PY to 3.5: Is it likely that the analysis corrected for all of the potential selection biases identified in A and B above?	NA
3.7 If N/PN to 3.2 or Y/PY to 3.5: Did sensitivity analyses demonstrate that the likely impact of the potential selection biases identified in A or B above was minimal?	NA
Risk of bias judgement	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	

Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

DOMAIN 4: Risk of bias due to post-exposure interventions	
4.1 Were there post-exposure interventions that were influenced by prior exposure during the follow-up period?	N
4.2 If Y/PY to 4.1: Is it likely that the analysis corrected for the effect of post exposure interventions that were influenced by prior exposure?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: Having a genetic polymorphism does not predict any post-exposure interventions	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 5: Risk of bias due to missing data	
5.1 Were complete data on exposure status available for all, or nearly all, participants?	Y
5.2 Were complete data on the outcome available for all, or nearly all, participants?	Y
5.3 Were complete data on confounding variables available for all, or nearly all, participants?	Y
5.4 If N/PN/NI to 5.1, 5.2 or 5.3: Is the result based on a complete case analysis?	NA
5.5 If Y/PY/NI: Was exclusion from the analysis because of missing data (in exposure, confounders, or the outcome) likely to be related to the true value of the outcome?	NA
5.6 If N/PN to 5.5: Were all or most predictors of missingness (in exposure, confounders, or the outcome) included in the analysis model?	NA
5.7 If N/PN to 5.4: Was the analysis based on imputing missing values?	NA
5.8 If Y/PY to 5.7: Was imputation performed appropriately?	NA
5.9 If N/PN to 5.7: Was an appropriate alternative method used to correct for bias due to missing data?	NA
5.10 If PN/N/NI to 5.1, 5.2 or 5.3: Is there evidence that the result was not biased by missing data?	NA
Risk of bias judgement	**LOW**
Rationale for judgement: no mention of loss to follow up	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 6: Risk of bias arising from measurement of the outcome	
6.1 Could measurement or ascertainment of the outcome have differed between exposure groups or levels of exposure?	N
6.2 Were outcome assessors aware of study participants' exposure history?	NI
6.3 If Y/PY/NI to 6.2: Could assessment of the outcome have been influenced by knowledge of participants' exposure history?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: no information on outcomes assessors' awareness of participant's exposure. However, outcome is likely to be accurately characterised	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Domain 7: Risk of bias in selection of the reported result	
7.1 Was the result reported in accordance with an available, pre-determined analysis plan?	NI
7.2 If N/PN/NI to 7.1: Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple exposure measurements within the exposure domain?	PN
7.3 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple outcome measurements within the outcome domain?	PN
7.4 Is the reported effect estimate likely to be selected, based on desirability of the magnitude (or statistical significance) of the estimated effect of exposure on outcome, from multiple analyses of the exposure-outcome relationship?	PN
7.5 Is the reported effect estimate likely to be selected, based on the basis of desirability of the results (e.g., statistical significance), from different subgroups?	PN
Risk of bias judgement	**LOW**
Rationale for judgement: No mention of pre-specified protocol, outcomes like similar studies	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

OVERALL RISK OF BIAS	**SOME CONCERNS**
Rationale for judgement: Lifetime exposure so follow-up does not begin at the start of the exposure window. Selection of participants is not likely to be influenced by exposure or cause of exposure (exposure genetic polymorphisms do not influence risk of stroke) or by the outcome.	
Is the risk of bias (due to confounding) sufficiently high, in the context of its likely direction and the magnitude of the estimated exposure effect, to threaten conclusions about whether the exposure has an important effect on the outcome?	N

Results

Study details							Loss of function carriers		Loss of function non-carriers		Effect measure		
Study	**Drug regimen**	**Alleles**	**Event**	**Ethnicity**	**FU time (days)**	**Outcome**	**No. patients**	**No. Events**	**No. patients**	**No. Events**	**HR**	**logHR**	**SElogHR**
Chen (2019)[52]	Clopidogrel + Aspirin (short-term)	*2, *3	Stroke - TIA	Asian	90	Any bleeding	190	30	139	18	1.219298	0.198276	0.298142
						Any stroke	190	22	139	8	2.011842	0.699051	0.412861
						Composite outcome	190	24	139	8	2.194737	0.786062	0.408248
						Haemorrhagic stroke	190	2	140	1	3.661417	1.29785	1.549193
						Ischaemic stroke	190	20	139	8	1.828947	0.603741	0.41833
						Mortality	190	2	140	1	3.661417	1.29785	1.549193
						Myocardial infarction	190	1	140	1	2.19685	0.787025	1.632993
						Severe bleeding	190	3	139	1	2.194737	0.786062	1.154701
						Vascular death	190	2	140	1	3.661417	1.29785	1.549193
Diaz-Villamarin (2018)[54]	Clopidogrel	*2, *3	Stroke - TIA	White	90	Composite outcome	18	7	49	7	3.01	1.10194	0.557978
Fu (2020)[55]	Clopidogrel	*2, *3	Stroke	Asian	180	Composite outcome	53	8	78	9	1.24	0.215111	0.495629
Fukuma (2017)[56]	Clopidogrel +/-other antiplatelet agents	*2, *3	Stroke - TIA	Asian	90	Ischaemic stroke	139	25	55	6	1.648681	0.499976	0.454606
Han (2017)[47]	Clopidogrel	*2, *3	Stroke	Asian	985.5	Any bleeding	244	14	149	13	0.60241	-0.50682	0.386584
						Any stroke	244	14	149	6	1.424863	0.354076	0.48795
						Composite outcome	244	15	149	6	1.5625	0.446287	0.482937
						Haemorrhagic stroke	244	3	149	2	0.943396	-0.05827	0.908188
						Ischaemic stroke	244	11	149	4	1.694915	0.527633	0.580591
						Myocardial infarction	244	1	150	1	1.834356	0.606693	1.632993
Hoh (2016)[57]	Clopidogrel + Aspirin	*2, *3, plus others	Stroke - TIA	Mixed	365	Composite outcome	51	0	138	1	0.27	-1.30933	0.631234
Lin (2021)[58]	Clopidogrel	*2, *3	Stroke	Asian	365	Any bleeding	51	1	39	1	2.242718	0.807689	1.632993
						Ischaemic stroke	51	13	38	2	4.843137	1.577563	0.759555

Study details							Loss of function carriers		Loss of function non-carriers		Effect measure		
Study	**Drug regimen**	**Alleles**	**Event**	**Ethnicity**	**FU time (days)**	**Outcome**	**No. patients**	**No. Events**	**No. patients**	**No. Events**	**HR**	**logHR**	**SElogHR**
Liu (2020)[59]	Clopidogrel	*2, *3	Stroke	Asian	180	Ischaemic stroke	159	31	130	10	2.534591	0.930032	0.363673
Lv (2022)[60]	Clopidogrel	*2, *3	Stroke	Asian	1620	Composite outcome	187	79	127	16	2.05	0.71784	0.233748
McDonough (2015)[61]	Clopidogrel + Aspirin	*2	Stroke - TIA	Mixed	1241	Any stroke	107	9	386	17	1.909841	0.64702	0.412231
		*2				Severe bleeding	107	4	386	19	0.759469	-0.27514	0.55012
Meschia (2020)[48]	Clopidogrel + Aspirin	*2, *3	Stroke - TIA	Mixed	90	Any stroke	131	3	326	12	0.622137	-0.47459	0.645497
						Composite outcome	131	3	326	12	0.622137	-0.47459	0.645497
						Ischaemic stroke	131	3	326	11	0.678695	-0.38758	0.651339
						Mild bleeding	131	2	326	6	0.829517	-0.18691	0.816497
						Severe bleeding	131	0	327	5	0.275877	-1.2878	1.490712
Ni (2017)[62]	Clopidogrel	*2, *3	Stroke	Asian	NR	Composite outcome	114	21	77	5	2.9	1.064711	0.499066
Patel (2021)[63]	Clopidogrel	*2, *3, plus others	TIA	White	NR	Ischaemic stroke		NR	NR	NR	NR	3.4	1.223776
Qiu (2015)[64]	Clopidogrel	*2, *3	Stroke	Asian	180	Composite outcome	129	12	82	3	2.542636	0.933201	0.645497
Sen (2014)[65]	Clopidogrel	*2, *3	Stroke	Mixed	NR	Ischaemic stroke	15	3	37	1	18.55487	2.920732	1.512385
Spokoyny (2014)[66]	Clopidogrel		Stroke - TIA	Mixed	NR	Ischaemic stroke	15	6	27	3	4.337005	1.467184	0.709959
Sun (2015)[67]	Clopidogrel	*2, *3	Stroke	Asian	381	Any bleeding	377	8	248	5	1.26	0.231112	0.586115
						Composite outcome	377	65	248	20	2.31	0.837248	0.259227
						Myocardial infarction	377	3	248	4	0.57	-0.56212	0.838402
						Vascular death	377	11	248	2	5.53	1.710188	0.798144
Tanaka (2019)[68]	Clopidogrel	*2, *3	Stroke - TIA	Asian	720	Composite outcome	319	18	182	10	1.026959	0.026602	0.394405
						Ischaemic stroke	319	12	182	5	1.369279	0.314284	0.532291
						Myocardial infarction	319	1	182	1	0.570533	-0.56118	1.414214
						Severe bleeding	319	3	182	1	1.711599	0.537428	1.154701
						TIA	319	3	182	2	0.855799	-0.15572	0.912871
	Clopidogrel	*2	Stroke	White	447	Composite outcome	44	10	86	9	2.921	1.071926	0.49937

Study details							Loss of function carriers		Loss of function non-carriers		Effect measure		
Study	**Drug regimen**	**Alleles**	**Event**	**Ethnicity**	**FU time (days)**	**Outcome**	**No. patients**	**No. Events**	**No. patients**	**No. Events**	**HR**	**logHR**	**SElogHR**
Tomak (2018)[69]						Ischaemic stroke	NR	NR	NR	NR	3.17	1.153732	0.462435
Tornio (2017)[70]	Clopidogrel	*2	Stroke	White	720	Composite outcome	27	11	67	17	2.23	0.802002	0.328459
Wang (2016a)[51]	Clopidogrel + Aspirin (short-term)	*2, *3	Stroke - TIA	Asian	90	Any stroke	854	80	609	41	1.391443	0.330342	0.192068
						Composite outcome	854	80	609	41	1.391443	0.330342	0.192068
						Composite outcome	198	NR	124	NR	1.97	0.678034	0.28774
						Ischaemic stroke	854	78	609	39	1.426229	0.355034	0.196116
						Mild bleeding	854	8	609	9	0.63388	-0.4559	0.485913
						Moderate bleeding	854	2	610	1	3.566413	1.27156	1.549193
						Severe bleeding	854	1	610	1	2.139848	0.760735	1.632993
Wang (2016b)[71]	Clopidogrel	*2, *3	Stroke	Asian	NR	Composite outcome	215	30	148	7	1.98	0.683097	0.404521
Yi (2017)[72]	Clopidogrel + Aspirin (short-term)	*2	Stroke	Asian	180	Composite outcome	128	29	156	18	3.02	1.105257	0.500229
Yi (2018)[53]	Clopidogrel + Aspirin (short-term)	*2	Stroke	Asian	1825	Composite outcome	247	42	169	14	1.026316	0.025976	0.308607
Zhang (2017)[73]	Clopidogrel + Aspirin (short term)	*2, *3	Stroke - TIA	Asian	180	Any bleeding	854	20	609	15	0.95082	-0.05043	0.341565

Objective 4

Baseline Details

Note: All studies below are also included for objective 5

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Badhuin et al (2022)[74, 93] **Publication type:** Journal article **Funding:** Non-industry **Country:** US, Canada, South Korea, Mexico **Start date:** NR **Study name:** TAILOR-PCI **Study design:** Diagnostic test accuracy cohort within an RCT	**Population:** Healthy people – pre-trial validation of test performance **Inclusion/exclusion criteria:** NR **Number of participants:** 373 **Mean age in years, SD, range:** NR **Male %:** NR **Ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 373 **Alleles tested for:** *2, *3, *17 **Who administered test:** Onsite testing staff	Test accuracy Ease of use of test Number of people with variant forms of *CYP2C19* (%)
	Population: Acute coronary syndrome or stable coronary artery disease and undergoing PCI – main trial **Inclusion criteria:** 18+ years, target condition, planned 12 months of dual antiplatelet therapy (DAPT) **Number of participants:** 2641 **Mean age in years, SD, range:** NR, NR, 26-95 **Male %:** 75 **Ethnicity:** 68% white, 23% east Asian, 4% south Asian, 2% African American, 2% other, 3% Hispanic or Latinx ethnicity	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 2587 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test accuracy Test failure rate Number of people with variant forms of *CYP2C19* (%)

