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

ADDITIONAL ANALYSES FOLLOWING THE SECOND COMMITTEE MEETING

1 Introduction

Following the Diagnostic Appraisal Committee 2 meeting (DAC2), the EAG were requested by NICE to run additional scenarios using alternative evidence sources (identified by committee members) for the baseline hazards of an event in the TIA/Minor stroke population. The following evidence sources were considered:

1. *Lioutas et al. 2021.(1)* This is a retrospective cohort from the Framingham study in the US with 10 year follow-up of 435 TIA patients, and was used in the EAG base-case to inform hazard rates for future stroke. The stroke risk is for TIA patients only, so doesn't include those with minor stroke, which may underestimate the risk of recurrent stroke in the combined population. Note that they found the risk of stroke has decreased over time, which may be due to increased clopidogrel use. The model baseline event rates represent patient taking clopidogrel.
2. *Amarenco et al 2018.(2)* This is a 5-year follow-up of a study that recruited 4789 TIA/minor stroke patients from 61 centres in 21 countries, but 5-year data is only available on 2948 patients from 42 of the centres. They state that the patients who were included in the 1-year analysis but were excluded from the 5-year analysis were fitter with lower stroke-risk, so the estimates are a likely over-estimate. Most patients were taking aspirin, so rates may be higher than those on clopidogrel.
3. *Ildstad et al 2019*. (3) This is a prospective study of 577 TIA patients in Norway, with 1-year follow-up. 49.2% were taking dual therapy, 31% aspirin, and 6.2% other anti-platelet therapy. They do not include minor-stroke patients, so may underestimate risk.
4. *Tomari et al. 2021.* (4) This is a prospective study 298 TIA and minor stroke patients in New South Wales, Australia, with 25% on dual therapy or clopidogrel, and 35% on aspirin.

Table 1 shows the cumulative probabilities for different time points reported in the different studies. At 1-year the cumulative risk is higher for Amarenco and Ildstad compared with Lioutas and Tomari. At 5-years the cumulative risk is higher for Amarenco compared with Lioutas.

Table 1 Cumulative probability of stroke events from the different studies

Cumulative probability	Lioutas 2021	Amarenco 2018	Ildstad 2019	Tomari 2021
7 days	0.011206891		0.009	0.01
30 days	0.016017862		0.033	
90 days	0.020463595			0.021
1 year	0.026890435	0.046008	0.054	0.032
5 years	0.051993369	0.081		

In our model we use the annualised hazard rates (rate per person year risk). These are estimated from each study population for various time intervals in Table 2 below.

Table 2 Hazard of stroke per person year risk on different time periods estimated from the different studies

Period	Lioutas 2021	Amarenco 2018	Ildstad 2019	Tomari 2021
0-7 days	0.5860		0.468	0.52
8-30 days	0.0763		0.416	
8 – 90 days				0.052
31-90 days	0.0270			
31 days – 1 year			0.0229	
91 days -1 year	0.0085			0.0147
1-5 years	0.006356	0.008748		
0-90 day average	0.0838		0.1583	0.091
0-1 year average	0.0269	0.0461	0.0541	0.0338
91d – 5 year average	0.0067	0.0146		

In our base-case we used the 0-90 day and 1-5 years rates from Lioutas 2021. We run scenarios here using Amarenco 2018 average hazard over the period 91d – 5 years for the long-term Markov model, and either Lioutas 2021 (Scenario BH1), Ildstad 2019 (Scenario BH2, or Tomari 2021 (Scenarion BH3) for the 90 day decision tree part of the model (see Table 3). The annualised hazards are converted to probabilities for the appropriate time-period in the model.

Table 3 Hazard of stroke per person year used in the model scenarios

Period	Scenario BH1	Scenario BH2	Scenario BH3	Base-Case
0-90 day average	0.0838	0.1583	0.091	0.0838
Post-90 day average	0.0146	0.0146	0.0146	0.006356

2 Results

All tests were cost-effective in the scenarios explored in the minor stroke/TIA population. Increasing the long-term stroke rate compared with the EAG base case resulted in a greater number of incremental QALYs for the testing strategies against the no test strategy. This resulted in a higher estimated net monetary benefit of the tests compared with the EAG base case.

