NICE National Institute for Health and Care Excellence

Laboratory-based CYP2C19 genotype testing to optimise the effectiveness of antiplatelet therapy for patients experiencing acute ischaemic stroke or transient ischaemic attack

Case studies

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Contents

Overview

Organisation: NHS Tayside, Scotland

Organisation type: NHS Trust

People who have had an ischaemic stroke or TIA (Transient Ischaemic Attack, sometimes called a 'mini stroke') are at increased risk of further occlusive vascular events including heart attacks and peripheral vascular disease, particularly those caused by platelet-based blood clots. Clopidogrel is an antiplatelet medicine that is prescribed to reduce this risk and is widely recommended in clinical guidelines for managing stroke.

Clopidogrel is a "pro-drug" which means it must be metabolised into its active form to be effective. This is largely done by an enzyme encoded by a gene called CYP2C19. Up to 30% of people in the UK carry variants of CYP2C19 that reduce the enzyme's function, known as 'loss-of-function' (LOF) variants. This means in these people clopidogrel does not work as well and it has been clinically established that they have a greater risk of recurrent events when prescribed clopidogrel than patients not carrying such variants. Furthermore, alternative antiplatelet medicines are available that are not affected in this way. A simple genetic test can identify patients carrying LOF variants who can be then offered these alternative antiplatelet medicines that will work for them. LOF variants are more common in certain ethnic groups, such as people with an Asian family background.

In common with current standard care for patients with stroke in the UK, prior to implementation of the CYP2C19 genotype testing in NHS Tayside, clopidogrel therapy was prescribed without knowledge of which patients carried LOF variants. This exposes a significant number of people to potential harm because the clopidogrel is not working as desired.

Testing in this way for LOF variants in people who have had stroke is an example of Pharmacogenomics which makes use of an individual patient's genetic information to individually optimise the safety and effectiveness of the medications they are prescribed. In this way Pharmacogenomics can improve health outcomes and to help address health inequalities.

Pilot phase

For an initial pilot phase of this project, we used innovation funding from Tayside health board to request genotype testing for the indicated population (600-800 patients per year) managed by the Acute Stroke Service for whom following an ischaemic stroke or TIA, antiplatelet therapy was indicated. This initiative was commenced in April 2022.

CYP2C19 Genotyping

Genotyping is performed by the NHS Tayside East of Scotland Regional Genetic Laboratory which validated the CYP2C19 assay using TaqMan technology to identify the LOF variants c.681G>A (CYP2C19*2) and c.636G>A (CYP2C19*3) and a gain of function variant c.-806C>T (CYP2C19*17). Tayside request these LOF variants as they are the most commonly occurring and are the ones the clinical evidence is based upon. In Tayside, it is not currently cost effective to test for rare and specific genotypes. However as genomic medicine becomes more commonplace in the future, array based technologies may mean that all variants will be automatically available.

A reporting template was collaboratively developed between the laboratory, clinicians and pharmacist. In order to ensure appropriate understanding of the results, in addition to detailing phenotype and genotype information, the report prominently displays straightforward clinical decision support allowing for easy clinician interpretation of the genotyping test and its implications on the clopidogrel pathway:

- **Clopidogrel Metabolism NOT impaired:** clopidogrel use is appropriate in this patient
- **Impaired Clopidogrel Metabolism:** select alternative clinically appropriate antiplatelet treatment

Clinical pathway

Alternative antiplatelet options were reviewed and based on existing clinical evidence and following national guidelines the combination of aspirin 75mg once daily and dipyridamole MR 200mg twice a day was identified as an alternative to be used in patients identified as having impaired Clopidogrel Metabolism subject to clinician review. An application was made to the Tayside Medicines Advisory Group for updated indications in patients with