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Choi et al. (2016)[78] **Publication type:** Journal article **Funding:** Non-industry **Country:** South Korea **Start date:** May 2013 **Study design:** Diagnostic test accuracy	**Population:** Acute coronary syndrome (ACS) undergoing PCI with drug-eluting stents **Inclusion criteria:** Aged 18+, symptomatic ACS including unstable angina/ non-STEMI 12hr from onset, stenosis >70% on angiography **Exclusion criteria:** Hemodynamic instability, malignancies, active bleeding, recent operation/ trauma, febrile disease, acute/ chronic inflammatory diseases, thrombocytopenia or anemia **Number of participants:** 119 **Baseline data only reported by metaboliser status:** **Mean age in years, SD:** Poor: 62.5, 12.1; Intermediate: 61.9, 10.9; Extensive: 64.3, 13.6; Ultra-rapid: 64.8, 12. **Male %:** Poor: 59.1%; Intermediate: 85.2%; Extensive: 79.5%; Ultra-rapid: 75%. **Ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 119 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test accuracy Number of people with variant forms of *CYP2C19* (%) Time to results

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: NCT01718535[82] **Publication type:** Trial registration **Funding:** Industry – test manufacturer **Country:** Canada **Start date:** September 2012 **Study design:** Diagnostic test accuracy	**Population:** NR **Inclusion criteria:** Aged 16+ **Exclusion criteria:** None **Number of participants:** 327 **Mean age in years, SD, range:** NR **Male %:** NR **Ethnicity:** NR	**Test name:** Spartan FRX (Genomadix Cube) **Number of participants tested:** 325 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test accuracy
Author, year: NCT04473586[76] **Publication type:** Online trial registry entry; additional information provided by Genomadix. **Funding:** Industry – test manufacturer **Country:** Canada **Start date:** February 2020 **Study design:** Diagnostic test accuracy	**Population:** NR **Inclusion criteria:** No food/ drink and no smoking within 30min of sample retrieval [redacted]) **Mean age in years, SD, range:** NR **Male %:** NR **Ethnicity:** NR	**Test name:** Spartan Cube (Genomadix Cube) [redacted] [redacted]tests **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test accuracy [redacted]

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: NCT04473573[77] **Publication type:** Online trial registry entry; additional information provided by Genomadix. **Funding:** Industry – test manufacturer **Country:** Canada **Start date:** October 2019 **Study design:** Diagnostic test accuracy	**Population:** NR **Inclusion criteria:** Availability to travel to 3 sites on 5 non-consecutive days **Number of participants:** 8 patients (960 tests) **Mean age in years, SD, range:** NR **Male %:** NR **Ethnicity:** NR	**Test name:** Spartan Cube (Genomadix Cube) **Number of participants tested:** 960 samples **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test accuracy [redacted]
Author, year: Petrek et al. 2016 [79, 83] **Publication type:** Journal Article **Funding:** Unclear **Country:** Czech Republic **Start date:** March 2013 **Study design:** Diagnostic test accuracy	**Population:** PCI **Inclusion criteria:** Random subset of patients **Exclusion criteria:** NR **Number of participants:** 53 **Mean age in years, range:** 57, 13-77 **Male %:** 74% **Ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 53 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test accuracy Test failure rate Time to results Ease of use of test

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Roberts et al. (2012)[75] **Publication type:** Journal article **Funding:** Industry – test manufacturer **Country:** Canada **Start date:** 26 Aug 2010 **Study name:** RAPID GENE **Study design:** RCT (diagnostic test accuracy cohort within an RCT)	**Population:** Healthy volunteers - pre-trial validation of test performance **Number of participants:** 37(267 tests) **Age, sex, ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 37 (tested 267 times total) **Alleles tested for:** *1, *2 **Who administered test:** NR	Test accuracy Number of people with variant forms of *CYP2C19* (%) Test failure rate
	Population: Undergoing PCI for treatment of non-ST-elevation ACS/ stable coronary artery disease – main trial. **Inclusion criteria:** 18-75 years, followed-up >1 week **Exclusion criteria:** Antiplatelet other than aspirin/ clopidogrel, or anticoagulation with warfarin/ dabigatran; history of stroke/ TIA; pregnancy; weight <60 kg; platelet <100 000 per µL; bleeding diathesis; haematocrit <30% or >52%, severe liver/renal disease **Number of participants:** 200 (102 rapid genotyping arm; 98 standard arm genotyped later) **Mean age in years, SD, range:** 60, 9, NR. **Male %:** 80 **Ethnicity:** 95% white	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 200 **Alleles tested for:** *1, *2 **Who administered test:** Trial nurses	Test accuracy Number of people with variant forms of *CYP2C19* (%) Time to results Ease of use of test

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: So et al. (2016)[80] **Publication type:** Journal article **Funding:** Mixed (Industry – test manufacturer and non-industry) **Country:** Canada **Start date:** NR **Study name:** RAPID-STEMI **Study design:** Prospective randomized study (diagnostic test accuracy cohort within an RCT)	**Population:** PCI for STEMI. **Inclusion criteria:** Aged 18-75; PCI for STEMI. **Exclusion criteria:** Pre-treatment with prasugrel/ ticagrelor, need oral anti-coagulant, history of stroke/ TIA, body weight <60kg, platelet count <100,000 ul-1, bleeding diathesis, haemtocrit <30% or >52%, severe liver dysfunction, renal insufficiency, or <24hr treatment with glycoprotein IIb/IIIa inhibitors **Number of participants:** 102 **Mean age in years, SD, range:** 58, 10, NR **Male %:** 77 **Ethnicity:** 91% Caucasian	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 102 **Alleles tested for:** *2, *17 **Who administered test:** NR	Test accuracy Number of people with variant forms of *CYP2C19* (%) Time to results

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Wirth et al. (2016)[81, 97] **Publication type:** Journal article **Funding:** Industry – other **Country:** Malta **Start date:** October 2014 **Study design:** Diagnostic test accuracy	**Population:** PCI with stent for ACS/ stable angina; eligible for DAPT post-PCI **Inclusion criteria:** As above **Exclusion criteria:** Aged <18 or >75, weight <60 kg, history of stroke/ TIA, active bleeding, coagulation disorders, platelet disorders and/or chronic liver disease **Number of participants:** 35 **Mean age in years, SD, range:** 65.8, 2.4, 49-75 **Male %:** 74 **Ethnicity:** 100% Caucasian	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 35 **Alleles tested for:** *2, *1 **Who administered test:** Clinical pharmacist researcher	Test accuracy Test failure rate Number of people with variant forms of *CYP2C19* (%) Time to results Ease of use of test Cost of testing

* When we are focusing on a cohort within an RCT, the 'number of participants' is the number of participants in the genotyping arm of a study (our cohort of interest), whilst the 'total number of participants tested' in the POCT column refers to the number tested with the POCT (not always the same number).

Abbreviations: PCI: percutaneous coronary intervention, NR: not reported, NA: not applicable, SD: standard deviation, STEMI: ST-segment elevation myocardial infarction, RCT: randomised controlled trial, DAPT: dual antiplatelet therapy, ACS: acute coronary syndrome

Risk of bias assessment

Study Details	Badhuin(2022)[208] *Pre-trial*

Domain 1: Patient selection	
373 volunteer samples analysed- no information about condition etc.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Volunteer samples, no case control design and likely avoided innappropriate exclusions.	

DOMAIN 2: INDEX TEST	
Genomadix cube test - conducted on samples. Test conducted on-site by onsite testing staff. Suggests Genomadix test was conducted first, then the report was sent off to the lab along with a saliva sample for Sanger sequencing.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Test order means Genomadix cube results would be available before lab test	

DOMAIN 3: REFERENCE STANDARD	
Sanger sequencing by centralised laboratory - conducted after spartan test completed.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted the reference standard. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING
373 samples tested and analysed

Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient flow was unlikely to have introduced bias - all patients received the same reference standard and were included in the analysis.	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Study Details	Badhuin(2022)[74] *Main trial*

Domain 1: Patient selection	
Seems no inappropriate exclusions took place.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Unlikely that patient selection introduced bias as this is a subset of a randomised controlled trial, no case-control design and likely avoided inappropriate exclusions.	

DOMAIN 2: INDEX TEST	
Spartan Rx test. Test conducted on-site by onsite testing staff. Spartan test was conducted on patients, then Taqman conducted 12 months later.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
Taqman assay conducted in the research laboratory. Spartan test was conducted on patients, then Taqman conducted 12 months later.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted the reference standard. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
2385 patients received both tests - this is our sample of interest.; NA	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes

Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient flow was unlikely to have introduced bias - all patients received the same reference standard and were included in the analysis.	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Study Details	Choi(2016)[78]

Domain 1: Patient selection	
Sampling procedure unclear. Not a case-control design. It seems the study avoided innapropriate exclusions.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: There is not much information given about patient selection however it seems unlikely this will have introduced bias in the accuracy of the genetic test. A case-control design was avoided and it seems likely that the study avoided innapropriate exclusions.	

DOMAIN 2: INDEX TEST	
The index test is the Spartan RX *CYP2C19* and was conducted and interpreted by researchers. It aimed to identify the *2, *3 and *17 allele. Results determined by Spartan and confirmed by ref standard.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
The reference standard was the Taqman SNP genotyping assay. It is unclear who conducted and interpreted it. Results determined by Spartan and confirmed by ref standard.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted and conducted the reference standard. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
All patients received both tests.; NA	
Did all patients receive a reference standard?	Yes

Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: It seems unlikely that patient flow introduced bias- no missing data and all received same tests.	

OVERALL RISK OF BIAS	**Low**
Rationale for judgement: No concerns	

Study Details	NCT01718535(NR)[82]

Domain 1: Patient selection	
"Recruitment of study participants was performed without knowledge of participant genotypes by enrolling associates of operators and associates of Spartan Bioscience and Mount Sinai Services", suggesting it was not consecutive or random.	
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient selection was not random or consecutive, however the study wasn't limited to a specific condition, but it seems unlikely this would bias genetic test accuracy. A case-control design was avoided, and unlikely there were innappropriate exclusions.	

DOMAIN 2: INDEX TEST	
Spartan index test. No information about how tests were conducted and interpreted. Study states it is looking to identify *2, *3 and *17 allele.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
Bidirectional sequencing is the lab test. No information about how it was conducted or interpreted.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard, bidirectional sequencing, is likely to correctly classify the target condition. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
327 patients enrolled but data analysed for 325. Two patients did not receive the reference standard (it says bidirectional sequencing not possible for 2 patients) - no reasoning provided for why this was.; NA	
Did all patients receive a reference standard?	No

Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Missing data is low and all patients who received the reference standard received the same one.	

OVERALL RISK OF BIAS	**Low**
Rationale for judgement: No concerns	

Study Details	NCT04473573(NR)[77]

Domain 1: Patient selection	
Limited information about patients - all ages, sexes and healthy volunteers eligible for inclusion if available to travel to 3 sites.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Limited information on sampling technique but it seems unlikely this would bias the accuracy of the genetic test.	

DOMAIN 2: INDEX TEST	
Spartan test conducted at 3 different test sites. Testing "performed by a total of six operators… … including individuals who are technologists, technicians and/or nurses". No info about interpretation.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
Bidirectional sequencing - no info about conduct and interpretation other than to say "Bi-directional sequencing results will not be shared with the participants, operators or Principal investigators."	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
From the data provided by the company, it seems there were no exclusions;	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes

Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient flow was unlikely to have introduced bias- all patients received the same reference standard and were included in the analysis.	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Study Details	NCT04473586(NR)[76]

Domain 1: Patient selection	
Non-randomised - no info about patient selection or patient condition other than the inclusion criteria being "Participants who will provide buccal samples and a saliva sample who have not eaten drank or smoked in the past 30 minutes".	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Unclear
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Limited information on sampling technique but it seems unlikely this would bias the accuracy of the genetic test.	

DOMAIN 2: INDEX TEST	
Spartan test conducted immediately after sample taken and 21hr after sample taken. No information on who conducted it. "The investigator will not see the bidirectional sequencing results"	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
Bidirectional sequencing "generated by a third part from a saliva sample collected from the same patient"	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	
Rationale for judgement: The reference standard is likely to correctly classify the target condition. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
From the data provided by the company, it seems there were no exclusions;	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes

Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient flow was unlikely to have introduced bias- all patients received the same reference standard and were included in the analysis.	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Study Details	Petrkova(2014)[83]

Domain 1: Patient selection	
Methods of patient selection are not reported. All patients were undergoing acute coronary angioplasty with stent implantation for ACS.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: There is not much information given about patient selection however it is unlikely this will have introduced bias in the accuracy of the genetic test. A case-control design was avoided. There is no information on exclusions but seems unlikely.	

DOMAIN 2: INDEX TEST	
"Obtained samples were tested by Spartan RX AnalyserTM according to the operator's manual". No information on how it was interpreted or order of tests.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
The reference standard was MassArray technology. No information on how it was conducted and interpreted, other than to say "patients' blood was sampled for DNA isolation and subsequent genotyping of *CYP2C19* polymorphisms"	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted and conducted the reference standard.The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
All patients received the index test and reference standard and were included in the results.; NA	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes

Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: It seems unlikely that patient flow would have introduced bias - the tests were conducted simultaneously, all patients did receive the same reference standard and were included in the results.	

OVERALL RISK OF BIAS	**Low**
Rationale for judgement: No concerns	

Study Details	Roberts(2012)[75] *Pre-trial*

Domain 1: Patient selection	
37 healthy volunteer samples.	
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Unclear
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Healthy volunteer samples, no case control design and likely avoided innappropriate exclusions.	