In the probabilistic analysis, we observed that when the long-term stroke rate is increased, there is less uncertainty over the cost-effectiveness of the tests. In the PSA which uses the rate from Amarenco et al. (2018) in the Markov model (Scenario BH1), we see an increase in the proportion of PSA iterations which are cost-effective. Using a £20,000 per QALY willingness to pay threshold, 86% of Genedrive iterations were cost-effective against no test, 84% of Genomadix iterations were cost-effective against no test, and 83% of lab tests were cost-effective against no test. In the CEAC, due to the strong correlation between the iterations where the tests were cost-effective, when testing was cost-effective Genedrive tended to dominate across WTP thresholds analysed.

In the scenario BH2 which uses 90day stroke rates from Ildstad et al. (2019) we observe fewer total QALYs in the TIA/minor stroke population due to the higher likelihood of stroke in the decision-tree period, but similar incremental QALYs between tests as scenario BH1. The results from the scenario BH3 which uses 90 day stroke rates from Tomari et al. (2021) are very similar to those for scenario BH1, since the short-term stroke rates in Tomari et al. (2021) are similar to those seen in Lioutas et al. (2021). In each scenario (BH1, BH2, and BH3) the no test strategy is dominated by the testing strategies with a higher number of incremental QALYs compared with the EAG base case presented in the second committee meeting.

2.1 Scenario BH1: Baseline Hazards for TIA/Minor Stroke (Lioutas 2021 for decision tree; Amarenco 2018 for Markov model)

Table 4 Fully incremental analysis results in the Minor stroke/TIA population using deterministic sensitivity analysis using stroke hazard rate from Amarenco et al. 2018 in the Markov model

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Lab test	vs Genomadix cube

Transient Ischaemic Attack/Minor stroke							
PoC test - Genedrive	£49,306	8.36					
Laboratory genetic test	£49,382	8.36	Yes	N/A	Dominated		
PoC test - Genomadix cube	£49,394	8.36	Yes	N/A	Dominated	£3,504	
No test	£49,719	8.34	Yes	N/A	Dominated	Dominated	Dominated

Table 5 Fully incremental analysis results in the Minor stroke/TIA population using probabilistic sensitivity analysis using stroke hazard rate from Amarenco et al. 2018 in the Markov model

Treatments	**Total costs £ (discounted)**	**Total QALYs (discounted)**	**Strictly dominated**	**Extendedly dominated**	**ICER (£)**		
					vs Genedrive	**vs Lab test**	**vs Genomadix cube**
Transient Ischaemic Attack/Minor stroke							
PoC test - Genedrive	£49,341	8.33					
Laboratory genetic test	£49,404	8.33	Yes	N/A	Dominated		
PoC test - Genomadix cube	£49,424	8.33	No	No	£2,646,476	£6,972	
No test	£49,743	8.31	Yes	N/A	Dominated	Dominated	Dominated

Figure 1 Genedrive incremental cost-effectiveness plane from the probabilistic sensitivity analysis applying the stroke rate from Amarenco et al. (2018) in the Markov model

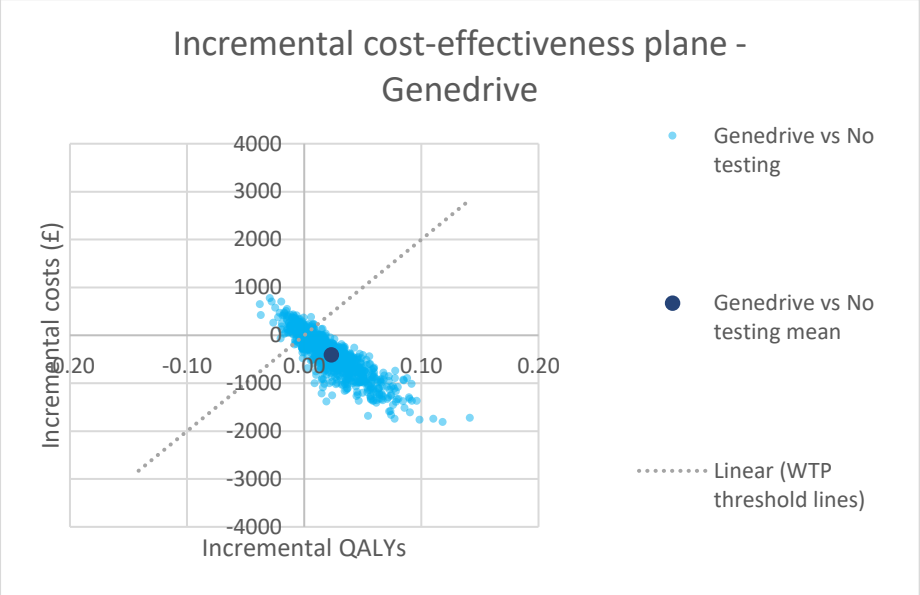


Figure 2 Genomadix cube incremental cost-effectiveness plane from the probabilistic sensitivity analysis applying the stroke rate from Amarenco et al. (2018) in the Markov model

