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

ERRATUM

Corrections to the Assessment Report:

- Minor errors to numbers in Table 10 and the accompanying text have been corrected (pp 65-66)
- Typos corrected in Tables 30 and 32 (pp 121-122)
- Typos corrected in Tables 33 and 34 (p125), and extra row added to Table 33 for clarity
- Text explaining utility for major bleed / ICH clarified (p. 127)
- Typo corrected in Table 43 (p137)
- Wording clarified (p.141)
- Typo in Table 59 corrected (p160)

Table 1 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	27%	25%
	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		0.03	23%	0%
	Clopidogrel + optional aspirin	1.20	0.56, 2.57	0.62			
	Clopidogrel + aspirin	0.47	0.22, 0.96	0.04			
Loading dose	No loading dose	1	Reference		0.00	19%	100%
	Loading dose	0.64	0.43, 0.96	0.03			
	Loading dose optional	1.14	0.54, 2.43	0.72			
Risk of bias	Low risk	1	Reference		0.02	27%	14%
	High risk	1.33	0.84, 2.12	0.21			
Primary event	Stroke	1	Reference		0.00	3%	100%
	Stroke or TIA	0.62	0.44, 0.86	0.01			
	TIA	1.53	0.58, 4.06	0.38			
PPI use	0-10%	1	Reference		0.02	18%	0%
	10-20%	0.99	0.58, 1.69	0.98			
	2 0-30%	1.32	0.63, 2.74	0.44			
	40-50%	1.51	0.57, 4.00	0.57			
	50-60%	0.15	0.03, 0.60	0.01			
	NR	1.02	0.64, 1.62	0.93			
Follow-up time	3 months	1	Reference		0.01	22%	59%
	6 months	1.11	0.62, 2.00	0.71			
	1 year	0.61	0.18, 2.02	0.40			
	1-3 years	1.34	0.77, 2.34	0.29			
	3-5 years	1.47	0.80, 2.71	0.20			
	NR	1.86	1.00, 3.43	0.06			
	Europe	1	Reference		0.04	32%	0%

Study location	China	0.75	0.38, 1.48	0.39			
	Asia	0.53	0.22, 1.29	0.15			
	US	0.56	0.22, 1.45	0.22			
	International	0.75	0.22, 2.55	0.63			
	Turkey	7.26	0.21, 256.43	0.26			

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 0.43, 0.96), in patients taking clopidogrel plus long-term aspirin relative to those taking only clopidogrel or clopidogrel plus short-term aspirin (RHR: 0.47, 95% CI 0.22, 0.96), 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 with and without LOF alleles when taking clopidogrel plus aspirin (HR 0.74 ; 95% CI 0.23, 2.38: stratified analyses results shown in Appendix 5). 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.

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 2). 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 2 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	0.099

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 3), 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 3). 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 4). 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 3 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 4 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 3)

Time Period	mRS 0-3 (Mild / Moderate Stroke)	mRS 4-5 (Severe Stroke)
0-30 days	0.0128	0.0157
31 - 90 days	0.0467	0.0574
91 days – 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 (**Error! Reference source not found.**). We did not find any data on bleeding rates in

Table 5 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 (**Error! Reference source not found.**)
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 (**Error! Reference source not found.**) applied
Ticagrelor, LOF	1.142 95%CI (0.7967, 1.587)	CHANCE-2[49] with hazard ratio from Objective 3 (**Error! Reference source not found.**) applied
Ticagrelor, No LOF	1.142 95%CI (0.7967, 1.587)	Assume equal to LOF

Table 6 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, (LOF or 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%.

Table 7 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 similar to 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 **Error! Reference source not found.**.

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 (**Error! Reference source not found.**) applied
Ticagrelor, LOF	1.142	95%CI (0.7967, 1.587)	CHANCE-2[49] with hazard ratio from Objective 3 (**Error! Reference source not found.**) applied
Ticagrelor, No LOF	1.142	95%CI (0.7967, 1.587)	Assumed equal to Ticagrelor No LOF
Major bleed/ICH			
Clopidogrel monotherapy (LOF or NoLOF)	1	1	Assumption that independent of LOF status, in line with clinical review (**Error! Reference source not found.**)
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, (LOF or 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]

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 0, with deterministic sensitivity analyses reported in Section **Error! Reference source not found.**. Probabilistic sensitivity analyses, scenario analyses, and diagnostic test cost and accuracy threshold analyses are reported in sections **Error! Reference source not found.** - **Error! Reference source not found.**.

Deterministic base-case analyses

Error! Reference source not found. - **Error! Reference source not found.** 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 both laboratory testing and the Genomadix Cube. The ICER for Genomadix relative to laboratory testing 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 **Error! Reference source not found.** - **Error! Reference source not found.** 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 8 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) – 40 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