DOMAIN 2: INDEX TEST	
No information on conduct or interpretation but seems Genomadix cube conducted before ref standard.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Order of tests means that reference standard results unlikley to have been available to person conducting the index test.	

DOMAIN 3: REFERENCE STANDARD	
DNA sequencing - limited information given on conduct and interpretation but seems Spartan conducted before ref standard.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
All patients received the index test and reference standard and were included in 2x2 table; NA	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes

Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient flow was unlikely to have introduced bias- all patients received the same reference standard and were included in the analysis.	

OVERALL RISK OF BIAS	**Low**
Rationale for judgement: No concerns	

Study Details	Roberts(2012)[75] *Main trial*

Domain 1: Patient selection	
Patients who met the inclusion criteria were consecutively enrolled, then randomised. A case control design was avoided - all patients had the same condition. It seems the study avoided innappropriate exclusions.	
Was a consecutive or random sample of patients enrolled?	Yes
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Low risk of bias because patients who met the inclusion criteria were consecutively enrolled, then randomised.	

DOMAIN 2: INDEX TEST	
The index test was Spartan RX *CYP2C19* point of care test. It was conducted by clinical trial nurses who had received a 30min training session but had no previous laboratory training. Seems Spartan test was conducted first and then the reference standard, but there is no information about interpretation of results.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: The conduct of the index test is outlined in the paper but the interpretation of the test is not. Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
The reference standard was DNA sequencing. DNA was extracted with the Arrow extaction robot and the Blood DNA 200 cartridge. Seems Spartan test was conducted first and then the reference standard, but there is no information about interpretation of results.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted and conducted the reference standard. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING

Test results reported for 91/102 randomised and tested in the genotyping arm, and 96/98 randomised and tested in the standard treatment arm. Missing patients were due to not undergoing PCI, being withdrawn by physician, undergoing different surgery, refusing to return for day 7 blood test and being lost to follow-up.	
Did all patients receive a reference standard?	Yes
Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: It seems unlikely that patient flow introduced bias. Not all patients are included in the analysis due to some being lost to follow-up but this doesn't seem like it is related to the true value.	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Study Details	So(2016)[80]

Domain 1: Patient selection	
Prospectively enrolled patients meeting inclusion criteria from University of Ottawa Heart Institute - no further detail on sampling method. All patients had to have undergone PCI for STEMI. It seems there were no innappropriate exclusions.	
Was a consecutive or random sample of patients enrolled?	Unclear
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Limited information on sampling technique but it seems unlikely this would bias the accuracy of the genetic test. A case control design was avoided. It seems the study avoided inappropriate exclusions.	

DOMAIN 2: INDEX TEST	
Spartan point of care test. Conducted appropriately, but no information on who did the test. Seems index test conducted/ interpreted first but limited explicit information on this. Threshold of looking for *2 allele specified.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
Taqman assay. Conduct appropriate - extracting genomic DNA and underwent genetic analysis in the core laboratory. Seems index test conducted/ interpreted first but limited explicit information on this.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted and conducted the reference standard. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
All patients received the tests and no exclusions.; NA	
Did all patients receive a reference standard?	Yes

Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: Patient flow was unlikely to have introduced bias. all patients received the same reference standard and were included in the analysis.	

OVERALL RISK OF BIAS	**Low**
Rationale for judgement: No concerns	

Study Details	Wirth(2016)[81]

Domain 1: Patient selection	
The study used non-probability sampling. A case control design was avoided.	
Was a consecutive or random sample of patients enrolled?	No
Was a case-control design avoided?	Yes
Did the study avoid inappropriate exclusions?	Yes
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: The study used non-probability sampling but it seems unlikely this would bias the accuracy of the genetic test.	

DOMAIN 2: INDEX TEST	
Genomadix cube conducted and interpreted by a clinical pharmacist researcher before lab test - not clear on order of interpretation but likely before ref standard.	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Could the conduct or interpretation of the index test have introduced bias?	**Low**
Rationale for judgement: Blinding is unlikely to influence interpretation in this study, therefore it is at low risk of bias for this domain.	

DOMAIN 3: REFERENCE STANDARD	
Both the taqman assay and the GenID assay were conducted by a clinical pharmacist researcher in liaison with a medical laboratory scientist at the Molecular Diagnostics Unit at Mater Dei Hospital MDH. They were classified by the clinical pharmacist researcher and classified in the same manner as with the Spartan RX assay. Seems ref standard interpreted and conducted after POCT.	
Was an appropriate reference standard used	Yes
Were the reference results interpreted without knowledge of the results of the index test?	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	**Low**
Rationale for judgement: The reference standard is likely to correctly classify the target condition. It is unclear who interpreted and conducted the reference standard. The result is unlikely to have been influenced by knowledge of the results of the index test.	

DOMAIN 4: FLOW AND TIMING	
All patients received all of the tests. One patient was excluded from the analysis as their Spartan index test was inconclusive and they could not be repeated as the patient had been discharged home.; NA	
Did all patients receive a reference standard?	Yes

Did patients receive the same reference standard?	Yes
Were all patients included in the analysis?	No
Could the selection of patients have introduced bias?	**Low**
Rationale for judgement: It seems unlikely that patient flow introduced bias. One patient was not included in results due to inconclusive result.	

OVERALL RISK OF BIAS	**LOW**
Rationale for judgement: No concerns	

Results

Study details	Index test details (POCT)	Reference standard (lab test)	Dataset	TP	FN	TN	FP	Sensitivity (95% CI)	Specificity (95% CI)	Discordant results
Badhuin et al (2022)[74, 93]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2 or *3	**Test name**: CLIA-based *CYP2C19* Sanger sequencing **Number participants tested:** 373 **Threshold for positive result:** NR	PRE-TRIAL	151	0	224	0	100	100	2 discordant due to pre-analytical sample mix-up at testing centre. Samples re-collected and re-tested, then concordant.
		Test name: Taqman **Number participants tested:** 2385 **Threshold for positive result:** *2 or *3	MAIN TRIAL	863	9	1502	11	99.0	99.3	21 discordant: 9 non-carrier by Spartan, but had *2 or *3 by TaqMan; 11 heterozygous *2 or *3 by Spartan, but non-carrier by TaqMan; 1 sample was heterozygous *2 by Spartan, but homozygous *2 by TaqMan.
Choi et al. (2016)[78]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2, *3	**Test name**: Taqman **Number participants tested:** 119 **Threshold for positive result:** *2, *3	NA	76	0	43	0	100	100	2 discordant:- *3/*17 on Spartan and *1/*3 on SNP; *1/*17 on Spartan and *1/*1 on SNP

Study details	Index test details (POCT)	Reference standard (lab test)	Dataset	TP	FN	TN	FP	Sensitivity (95% CI)	Specificity (95% CI)	Discordant results
NCT01718535.[82]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2 or *3	**Test name**: Bidirectional sequencing **Number participants tested:** 325 **Threshold for positive result:** *2 or *3	NA	181	0	144	0	100	100	None
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study details	Index test details (POCT)	Reference standard (lab test)	Dataset	TP	FN	TN	FP	Sensitivity (95% CI)	Specificity (95% CI)	Discordant results
	[redacted]	[redacted] *	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Petrek et al. 2016 [79, 83]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2, *3	**Test name**: MassArray technology **Number participants tested:** 53 **Threshold for positive result:** *2, *3	NA	NR	NR	NR	NR	100	100	None
Roberts et al. (2012)[75]	**Test name:** Genomadix Cube/ Spartan **Threshold for defining positive result:** *2	**Test name**: DNA sequencing **Number of participants tested:** 37 (total of 267 tests done in 37 people- 1 inconclusive) **Threshold for defining positive result:** *2	PRE-TRIAL	155	0	111	0	100	100	None Test level data; patient level data not reported
Roberts et al. (2012)[75]		**Number of participants tested:** 200 (data reported for 187 followed up)	MAIN TRIAL	45	0	141	1	100% (95% CI 92.3-100)	99.3% (95% CI 96.3-100)	One incorrectly classified as *2 carrier on Spartan

Study details	Index test details (POCT)	Reference standard (lab test)	Dataset	TP	FN	TN	FP	Sensitivity (95% CI)	Specificity (95% CI)	Discordant results
So et al. (2016)[80]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2	**Test name**: Taqman **Number participants tested:** 102 **Threshold for positive result:** *2		NR	NR	NR	NR	100% (95% CI 88.0-100)	97% (88.5-99.5)	There were some FP but it was not clear how many or how these were discordant.
Wirth et al. (2016)[81, 97]	**Test name:** Genomadix Cube/ Spartan **Threshold for positive result:** *2	**Test name**: Taqman assay **Number participants tested:** 35 (data for 34 due to inconclusive result) **Threshold for positive result:** *2		13	0	21	0	100	100	One incorrectly classified as *2/*2 on Spartan vs one 2* on Taqman and on GenID
		Test name: GenID assay **Number participants tested:** 34 **Threshold for positive result:** *2		13	0	21	0	100	100	None

* Number of people with LOF alleles deduced from Table 2[74]; it was not possible for numbers for both Taqman & Genomadix Cube to be correct in this table with the other information needed to calculate data for the 2x2 table; we therefore assumed that the numbers for Taqman were correct to allow us to construct our 2x2 table
Abbreviations: TP: true positive, FN: false negative, TN: true negative, FP: false positive, AUC ROC: area under the receiver operating characteristics curve, NR: not reported, NA: not applicable. Threshold for defining positive result: positive result meaning having loss of function.

Objective 5

All but one[82] of the studies included for objective 4 also provided data on test performance and so were also included for objective 5.

Baseline Details

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Al-Rubaish et al. (2021)[84] **Funding:** Non-industry **Country:** Saudi Arabia **Start date:** 2018 **Study design:** Technical performance study	**Population:** Ischaemic stroke **Inclusion criteria:** Consecutive patients with ischaemic stroke **Exclusion criteria:** NR **Number of participants:** 256 **Mean age in years, SD, range:** 61, 12.5, 18-89 **Male %:** 65 **Ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 256 **Alleles tested for:** *1, *2 **Who administered test:** NR	Number of people with variant forms of *CYP2C19* (%) Time to results

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Bergmeijer et al. (2014)[85, 94] **Publication type:** Journal article **Funding:** Non-industry (Spartan provided the tests) **Country:** Netherlands, Italy, Belgium **Study name:** The Popular Genetics Study **Start date:** June 2011 **Study design:** Technical performance study	**Population:** ST-segment elevation myocardial infarction (STEMI) **Inclusion criteria:** Aged ≥21; symptoms of acute myocardial infarction; primary PCI with stent implantation for STEMI **Number of participants:** 1238 **Baseline data only provided for 1038/1238 participants as data not yet available for others** **Mean age in years, SD, range:** 61.9, 11.2, NR **Male %:** 74 **Ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 411 **Alleles tested for:** *2, *3 **Who administered test:** Laboratory staff (1 site), local investigator or nurse (6 sites)	Test failure rate Ease of use of test Time to results

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Cavallari et al. (2018)[86] **Funding:** Non-industry (Spartan provided genotyping platforms and kits) **Country:** USA **Start date:** April 28, 2016 **Study design:** Technical performance study	**Population:** Percutaneous coronary intervention (PCI) **Inclusion criteria:** Patients undergoing emergent/ planned left heart catheterization with intent to undergo PCI **Number of participants:** 931 patients genotyped (392 underwent PCI) **Baseline data available only for those who underwent PCI:** **Mean age in years, SD, range:** 63, 11, NR **Male %:** 69 **Ethnicity:** White 74.5%, black 23.7%, asian 0.8%, other or not reported 1%.	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 931 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test failure rate Number of people with variant forms of *CYP2C19* (%) Time to results Ease of use of test
Author, year: Davis et al. (2020)[87] **Funding:** Non-industry. **Country:** USA **Start date:** NR **Study design:** Diagnostic test accuracy study (but no relevant accuracy data for this review)	**Population:** NR **Inclusion criteria:** NR **Exclusion criteria:** NR **Number of participants:** 23 **Age, sex, ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 23 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Ease of use of test

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Franchi et al. (2020)[88] **Publication type:** Journal article **Funding:** Non-industry (Spartan provided the Spartan RX system and reagents used free of charge) **Country:** USA **Start date:** NR **Study design:** Technical performance study	**Population:** Diagnostic coronary angiography **Inclusion criteria:** Consecutive patients aged 18-75 years scheduled to undergo diagnostic coronary angiography with intent to undergo ad hoc PCI **Number of participants:** 781 **Age, sex, ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 781 **Alleles tested for:** *1, *2, *3, *17 **Who administered test:** NR	Number of people with variant forms of *CYP2C19* (%) Time to results
Author, year: Gurbel et al. (2018)[89] **Conference abstract** **Funding:** NR **Country:** USA **Start date:** February 2017 **Study design:** Technical performance study	**Population:** Patients undergoing catheterisation **Inclusion criteria:** NR **Exclusion criteria:** NR **Number of participants:** 578 **Age, sex, ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 578 **Alleles tested for:** *1, *2, *3, *17 **Who administered test:** NR	Number of people with variant forms of *CYP2C19* (%) Time to results