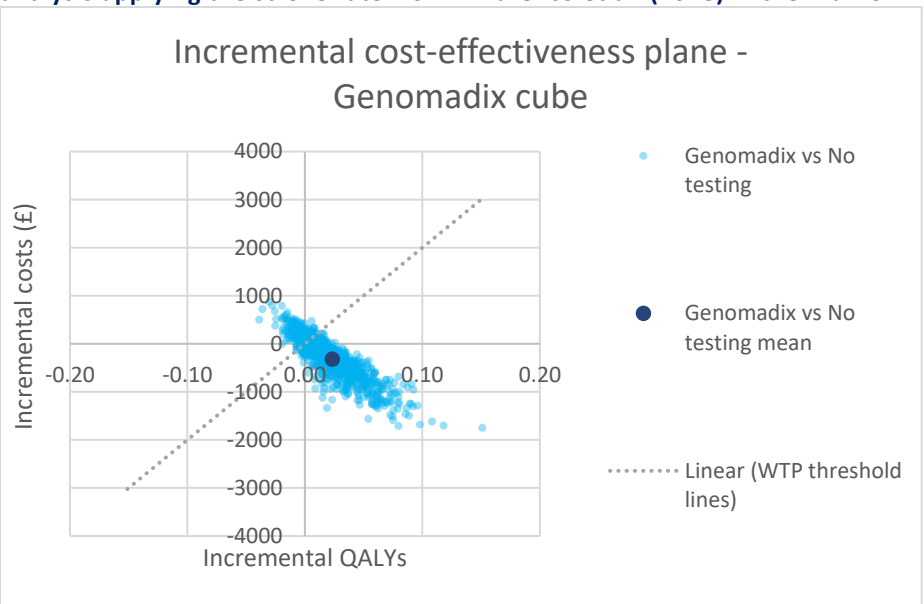


Figure 3 Lab test incremental cost-effectiveness plane from the probabilistic sensitivity analysis applying the stroke rate from Amarenco et al. (2018) in the Markov model