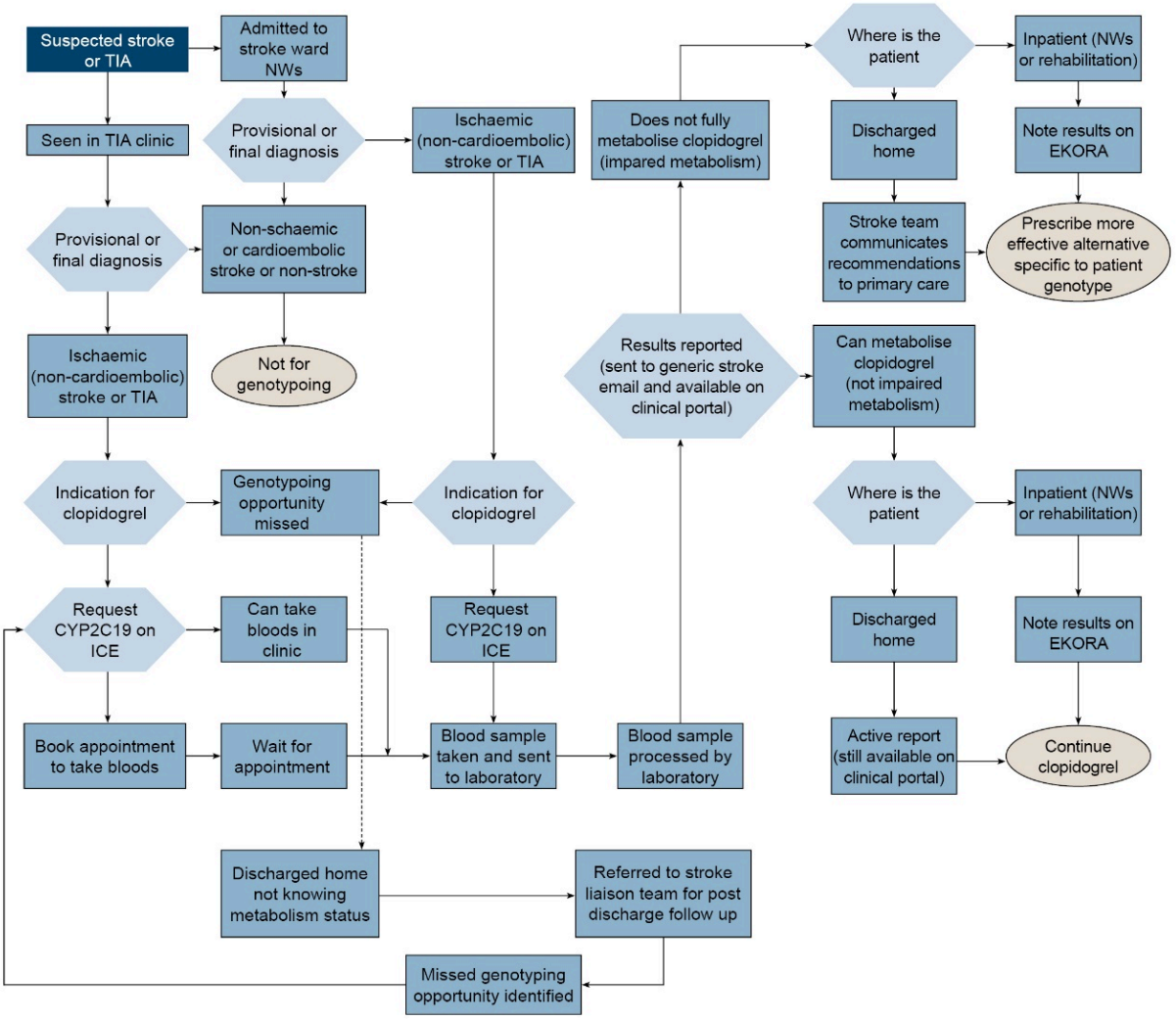
genetically determined impaired clopidogrel metabolism. The local area prescribing formulary was then updated. Later and in line with new Royal College of Physician's national stroke guidelines (2023) Ticagrelor also became an alternative.

Target patients were identified as those presenting to Ninewells hospital with an acute ischaemic (non-cardioembolic) stroke or TIA with a likely indication for long term clopidogrel therapy. Either admitted to hospital or referred for outpatient assessment via a TIA clinic. They would be assessed and reviewed by the medical team and the specialist stroke clinical pharmacist. Once relevant patients were identified, genotyping tests were ordered along with other routine tests on the standard electronic test requesting system used within our health board (ICE by Sunquest). The reason for the blood test was explained to the patient, verbal consent obtained and the sample sent to the NHS Tayside Genetic laboratory. Antiplatelet treatment was initiated as per standard care whilst waiting for the test to be reported.

Genotyping reports from the laboratory were sent to the requesting clinician by email and also added electronically to the patient's medical record accessible by both primary and secondary care. Reporting time from sample being received by the laboratory to report generation varied between 5-7 days.