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: McDermott et al. (2020)[92] **Conference poster/ abstract** **Funding:** NR **Country:** United Kingdom **Start date:** NR **Study design:** Technical performance study	**Population:** NR **Inclusion criteria:** NR **Exclusion criteria:** NR **Number of participants:** NR **Age, sex, ethnicity:** NR	**Test name:** Genedrive (early version) **Number of participants tested:** NR **Alleles tested for:** *1,*2,*3,*4,*4b,*10, *17 **Who administered test:** NR	Time to results Ease of use of test Cost of testing
Author, year: Tomaniak et al. (2017)[90, 95, 96] **Funding:** Non-industry **Country:** Poland **Start date:** NR **Study name:** ONSIDE TEST study **Study design:** Technical performance study	**Population:** Stable coronary artery disease **Inclusion criteria:** Patients aged 18-75 with stable coronary artery disease **Number of participants:** 34 **Mean age in years, SD, range:** 61.8, 10.6, NR **Male %:** 77.8 **Ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 34 **Alleles tested for:** *1, *2 **Who administered test:** NR	Test failure rate Number of people with variant forms of *CYP2C19* (%) Time to results

Study details	Participants*	POCT Test Details	Outcomes reported
Author, year: Zhou et al. (2017)[91, 98] **Publication type:** Journal article **Funding:** Non-industry **Country:** USA **Start date:** NR **Study design:** Diagnostic test accuracy (but no accuracy data relevant for this review)	**Population:** Volunteers and control samples – condition NR - for validation of the test **Number of participants:** 12 samples (9 volunteers, 3 Coriell samples, 4 CAP survey samples) **Age, sex, ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 12 samples **Alleles tested for:** *2, *3, *17 **Who administered test:** Four laboratory technologists	Number of people with variant forms of *CYP2C19* (%) Time to results
	Population: Post-PCI patients **Number of participants:** 342 **Age, sex, ethnicity:** NR	**Test name:** Spartan RX (Genomadix Cube) **Number of participants tested:** 342 **Alleles tested for:** *2, *3, *17 **Who administered test:** NR	Test failure rate Number of people with variant forms of *CYP2C19* (%) Time to results

Results

Study details	Test name	Alleles tested for	Outcomes	Results
Al-Rubaish et al. (2021)[84]	Spartan RX (Genomadix Cube)	*1, *2	Number of people with variant forms of *CYP2C19* (%)	54 (21.1%)
			Time to results	First 50 patients: 90-120min to complete the results
Badhuin et al (2022)[74, 93] **Pre-trial**	Spartan RX (Genomadix Cube)	*2, *3, *17	Ease of use of test	Non laboratory trained personnel can successfully perform rapid genotyping in a POC setting
			Number of people with variant forms of *CYP2C19* (%)	151/373 (40%)
Badhuin et al (2022)[74, 93] **Main trial**	Spartan RX (Genomadix Cube)	*2, *3, *17	Test failure rate	172 (6%) patients with unavailable test result. 54/2642 (2%) had no Spartan result available (no definition of what this means); 118 (4%) had inconclusive results.
			Number of people with variant forms of *CYP2C19* (%)	837/2587 (32%)
Bergmeijer et al. (2014)[85, 94]	Spartan RX (Genomadix Cube)	*2, *3	Test failure rate	39 (8%) patients with unavailable test result - inconclusive results.
			Ease of use of test	**Description of feature of the test:** Buccal swab more patient friendly than venapuncture for blood sample, but test is limited to testing *2, *3, *17 for one patient at a time per genotyping device.
			Time to results	Result available within 1hr after collection of buccal swab.
Cavallari et al. (2018)[86]	Spartan RX (Genomadix Cube)	*2, *3, *17	Test failure rate	129 (14%) with unavailable test result - 56 inconclusive results and 73 device errors.
			Number of people with variant forms of *CYP2C19* (%)	113/392 (29%)

Study details	Test name	Alleles tested for	Outcomes	Results
			Time to results	For all patients genotyped: Median genotype test turnaround time was 96min (interquartile range of 78-144)
			Ease of use of test	Could not be used as POCT due to absence of licensed molecular medical technologist so must be sent to central laboratory (the case for all of USA), and only a single sample genotyped at a time limiting number of patients that can be offered genotyping.
Choi et al. (2016)[78]	Spartan RX (Genomadix Cube)	*2, *3, *17	Number of people with variant forms of *CYP2C19* (%)	76 (63.9%)
			Time to results	**Description of feature of the test:** time from sample to result ~60min
Davis et al. (2020)[87]	Spartan RX (Genomadix Cube)	*2, *3, *17	Ease of use of test	**Description of features of the test**: Barriers to implementation: time constraints, personnel requirements and coordination, storage and sample stability, samples unable to be collected by bedside nurses, patients unable to provide samples, sample recollection due to interference or improper techniques
Franchi et al. (2020)[88]	Spartan RX (Genomadix Cube)	*1, *2, *3, *17	Number of people with variant forms of *CYP2C19* (%)	242/781 (28.5%)
			Time to results	Allele status within 1hr - readily available when the decision on choice of oral P2Y12-inhibiting therapy most commonly occurs.
Gurbel et al. (2018)[89]	Spartan RX (Genomadix Cube)	*1, *2, *3, *17	Number of people with variant forms of *CYP2C19* (%)	168/578 (29%)
			Time to results	Results available in all patients within 90min
NCT04473586[76]	Spartan Cube (Genomadix Cube)	*2, *3, *17	[redacted]	[redacted]
			[redacted]	[redacted]

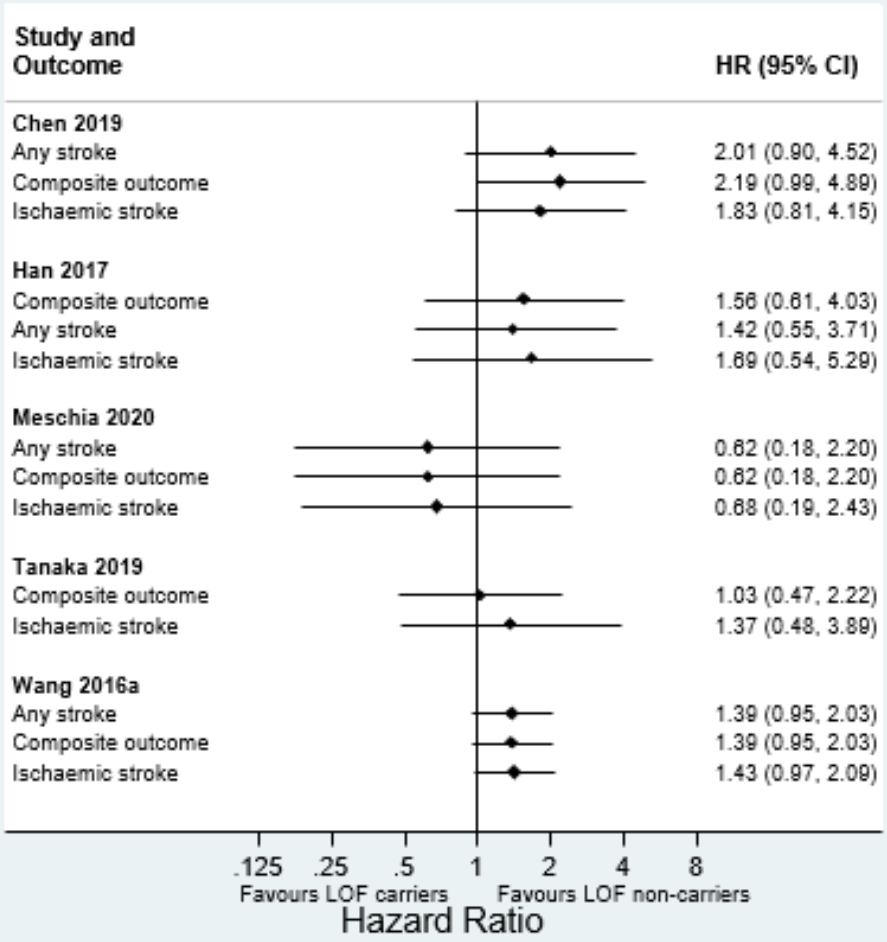
Study details	Test name	Alleles tested for	Outcomes	Results
NCT04473573[77]	Spartan Cube (Genomadix Cube)	*2, *3, *17	[redacted]	[redacted]
			[redacted]	[redacted]
Petrek et al. 2016 [79, 83]	Spartan RX (Genomadix Cube)	*2, *3, *17	Test failure rate	10 (18.9%) with unavailable test result due to failure during amplification process (n=4), inconclusive result (n=3), only two of three alleles tested for gave results (n=3)
			Time to results	Turnaround time (from buccal swab sampling to result print-out) was 60 min
			Ease of use of test	Simple and non-invasive
Roberts et al. (2012)[75] **Pre-trial**	Spartan RX (Genomadix Cube)	*1, *2	Number of people with variant forms of *CYP2C19* (%)	155 (59%)
			Test failure rate	1 (0.4%) test with unavailable test result – did not identify genotype.
Roberts et al. (2012)[75] **Main trial**	Spartan RX (Genomadix Cube)	*1, *2	Number of people with variant forms of *CYP2C19* (%)	46/187 (25%)
			Time to results	Main trial: Within 60min from test activation
			Ease of use of test	Main trial: Nurses with no previous laboratory training implemented test after 30min training session.
So et al. (2016)[80]	Spartan RX (Genomadix Cube)	*2, *17	Number of people with variant forms of *CYP2C19* (%)	37 (36%)
			Time to results	Within 55min of test carrier status for all alleles was available
Genomadix (test manufacturer) response to request for information	Spartan RX (Genomadix Cube)	NA	Cost of testing	**Description of feature of the test:** a) Platform cost: 3,500 GBP per testing platform, b) Testing assay cost: 175 GBP per test kit, c) external control kits: 50 GBP per external control kit

Study details	Test name	Alleles tested for	Outcomes	Results
			Time to results	**Description of feature of the test:** Time to result is 64 minutes.
Tomaniak et al. (2017)[90, 95, 96]	Spartan RX (Genomadix Cube)	*1, *2	Test failure rate	4 (11.8%) patients with unavailable test result – inconclusive results.
			Number of people with variant forms of *CYP2C19* (%)	14 (14.83%)
			Time to results	Mean (SD): 56min (11), from material collection to the testing results
Wirth et al. (2016)[81, 97]	Spartan RX (Genomadix Cube)	*2, *1	Test failure rate	5/35 (14.3%) patients with unavailable test result – 4 tests resulted in error (11.4% - no further details); 1 test inconclusive.
			Number of people with variant forms of *CYP2C19* (%)	13/34 (38%)
			Time to results	Collection of sample to genotyping result within 1 hour
			Ease of use of test	Simple procedure, portable, convenient, no laborious preparation, minimal training required to conduct test. User-friendly interpretation with no training required. Storage conditions limit ease of use.
			Cost of testing	Estimated cost per patient test: 225 euros (Taqman estimated at 13 euros and GenID at 23 euros). No indication of how this was calculated.
Zhou et al. (2017)[91, 98] **Pre trial**	Spartan RX (Genomadix Cube)	*2, *3, *17	Number of people with variant forms of *CYP2C19* (%)	7/12 (58%)
			Time to results	**Description of feature of the test (pre trial and main trial):** results are returned in one hour turnaround time
Zhou et al. (2017)[91, 98] **Main trial**	Spartan RX (Genomadix Cube)	*2, *3, *17	Test failure rate	25 (7.3%) with unavailable test results - 14 inconclusive results (4%), 10 failed controls (3%), 1 instrument failure (0.3%) (no further information given).
			Number of people with variant forms of *CYP2C19* (%)	99 (37%)

Study details	Test name	Alleles tested for	Outcomes	Results
			Time to results	**Description of feature of the test (pre trial and main trial):** results are returned in one hour turnaround time
McDermott et al. (2020)[92]	Genedrive (early version)	*1,*2,*3,*4,*4b,*10, *17	Time to results	**Description of feature of the test:** ~40min
			Ease of use of test	**Description of features of the test**: Portable, rapid (~40mins), no cold chain, simple read out for non-specialist users.
			Cost of testing	Decision analytic model, comprising decision tree linked with a state transition Markov model, suggested POCT would generate net benefit of 0.130 QALYs and monetary benefit of £2595 per patient (uncertain evidence).

