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Elizabeth Blackwell Institute for Health Research

Elizabeth Blackwell Institute Research for Health Scheme 2017

Stage 1 - Call for Challenges Application Form

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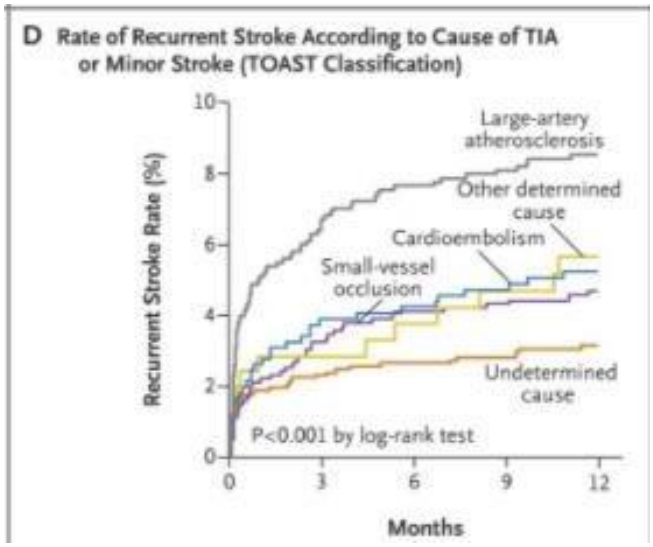
Please describe the specific problem which needs addressing
Stroke on anti-platelet treatment: can it be prevented by individualised treatment based on measurement of platelet reactivity?

Many people suffer ischaemic stroke despite “best medical treatment”, including anti-platelet medications. In these cases of “treatment failure” the best management strategy for further antithrombotic treatment is not clear. Improving the effectiveness of anti-thrombotic treatment by individualising treatment has the potential for preventing large numbers of strokes in the UK and worldwide.

Anti-platelet treatment is the standard secondary prevention treatment for the vast majority of ischaemic stroke. In the UK this is usually aspirin 75 mg daily or clopidogrel 75 mg daily, as recommended in stroke guidelines (NICE and Royal College of Physicians stroke guidelines). Sometimes combinations of aspirin and clopidogrel, or aspirin and dipyridamole are used.

Anti-platelet treatment is in particular effective in preventing ischaemic stroke caused by large artery atherosclerosis and embolism. It is in these cases that the rate of recurrent stroke is highest, despite medical treatment (as shown in the graph below, taken from a recent study measuring one year risk of ischaemic stroke following transient ischaemic attack or minor stroke: N Engl J Med 2016; 374: 1533-42).



The degree to which platelet activation is inhibited by anti-platelet treatment varies between individuals. For example, a number of genetic polymorphisms have been identified that affect the degree to which platelet activation is inhibited by aspirin and clopidogrel (see for example the following review in relation to clopidogrel: Pan et al 2017; 135: 21-33). Results of studies looking for associations between genetic variability with treatment outcomes vary; however, one prominent example is the influential CHANCE clinical trial of dual anti-platelet therapy using aspirin plus clopidogrel versus aspirin alone in minor stroke, where a beneficial effect of clopidogrel on recurrent stroke was only seen in the group that did not carry a loss of function allele (JAMA 2016; 316: 70-8).

Possible solutions to the problem of anti-platelet “treatment failure” might include measurement of platelet reactivity and either prescribing an alternative anti-platelet agent or tailoring the dose of anti-platelet treatment to measurements of platelet reactivity. Other anti-platelet agents such as ticagrelor and prasugrel are in production but their benefit in stroke prevention is unproven.

Platelet activity testing is now widely available, including a variety of commercially available testing devices. The utility of these devices is debated but their use in clinical practice is increasing. For example the “VerifyNow” device is used at North Bristol Trust to guide antiplatelet treatment during vascular stenting procedures by interventional neuroradiologists. Dosing of clopidogrel is increased for “hypo-responders” who are at higher risk of thrombosis, and reduced for “hyper-responders” who are at risk of haemorrhagic complications.