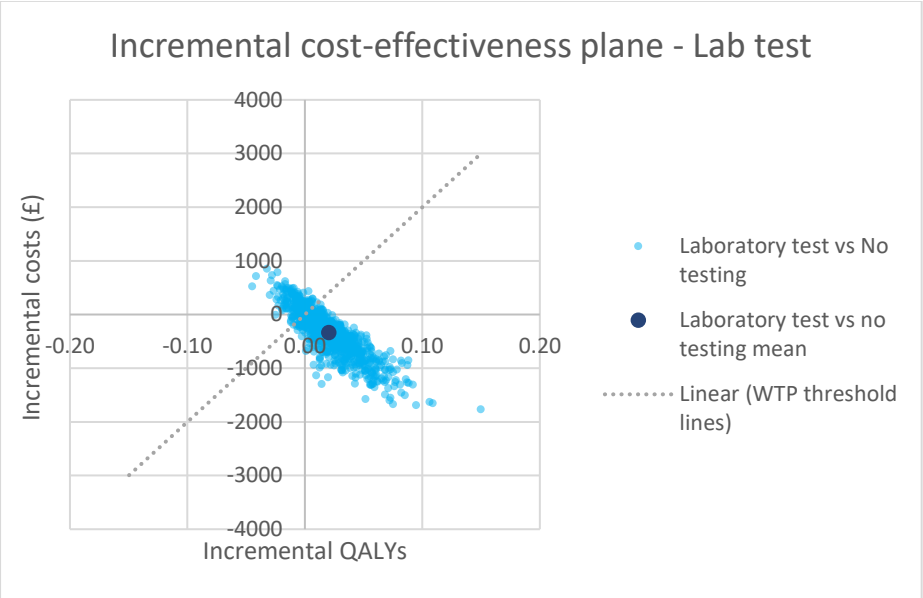
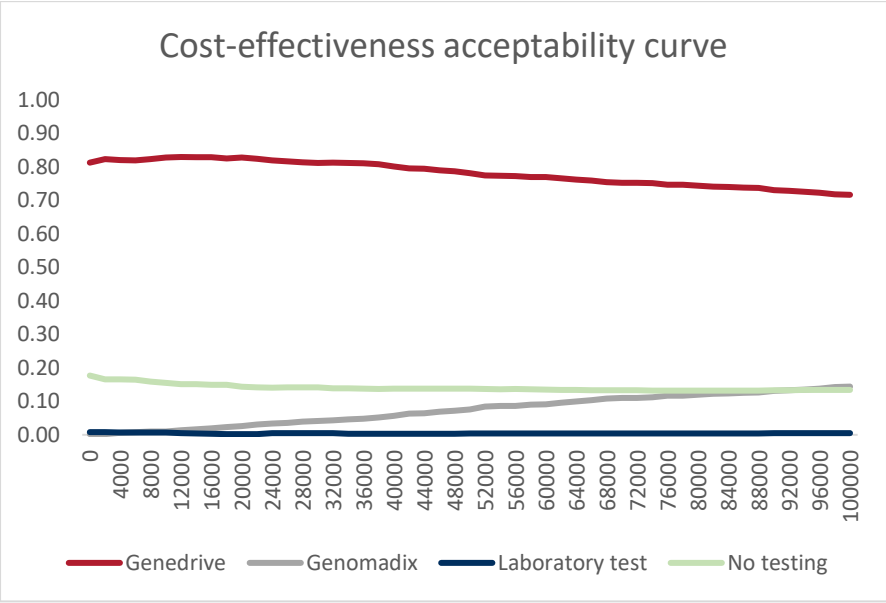


Figure 4 Cost-effectiveness acceptability curve in the minor stroke/TIA population using Amarenco et al. (2018) hazard rate for stroke in the Markov model



2.2 Scenario BH2: Baseline Hazards for TIA/Minor Stroke (Ildstad 2019 for decision tree; Amarenco 2018 for Markov model)

Table 6 Fully incremental analysis results using deterministic sensitivity analysis using stroke hazard rate from Ildstad et al. 2018 in the decision tree and in the Markov model

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Lab test	vs Genomadix cube
Transient Ischaemic Attack/Minor stroke							
PoC test - Genedrive	£50,523	8.31					
Laboratory genetic test	£50,597	8.31	Yes	N/A	Dominated		
PoC test - Genomadix cube	£50,611	8.31	Yes	N/A	Dominated	£8,334	
No test	£51,081	8.28	Yes	N/A	Dominated	Dominated	Dominated

2.3 Scenario BH3: Baseline Hazards for TIA/Minor Stroke (Tomari 2021 for decision tree; Amarenco 2018 for Markov model)

Table 7 Fully incremental analysis results using deterministic sensitivity analysis using stroke hazard rate from Tomari et al. 2021 in the decision tree and in the Markov model

Treatments	Total costs £ (discounted)	Total QALYs (discounted)	Strictly dominated	Extendedly dominated	ICER (£)		
					vs Genedrive	vs Lab test	vs Genomadix cube
Transient Ischaemic Attack/Minor stroke							
PoC test - Genedrive	£49,423	8.36					
Laboratory genetic test	£49,499	8.35	Yes	N/A	Dominated		
PoC test - Genomadix cube	£49,511	8.36	Yes	N/A	Dominated	£3,760	
No test	£49,850	8.33	Yes	N/A	Dominated	Dominated	Dominated

3 References

1. 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):373-81.
2. Amarenco P. Five-Year Risk of Stroke after TIA or Minor Ischemic Stroke. N Engl J Med. 2018;379(16):1580-1.
3. Ildstad F, Ellekjær H, Wethal T, Lydersen S, Sund JK, Fjærtoft H, et al. Stroke risk after transient ischemic attack in a Norwegian prospective cohort. BMC Neurol. 2019;19(1):2.
4. Tomari S, Levi CR, Holliday E, Lasserson D, Valderas JM, Dewey HM, et al. One-Year Risk of Stroke After Transient Ischemic Attack or Minor Stroke in Hunter New England, Australia (INSIST Study). Front Neurol. 2021;12:791193.