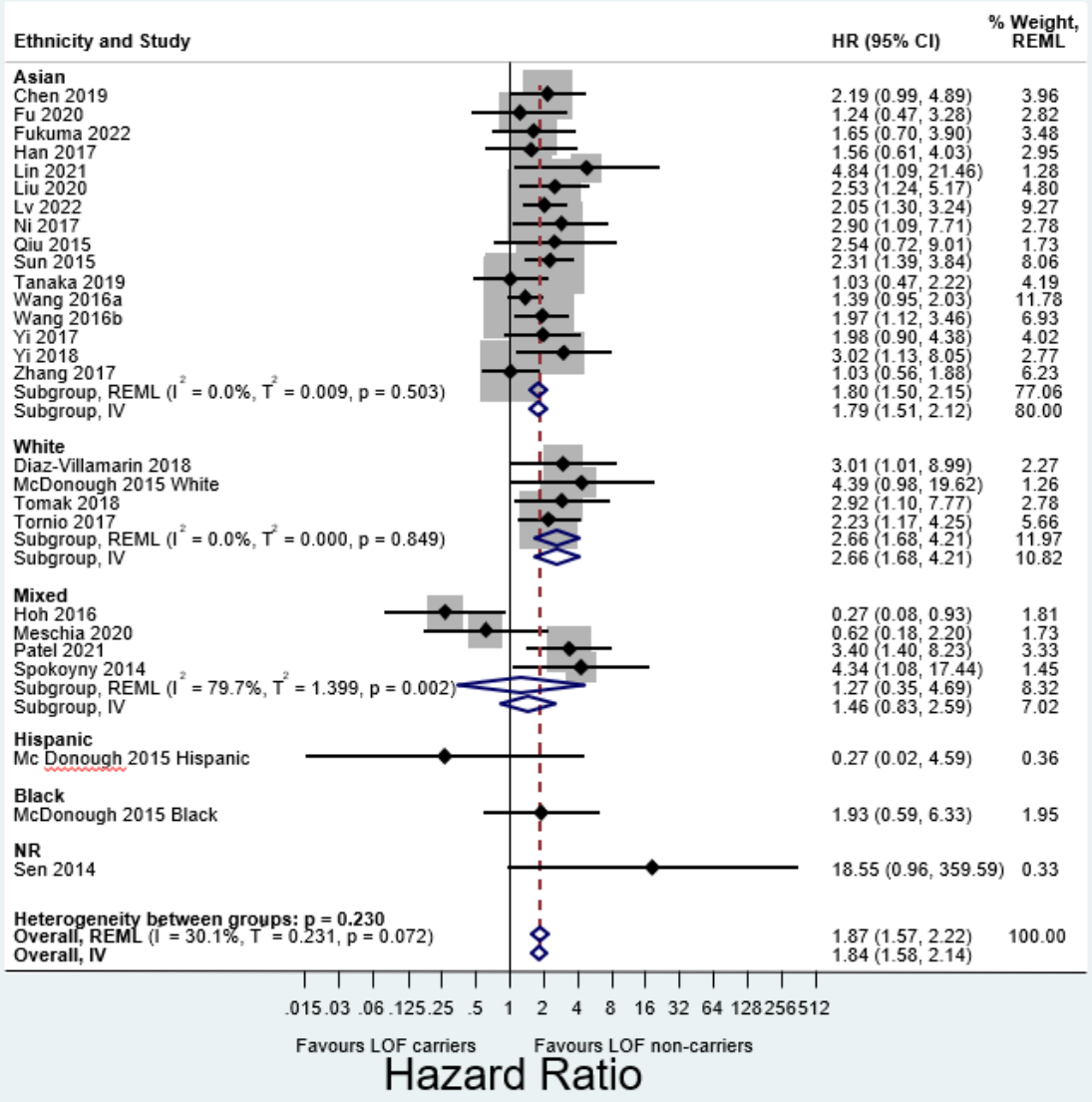
Appendix 5: Additional Analyses for Objective 3

a. Forest plot showing consistency in estimates of secondary vascular events across studies that evaluated multiple vascular occlusive event outcomes

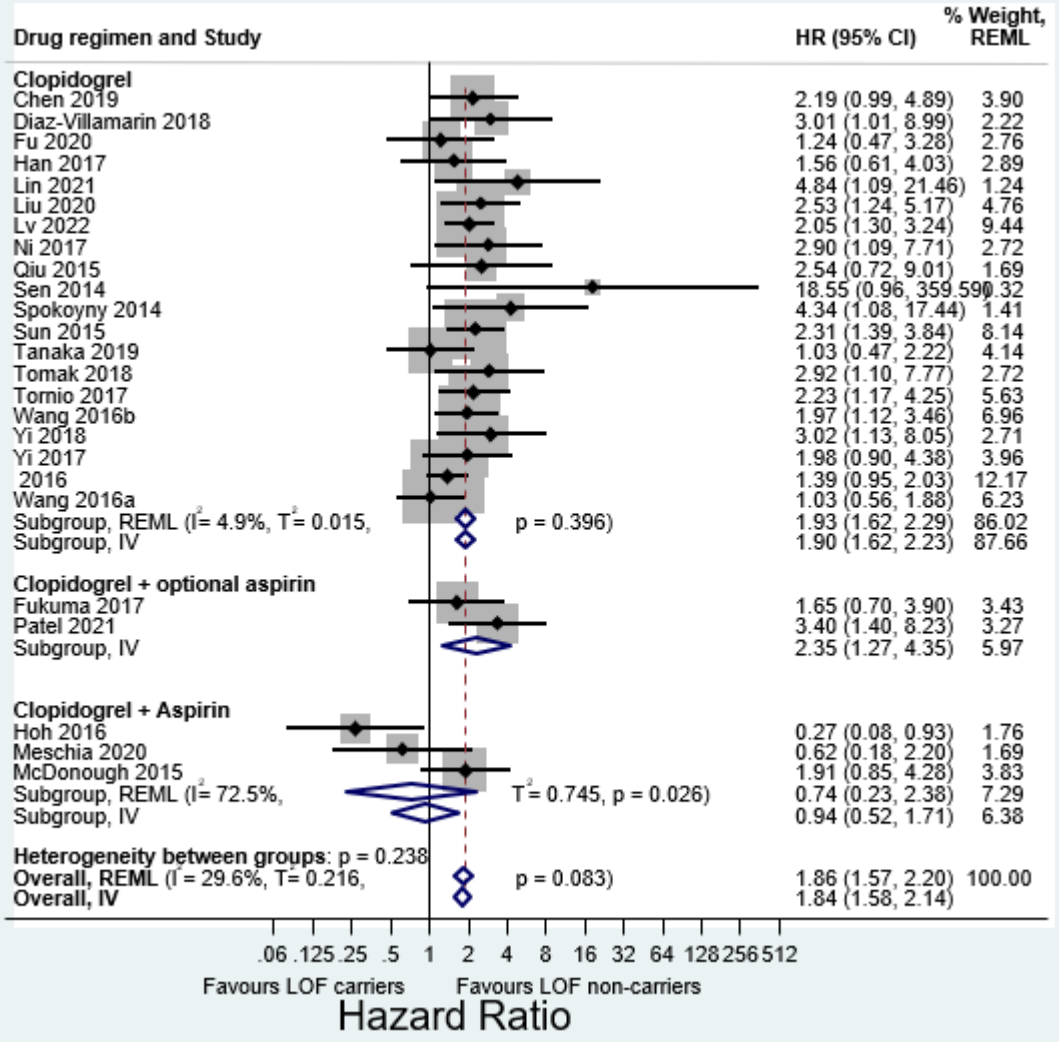


b. Forest plots showing stratified analyses for risk of secondary vascular occlusive events in carriers of LOF compared with non-carriers