These individual reports would be collaboratively reviewed by the requesting clinician and specialist stroke pharmacist, if the patient was still an in patient, and antiplatelet medication optimised based on the test result. For patients identified as impaired metabolisers who had already been discharged home, optimised antiplatelet medication advice would be communicated to the primary care team. The NHS Tayside stroke nurse liaison team provided further crucial follow-up to patients post discharge from the stroke ward. They not only contributed to ensuring patients were optimised on the appropriate antiplatelet medicine (if this had not happened whilst an in patient) but they also identified those patients which were not genotyped whilst in-patients but should have been. This team would liaise with the stroke pharmacist to have missing tests ordered, reviewed and actioned.

Clinical pathway flowchart



Education

The pathway was disseminated to the medical team and other healthcare professionals (HCP) involved in the care of stroke patients in formal and informal educational sessions delivered in a blended format: face-to-face and online, targeting both primary and secondary care HCP.

The clinical project lead and the clinical pharmacist developed targeted educational sessions for: stroke consultants and senior decision makers; junior doctors; stroke nurse liaison team and pharmacists based in both primary care and secondary care and in the community.

Engagement of the senior members of the stroke team was critical as this ensured early adoption of the initiative and vertical dissemination amongst the medical team. As junior doctors rotated through the stroke department they were inducted to this initiative and it

became part of their way of working.

To raise awareness of the initiative and support a successful transition of care, educational sessions were also developed for primary care and community pharmacists as well as pharmacy technicians.

Patient leaflets were created to aid communication with patients.

Implementation

The pharmacist and pharmacy technician, as part of their roles have an early clinical role in the patient's admission to hospital, usually in the first 24 hours. Amongst other activities: completing medicines reconciliation, medication review and participating in daily ward rounds. Pharmacists have the skills and are ideally placed to identify patients with an early indication for clopidogrel: where CT scans have excluded haemorrhagic stroke; and don't have an history of AF. In this initiative the clinical pharmacist could independently request the genotyping tests as well as participate in ward rounds raising awareness about this genotyping initiative and educating and supporting junior and senior doctors in adopting this test into their work routine.

Outcomes and learning

Outcomes

During the 1 year pilot between April 2022 and March 2023 723 genetic tests were performed, 204 patients (28.2%) were found to have at least one CYP2C19 loss-of-function allele and 168 patients were prescribed an alternative antiplatelet therapy. The remaining patients with CYP2C19 loss-of-function alleles did not have their antiplatelets modified due to changes in diagnosis or not surviving.

Based on previous research, we estimated that the number needed to treat by switching to effective antiplatelet therapy in loss of function carriers was 10. Therefore, on this basis we prevented approximately 17 patients from having a major follow up cardiovascular event in the first pilot year.

From April 2023, NHS Tayside agreed to fund this initiative permanently (based on the amount of follow up CV events prevented). This is the first Health Board in the UK to offer this.

Learning

NHS Tayside, have a large central genomics laboratory servicing all it's (and other Health Boards) requests. This means it is potentially less complicated than other areas where different laboratories may service requests for the same stroke service. Centralising testing reduces variability. There is a concern that localising testing with point of care tests may lead to variation and could worsen health inequalities.

There is a need to think about and pre-empt the broader implications for pharmacogenomics. There are major opportunities for increased cost efficiencies. Clopidogrel is widely prescribed for other conditions such as peripheral arterial disease and acute coronary syndrome. In addition to this, other drugs are metabolised by the same gene. Scotland are considering working on a strategy to enable pharmacogenomics to become more general and widely available for other disease areas to make drugs safer and more effective.

There will be considerable challenges to rolling out a laboratory-based test for all people who have had a stroke or TIA nationally. This is because of the need to expand testing capacity and the shortage of Clinical Scientists and other trained laboratory staff to deliver the testing.

Consideration should also be given to offering genotype testing to a wider cohort than acute patients.

A major challenge for improving the safety and effectiveness of medications by making use of a patient's genetic information is incorporating relevant information into a patient's medical record and triggering a clinical decision support for new prescribing where this information exists. This means that pharmacogenomics must be fully integrated into medicines management systems in both primary and secondary care.

Supporting information

During this initiative patients have universally been very keen without exception to being genotyped to improve the safety and effectiveness of their prescribing.

Mr Anderson, our first patient said:

> It really is a step into the future and one that will benefit patients in the coming months and years,

> It is quite amazing that a simple blood test can show if my medication is working as effectively as possible and it is reassuring that my medication can be tailored more precisely to me.

> I've still got a lot of life to live. I've got three grandchildren, I want to get back to them and I'll do whatever I need to do.

See also, the STV news story: how simple blood tests are transforming treatment for stroke patients.

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