Clinical and cost-effectiveness of clopidogrel resistance genotype testing after ischaemic stroke or transient ischaemic attack: a systematic review and economic model

Joe Carroll,[1,†] Catalina Lopez Manzano,[1,†] Eve Tomlinson,[1] Ayman Sadek,[1] Chris Cooper,[1] Hayley E Jones,[1] Lorraine Rowsell,[2] John Knight,[2] Andrew Mumford,[3] Rachel Palmer,[3] William Hollingworth,[1] Nicky J. Welton[1,‡] and Penny Whiting[1*,‡]

[1]Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[2]Patient representative
[3]South West NHS Genomic Medicine Service Alliance, UK

[*]Corresponding author penny.whiting@bristol.ac.uk
[†]Joint first author
[‡]Joint last author

Published September 2024
DOI: 10.3310/PWCB4016

Scientific summary

Clinical and cost-effectiveness of clopidogrel resistance genotype testing after ischaemic stroke or transient ischaemic attack: a systematic review and economic model

Health Technology Assessment 2024; Vol. 28: No. 57
DOI: 10.3310/PWCB4016

NIHR Journals Library www.journalslibrary.nihr.ac.uk

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 (POCTs). 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 (RoB) assessment were performed by one reviewer and checked by a second. Risk of bias was assessed using the RoB 2 [randomised controlled trials (RCTs)], ROBINS-E (observational studies) and modified QUADAS-2 (diagnostic accuracy studies) tools.

For each objective, we provided a narrative summary of study details, RoB and results. Random and fixed-effects meta-analysis was performed to generate summary effect estimates; heterogeneity was investigated using stratified analyses and metaregression. 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: (1) TIA/minor ischaemic stroke and (2) non-minor ischaemic stroke; and also present results for a mixed ischaemic stroke and TIA population. We modelled patients moving between five health states: no recurrent stroke, minor stroke, major bleed or intracranial 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 lifetime horizon. Costs and quality-adjusted life-years (QALYs) were estimated using a 3.5% discount rate for both and summarised as expected net monetary benefit at willingness to pay of £20,000 per QALY, where higher expected net benefit is preferred.

Model inputs were derived from the clinical effectiveness review, reviews of previous cost-effectiveness models of *CYP2C19* testing and cost-effectiveness models of antiplatelets for stroke prevention, results from the survey of laboratories, information provided by Genedrive and Genomadix, and additional targeted searches. Uncertainty was explored using probabilistic 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 RoB 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 75 mg/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 100 mg/day.

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

Objective 2

Seven RCTs compared treatment with clopidogrel with alternative antiplatelet therapies compared in people with LOF alleles. Four were at low RoB, 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 to 0.90; two studies), including ischaemic stroke (HR 0.77, 95% CI 0.65 to 0.93; two studies). One study suggested that ticagrelor was associated with an increased risk of bleeding (HR 2.18, 95% CI 1.66 to 2.86); the other found no difference in the risk of bleeding with ticagrelor compared to clopidogrel (HR 1.01, 95% CI 0.60 to 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 five 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 RoB 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 to 2.08; 18 studies), stroke (HR 1.46, 95% CI 1.09 to 1.95; 5 studies) and ischaemic stroke (HR 1.99, 95% CI 1.49 to 2.64; 12 studies) than those without LOF alleles. Metaregression 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 0.43 to 0.96], and 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 to 0.96). Metaregression 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, 1–3 years and 3–5 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 to 1.40; five studies).

Objective 4

Eleven studies reported data on the accuracy of the POCTs 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 RoB. 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% to 100%) and summary specificity was also 100% (95% CI 99% to 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 POCTs. 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 minutes and 90–120 minutes. One study of Genedrive reported that it gives results in around 40 minutes. 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 (NGS) (two labs), MassARRAY (three labs), loop-mediated isothermal amplification (LAMP) (three labs), polymerase chain reaction (PCR)-based single-nucleotide polymorphisms (SNP) genotyping assays (e.g. TaqMan) (one 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 (TAT) from 24–72 hours to 1–2 weeks. Most labs reported that additional testing capacity and faster TAT 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 (four 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 *CYP2C19* testing was cost-effective, with both laboratory and point-of-care *CYP2C19* testing strategies generating more QALYs and lower costs compared with no testing. In the non-minor ischaemic stroke population, the expected net benefits were £6230, £6214 and £6138 for Genedrive, the laboratory test and the Genomadix Cube *CYP2C19* test, respectively. In the TIA/minor stroke population, the expected net benefits were £2932, £2802 and £2829 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. Only cost data were available for Genedrive, and so results for this test are illustrative only until more data on test performance data are available. Omitting Genedrive, the highest expected net benefit is for the laboratory test in the non-minor ischaemic stroke population, and the Genomadix Cube *CYP2C19* test in the TIA/minor stroke population.

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 HR for major bleed/intracerebral haemorrhage (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.

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 POCTs 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

This study is registered as PROSPERO CRD42022357661.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Evidence Synthesis programme (NIHR award ref: NIHR135620) and is published in full in *Health Technology Assessment*; Vol. 28, No. 57. See the NIHR Funding and Awards website for further award information.

Health Technology Assessment

ISSN 2046-4924 (Online)

Impact factor: 3.6

A list of Journals Library editors can be found on the NIHR Journals Library website

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 3.6 and is ranked 32nd (out of 105 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2022 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), EMBASE (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal
Manuscripts are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This article

The research reported in this issue of the journal was funded by the HTA programme as award number NIHR135620. The contractual start date was in August 2022. The draft manuscript began editorial review in March 2023 and was accepted for publication in July 2023. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).