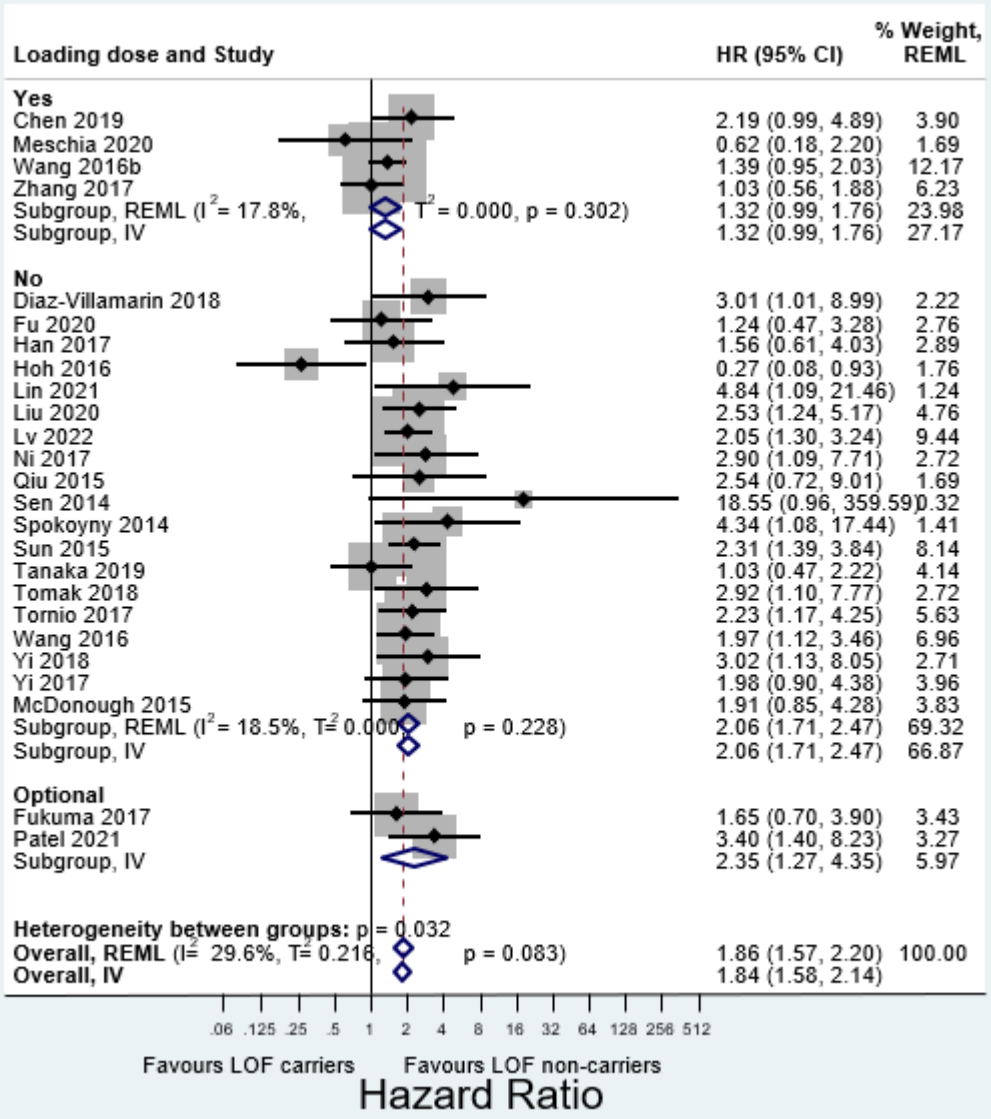
Ethnicity



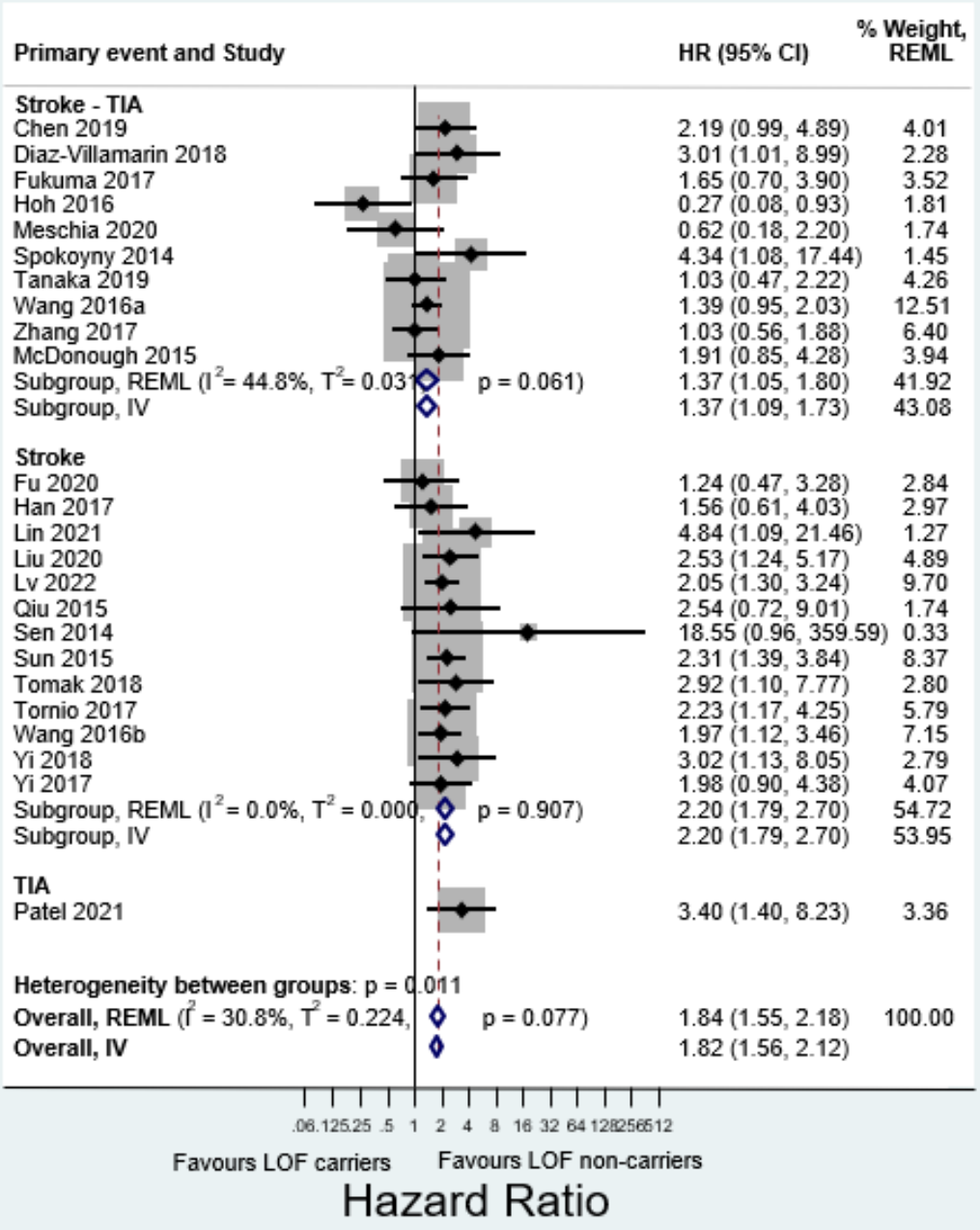
Clopidogrel regimen



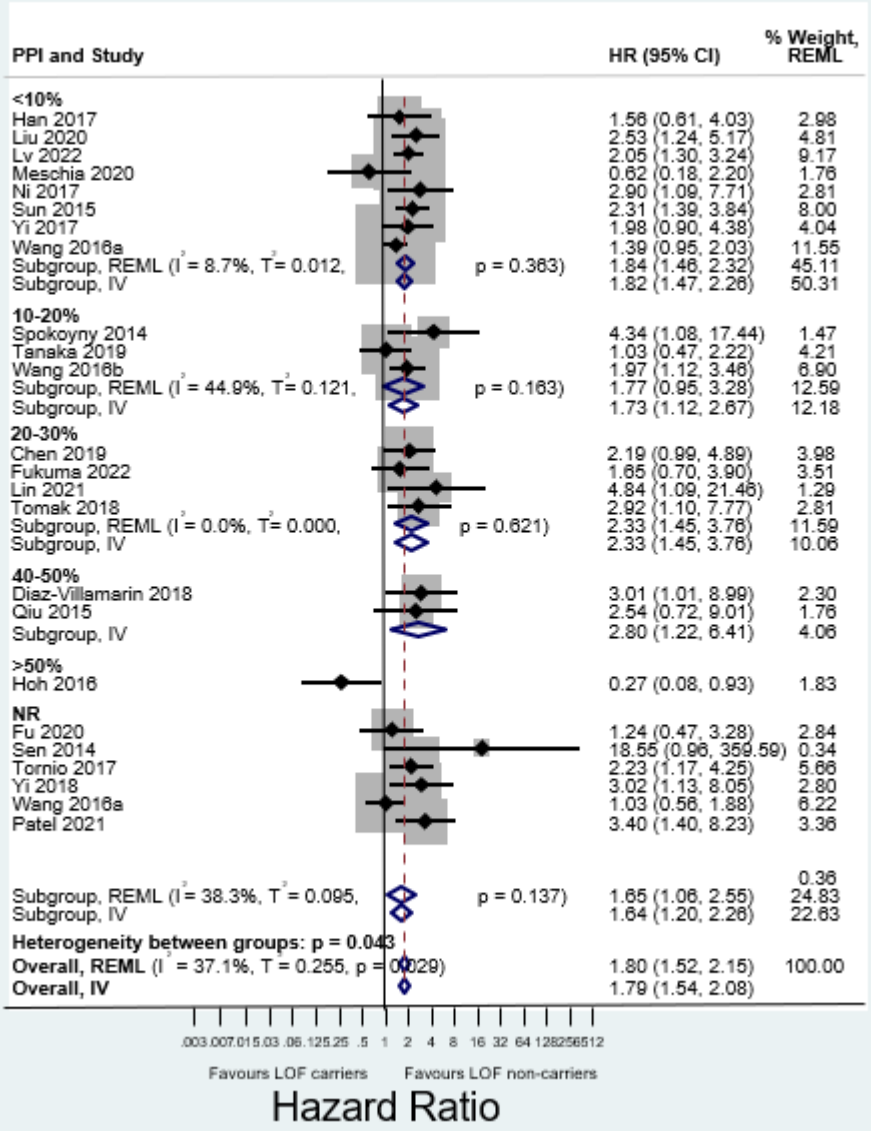
Clopidogrel Loading dose



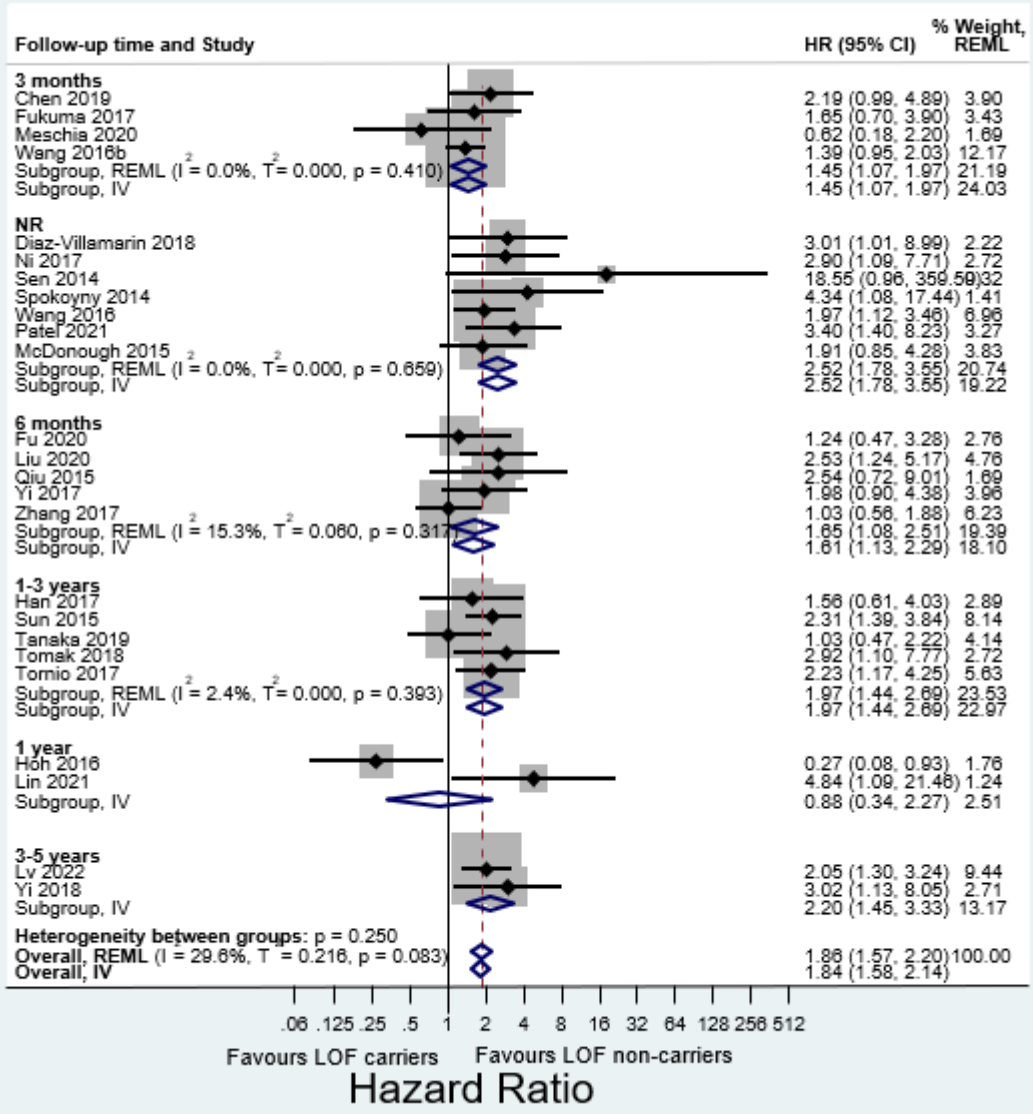
Primary event – stroke, TIA or both



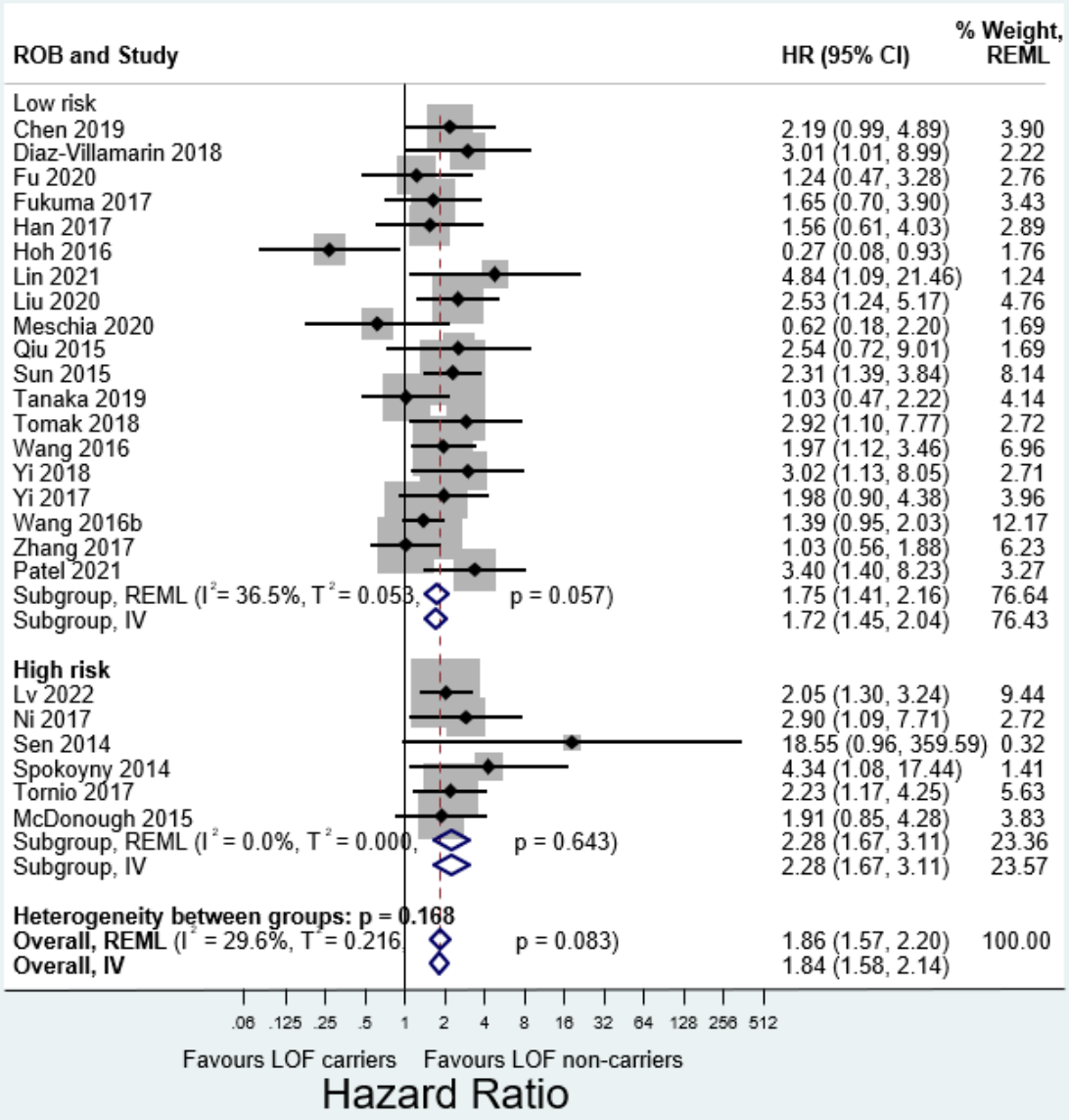
Proportion of participants taking proton pump inhibitors