It would be useful to know more precisely what the size of the problem and potential benefit is to the NHS and internationally. An initial observational study examining the association between genetic polymorphisms and recurrent stroke risk might be useful, and could be extended to include measurement of platelet reactivity; such as study is potentially deliverable through the NIHR Clinical Research Network. A clinical trial of modulating anti-platelet drug use and/or dosing according to either platelet reactivity or other genotypic/phenotypic features would hopefully follow on from this.

To develop this idea we need to access expertise in the fields of platelet biology and genetics, as well as clinical trial design and management. The University of Bristol contains research groups with expertise in all of these areas.

A possible initial vehicle for collecting samples for this study is the SIGNUM study, a biomarker study run by UCL in which UHBristol and NBT are participating. The intention is for this study to run nationally; there are currently 25 study sites and a further 20 are planned in the near future. Dr Clatworthy is in close communication with the Chief Investigator and Trial Manager for this study, which may provide an initial vehicle for gaining blood samples and genetics from large numbers of patients with stroke and TIA.

How does this issue impact on you, your community, your colleagues or your patients?

Stroke is a leading cause of mortality and disability in the UK and worldwide; treatment failure of anti-platelet agents substantially adds to this burden of disease.

In my own experience, failure of preventive treatments often has a profound psychological impact on patients who have been prescribed treatment which was intended to prevent a stroke. These people are often very frightened that future treatment will also be unsuccessful and that they will suffer a further, potentially devastating stroke.

As stroke specialist physicians we see many people who have had stroke despite anti-platelet treatment. Choice of anti-thrombotic treatment in these cases varies between clinicians as there is equipoise and uncertainty between different treatment options. In general different standard treatment and dosing regimens are used rather than dose adjustment.

It seems that it ought to be possible to improve this situation by individualising treatment. There are different possible options, including avoidance of drugs to which individuals are genetically less likely to respond, and adjusting treatment dose according to platelet reactivity measurement.

Can you estimate how many patients or staff are affected by this problem?
Can you describe any associated financial implications for the NHS or patients? ***(Don't worry if you are not able to answer this question at this stage – it is not compulsory)***

Stroke affects more than 150,000 people annually in the UK alone, and approaching 40,000 people die each year in the UK due to stroke, accounting for 11% of deaths in the UK (Royal College of Physicians Stroke Guideline 2016). The overall economic cost of stroke in the UK is estimated at approximately £9 billion each year. The 2016 Royal College of Physicians Stroke Guideline states that the risk of recurrent stroke is approximately 26% over 5 years and 39% over 10 years. This guideline also states that a conservative estimate of the UK incidence of first-ever TIA is 50 per 100,000 population per year. Taking the UK population to be 64 million, this gives a conservative incidence rate of 32,000 first-ever TIAs per year.

In Bristol, North Somerset and South Gloucestershire (BNSSG) in 2015-16 approximately 12001250 people were admitted to hospital with stroke (SSNAP data). A comparable number of people were diagnosed with TIA. The estimated cost of stroke to the health and social care system in Bristol, North Somerset and South Gloucestershire for people admitted to hospital with stroke over a single year (2015-16) is over £50 million over 5 years, or approximately £45,000 on average per person with stroke (£22,000 over 1 year, Sentinel Stroke National Audit Programme (SSNAP) Health Economic Analysis).

In BNSSG in 2015-16, 28% of the 1213 people admitted with stroke were recorded as having a previous stroke or TIA (SSNAP data). This is approximately 340 people. Approximately 85% of strokes were ischaemic (SSNAP). If this rate of recurrent stroke could be reduced by 2% (absolute rate) this might be around 6 people per year, saving approximately £22,000 x 6 = £132,000 in the first year, with these savings increasing over time due to accumulating health and social care costs of each cohort of patients.

Nationally in England and Wales, 81,865 people were recorded as admitted following stroke in 2015-16 (71,250 ischaemic), of whom 26.7% (approx. 22,000) had a prior stroke or TIA. Reducing the rate of estimated recurrent ischaemic stroke by 2% this might be 380 people per year. In the first year this might save an estimated £8.4 million in health and social care costs due to stroke.

These figures include only the potential benefits of preventing recurrent stroke. Primary stroke prevention and prevention of cardiovascular disease such as myocardial infarction would add to this figure. The potential international savings would of course be substantially greater.