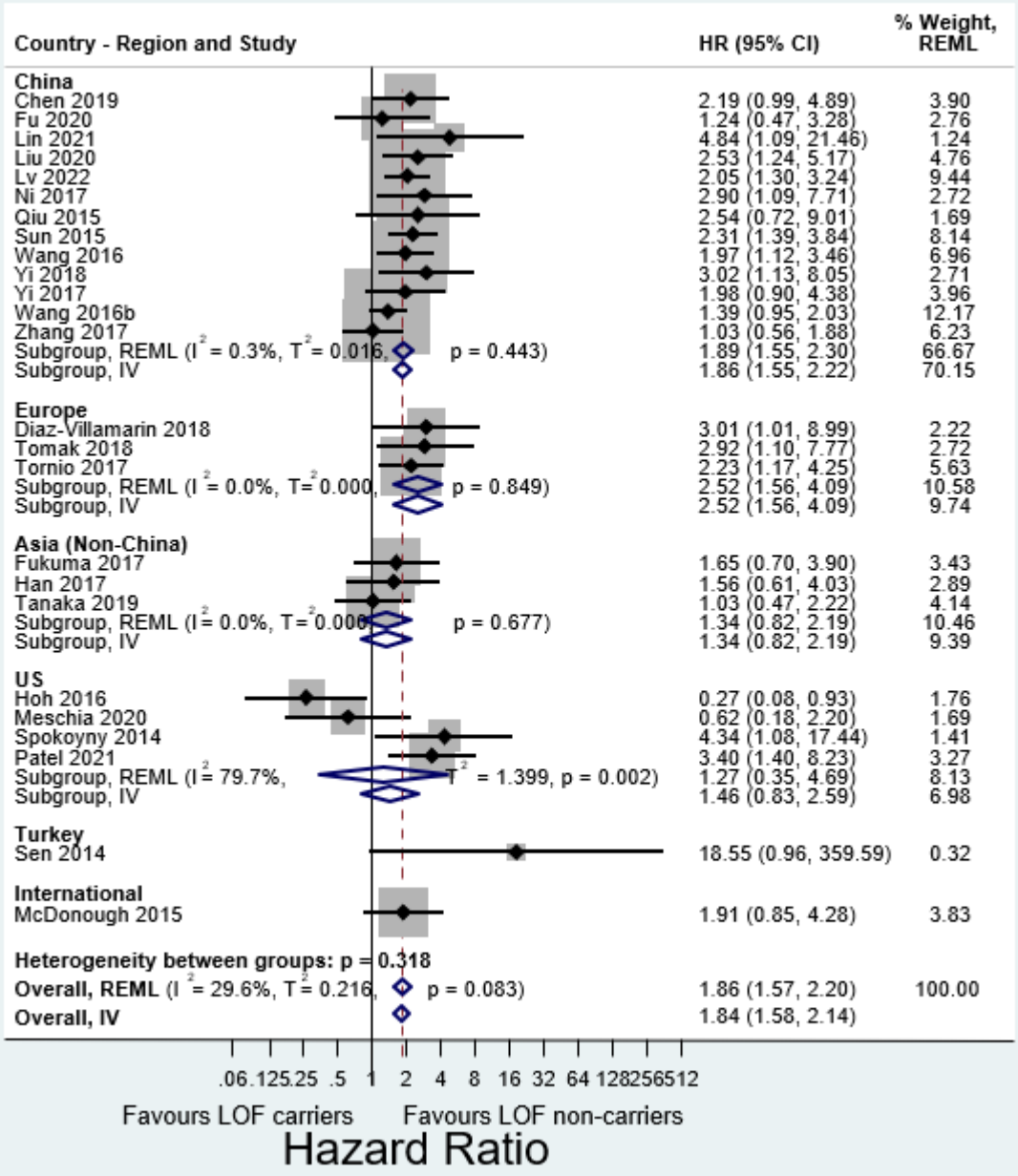
Duration of follow-up



Risk of bias

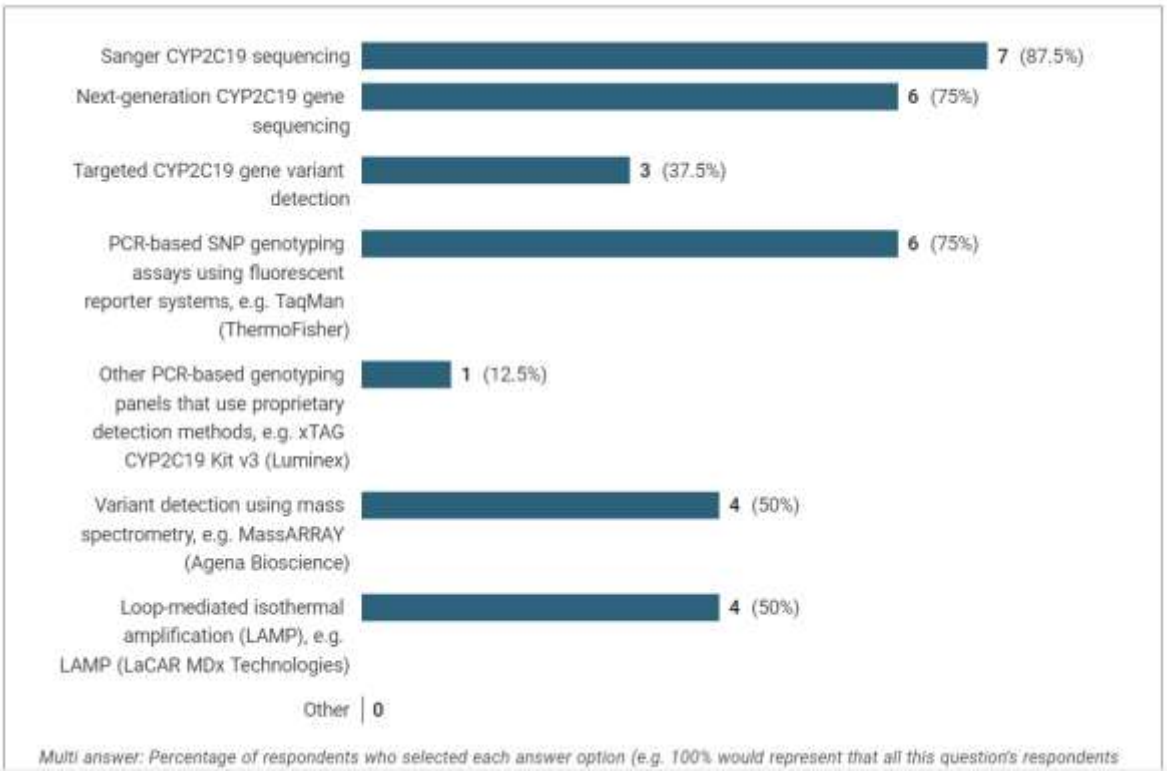

ROB and Study
HR (95% CI)
% Weight, REML
Low risk
Chen 2019 2.19 (0.99, 4.89) 3.90
Diaz-Villamarin 2018 3.01 (1.01, 8.99) 2.22
Fu 2020 1.24 (0.47, 3.28) 2.76
Fukuma 2017 1.65 (0.70, 3.90) 3.43
Han 2017 1.56 (0.61, 4.03) 2.89
Hoh 2016 0.27 (0.08, 0.93) 1.76
Lin 2021 4.84 (1.09, 21.46) 1.24
Liu 2020 2.53 (1.24, 5.17) 4.76
Meschia 2020 0.62 (0.18, 2.20) 1.69
Qiu 2015 2.54 (0.72, 9.01) 1.69
Sun 2015 2.31 (1.39, 3.84) 8.14
Tanaka 2019 1.03 (0.47, 2.22) 4.14
Tomak 2018 2.92 (1.10, 7.77) 2.72
Wang 2016 1.97 (1.12, 3.46) 6.96
Yi 2018 3.02 (1.13, 8.05) 2.71
Yi 2017 1.98 (0.90, 4.38) 3.96
Wang 2016b 1.39 (0.95, 2.03) 12.17
Zhang 2017 1.03 (0.56, 1.88) 6.23
Patel 2021 3.40 (1.40, 8.23) 3.27
Subgroup, REML (I² = 36.5%, T² = 0.053, p = 0.057) 1.75 (1.41, 2.16) 76.64
Subgroup, IV 1.72 (1.45, 2.04) 76.43
High risk
Lv 2022 2.05 (1.30, 3.24) 9.44
Ni 2017 2.90 (1.09, 7.71) 2.72
Sen 2014 18.55 (0.96, 359.59) 0.32
Spokoyny 2014 4.34 (1.08, 17.44) 1.41
Tornio 2017 2.23 (1.17, 4.25) 5.63
McDonough 2015 1.91 (0.85, 4.28) 3.83
Subgroup, REML (I² = 0.0%, T² = 0.000, p = 0.643) 2.28 (1.67, 3.11) 23.36
Subgroup, IV 2.28 (1.67, 3.11) 23.57
Heterogeneity between groups: p = 0.168
Overall, REML (I² = 29.6%, T² = 0.216, p = 0.083) 1.86 (1.57, 2.20) 100.00
Overall, IV 1.84 (1.58, 2.14)
.06 .125 .25 .5 1 2 4 8 16 32 64 128 256 512
Favours LOF carriers
Favours LOF non-carriers
Hazard Ratio

Country - Region



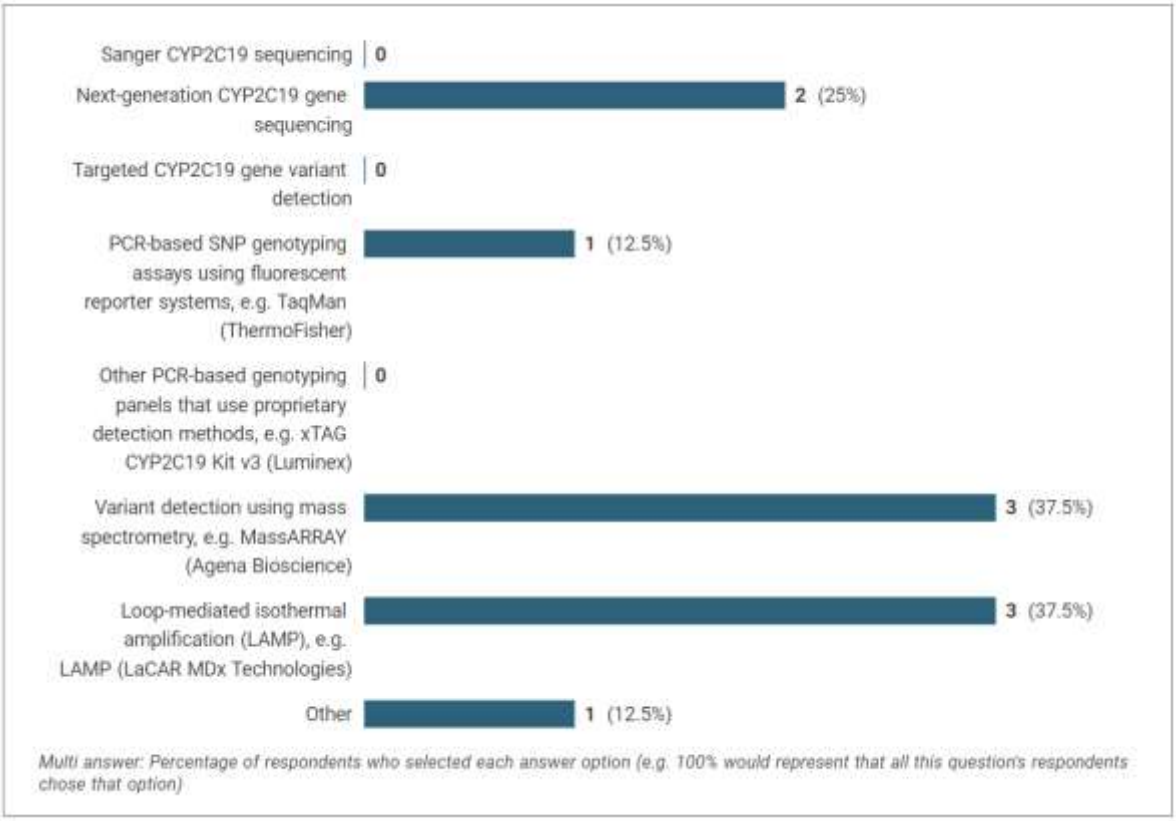
Appendix 6: Survey Results

a. Which of the following test platforms that would be capable of performing *CYP2C19* genotypying does your laboratory have (even if not currently in use for this purpose)?



b. Of the tests that you have in your laboratory, which would be your preferred platform for running *CYP2C19* testing in your laboratory if you were needing to run an estimated 10 000 tests per year.*

*This is a very rough approximation of the number of tests that each laboratory hub would need to run based on a total estimate of 100 to 150 000 test per year across the UK - the exact number would be dependent on your catchment population



If you selected other, please specify:

QuantStudio 12K Flex Real-Time PCR System or X9 Real-Time PCR System

Please briefly summarise why you would prefer this platform:

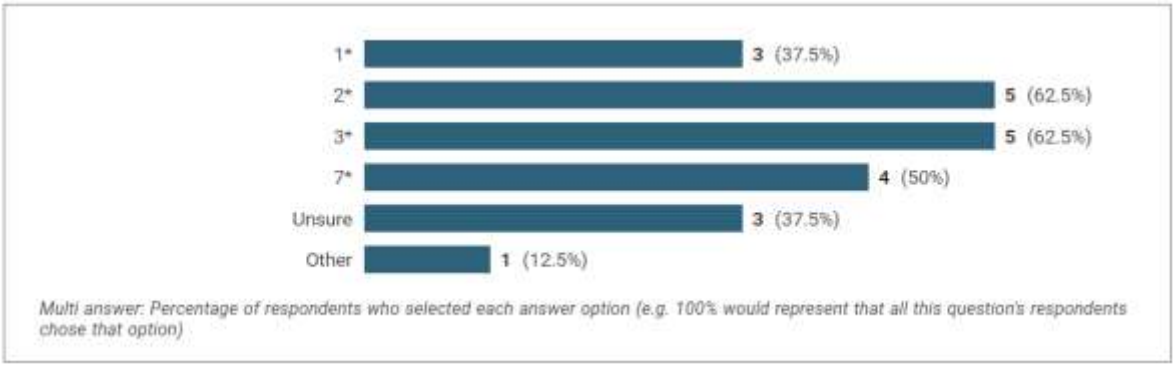
An ideal platform for targeted variant detection: ability to target multiple variants in a single assay applying automated PCR prep and automated genotype calling (validated within our lab for HFE and DPYD testing on this platform), reduced TAT and reduces the necessary staff resources. The ability to PCR direct from blood is also feasible for this technology (in validation for HFE and DPYD within this lab). This Hub is also implementing a new LIMS system which will enable automated reporting from the genotype report generated by the Agena software.

Can be done directly from blood and does not require extraction. easy method to set up and automate.
efficiency and cost and TAT
The technique used would depend on the number of variants requiring testing and which variants they are. For both Agena MassArray and LAMP commercial kits are available for *CYP2C19* testing but offering different variants. MassArray offers *2-*8 and *17. The current LaCAR test covers *2,*3 and *17. It is possible to design bespoke assays, this is likely easier with the MassArray. If the *CYP2C19* assay was combined with other testing the MassArray is probably better suited for covering increased numbers of variants. The benefit of the LAMP assay is the speed and lack of need for a DNA extraction. For a wider panel an NGS solution might be worth considering.
Higher throughput
High through-put and massively parallel. Automated bioinformatics analysis. Pre-existing workflows established.
These instruments have higher throughput and can have automated loading. For example, the X9 can test 96 samples for 96 different SNPs in a 2 hour run.
Cost effective Time efficient Minimal staff time Two-step process High throughput Robust technology Simple analysis and reporting

Are there other platforms available that you would ideally use for *CYP2C19* testing, if so please name and briefly explain why you think this would be better than the test you selected as your preferred test above:

Sanger would be used for those indiscriminate calls by LAMP - back up test.
no
NGS Genexus - looking at this option due to speed and capacity

c. Which alleles would you test for in a request for a *CYP2C19* test?



If you selected Other, please specify:

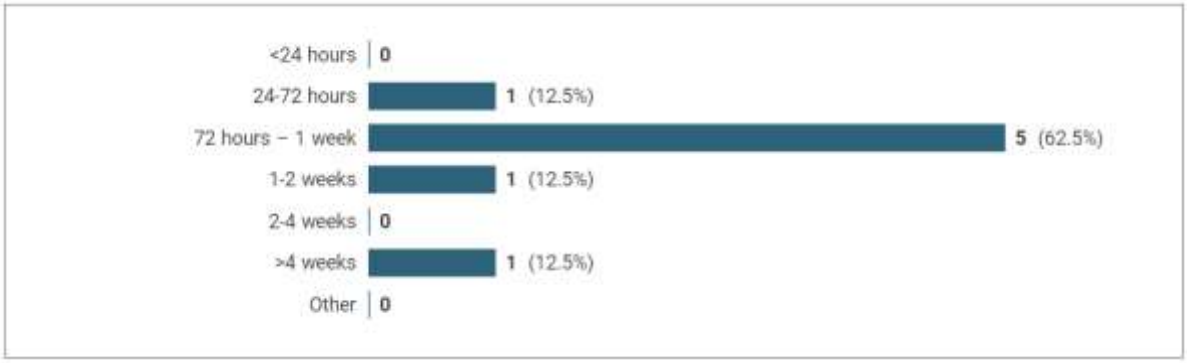
An NGS assay would be able to detect all sequence variants associated with the disorder provided there is no pseudogene interference with *CYP2C19*.

d. Would the test be affected by testing for all loss of function alleles compared to only testing for *2 or *3 alleles?

If yes, how would this affect the test (e.g. longer turnaround time, greater cost etc)

increased cost
Longer TAT and cost as well as staff resource to deliver testing.
It could potentially impact the choice of technology chosen. This would impact the cost and TAT.
This depends on the chosen method as does the question below
Possibly greater turnaround time due to more variants being assessed. Cost is highly dependent on number of samples tested.

e. What would be the estimated time from receiving a sample to result data being returned to the person that requested the test?



f. To help estimate the cost of introducing *CYP2C19* testing, please could you give an estimate for each of the following:

Staff time

1-2 days, 1 -2 hours set up, 2 hours analysis, 2 hours checking and reporting.
reception, extraction, workflow, reporting
Unable to comment
1 x band 3, 1 x band 5 and 1 x band 7 WTEs
Unable to provide at this time.
0.5 WTE for performing test 0.5 WTE for DNA extraction 0.2 WTE for admin
22mins/sample

Staff grade

Band 5 set up, Band 6 analysis and reporting Band 7 checking and authorisation of reports.
Band 3 up to Band 8a
Unable to comment
1 x band 3, 1 x band 5 and 1 x band 7 WTEs
Unable to provide at this time.
Band 5 Band 4 Band 3
AfC Band 2,3,4 for laboratory work AfC Band 7 authorising reports

Cost per test to run

£40 per test (reagent cost only)
~ £15 per test
~£100
Again method dependent - £100-£250
Unable to provide at this time.
~£200 per sample There would additional costs in data analysis either by scientists or using automated calling and reporting system = £5-10 per sample
£25.09 inc VAT (reagents/consumables, staff time, and overheads)

Maintenance of machines/quality assurance

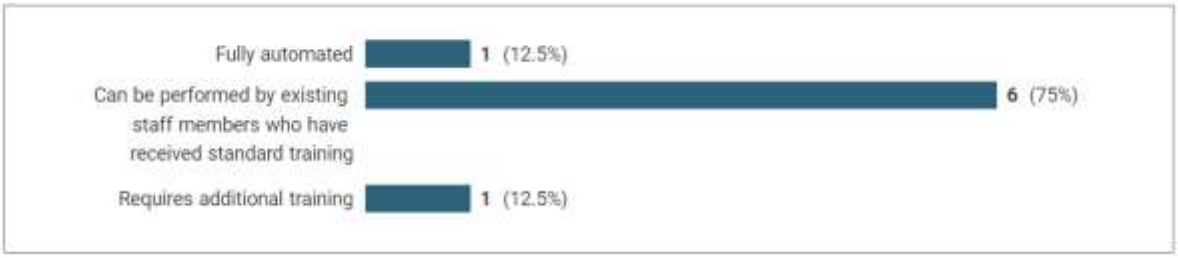
Monitoring of PCR instrumentation, inclusion and monitoring of internal quality controls, participation in EQA or interlaboratory sample exchange, UKAS accreditation.
£15k maintenance and yes EQA (??)

Unable to comment
Unable to provide at this time.
£5000 pa for qPCR machine BUT for 10,000 sample pa we would need to increase our existing DNA extraction capacity, which may mean another automated DNA extraction system = £150k capital investment

Additional administrative resources to record test result

LIMs upload to electronic care record where link does not exist - admin support to send results and upload to ECR.
yes ??
Unable to comment
1 x band 4 admin
Unable to provide at this time.
Preferable electronic test ordering but may require admin support for dealing with enquiries
None

g. How easy is the test to perform?



If additional training would be required, please provide a brief summary of what this would entail

No. Technology in use within the laboratory.
Either a MassArray or LAMP could be carried out by existing trained staff. Further staff may need training due to increase use of particular technology and all staff would need small amount of training for any differences between the current assays used and the

Any new tests require training for staff to perform the test, operate the instrument and interpret data if required

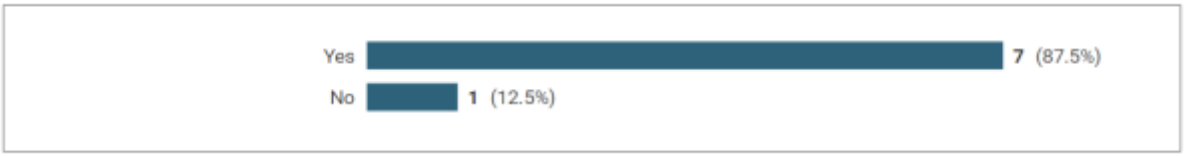
Could you give an estimate of the proportion of samples that would not return a valid result?

<1% based on current targeted testing for germline variants using the Agena / MALDI-TOF platform.
~90%
less than 1%
This will depend on the particular assay used but should be <1%.
Difficult to say - under 1%
An experimental validation would b required to set the testing up. This would identify and resolve any assay related issues. Once validated the test would then expected to have a low fail rate - i.e. <1% samples assuming the test is performed on DNA extracted from blood.
<1-3% but this would need to be validated if a new test and equipment is required
5%

h. Please estimate your current testing capacity - estimated number of tests of this type that could be performed in your laboratory at present in a one week period

0
92 per run - up to x2 weeks
Unable to comment
Currently deliver 110 per week
Zero.
We would not be able to process any samples without additional staff and equipment
Up to 200 tests/week

i. Would a faster turnaround be possible with additional resources?



If yes, what resources would be required?

Additional staff.
Additional staffing at all grades.
could run every day
More staff and equipment. This may require additional lab space. This would depend on the test used.
More technical staff and potentially additional instruments to increase capacity and allow more automation
Additional staff.
More automation and lablims support - as above

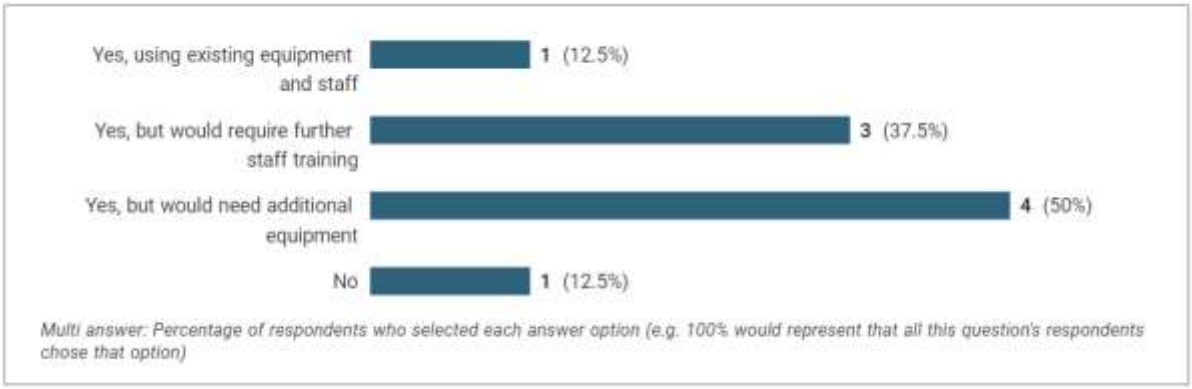
j. Would additional testing capacity (i.e. greater number of tests) be possible with additional resources?

If yes, what resources would be required?

based on predicted numbers: Additional staff Automation platform increased laboratory space Chip prep module for the MALDI-TOF machine
Additional staffing at all grades.
extraction etc etc

More staff and equipment. This may require additional lab space. This would depend on the test used.
More technica/IT staff staff and potentially additional instruments to increase capacity and allow more automation
Additional staff.
More automation and lablims support - see above
More staff Liquid handling platform to automate DNA dilutions Additional QuantStudio5

k. Could the test be performed in local testing laboratories?



l. What do you see as the major facilitators and barriers to implementing *CYP2C19* testing within your region?

Given scale of predicted activity: Test ordering should ideally be electronic (currently not possible within LIMS) Sample receipt (additional space required to manage sample numbers) Additional staff dedicated to sample processing. Validation time required for automated processing, genotyping and reporting. All of which is entirely possible (& in progress for smaller scale tests) but requires additional staff resources.
Staff resource is the major barrier to implementing this test. LAMP testing is currently being successfully used to deliver HFE testing so would be easy to implement where there sufficient staffing in place.
reporting guidelines

Facilitators: Previous knowledge of pharmacogenomics testing in lab (technical staff and Clinical scientists) and within GLH/GMSA. Appropriate equipment available within the department although capacity would need to be reviewed. Barriers: Ensuring awareness of testing with all clinicians across the geography. Capacity of laboratory to perform test alongside other clinical requirements.
Throughput on existing instruments and staffing
We do not currently perform any tests of this scale in the NHS so do not have the infrastructure. We need automation, lablims support and skilled staff.
Laboratory staffing resources.
Facilitators Strong support from Stroke Clinicians, Specialist Pharmacist and Senior Managers within Trust Barriers Fixed budget for pilot so had to confine requests to Stoke Unit and Cardiology Unable to accept requests from GPs Difficulty for some medical disciplines to understand output of genetic results Separate requesting and reporting systems for acute and primary care

m. Would it be possible to implement a rapid point of care test (input = buccal swab for a single patient) in your lab workflow?

yes
Not at this point.
no
It should be possible to implement this test within the lab workflow. Time for sample to be received in the laboratory might be an issue. May require extra freezers to hold kits under appropriate conditions.
Yes with staff
In principle, yes. Although there is no precedent for this in our lab.
POC is not the most efficient process for the number of samples that would need to be tested per week (192 per week based on processing 10000 sample in 52 week). Samples would be batched and not tested one by one as using POC

Yes

If not, why/what extra resources might you need?

staff.
This would require staff to be able to drop all other duties to perform this test. This is not currently feasible with the staffing levels in the department. Other duties considered necessary would not be completed.
POC platform
Staff to support
see above
Not enough staff to deliver rapid POCT Extraction and genotyping processes not suited to service based out with the lab Delivering POCT would require different testing technology and cost would increase.