Changes in antiplatelet use prior to incident ischaemic stroke over 7 years in a UK centre and the association with stroke subtype

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Abstract

Background: guidelines have changed in relation to the indication of antiplatelet therapy for the primary and secondary prevention of stroke. Of interest is how the proportion of patients who had or had not taken antiplatelet agents prior to an incident stroke has changed over time, whether the type of antiplatelet agents used has altered and whether prior antiplatelet use is associated with a particular ischaemic stroke subtype.

Methods: a stroke register was retrospectively examined. All ischaemic stroke patients admitted between January 2004 and March 2011 to a single University Hospital with a catchment population of ~750,000 were included. We excluded those who were on anticoagulants prior to the ischaemic stroke.

Results: a total of 4,307 ischaemic stroke patients [male 47.5%, mean age 77.6 (SD 11.7) years] were included. Of them, 54.7% (SD 2.2%) were not on any antiplatelet therapy prior to their incident stroke. The type and pattern of antiplatelet use prior to stroke did not change significantly during the 7-year study period, and there were no statistically significant differences between different ischaemic stroke subtypes with regards to prior antiplatelet use.

Conclusions: our findings highlight the requirement to improve currently available risk prediction scores as well as the potential clinical impact of antiplatelet resistance within the at risk population who are already on antiplatelets. These findings also indicate that targeting of multiple risk factors may be very important in stroke prevention.

Keywords: antiplatelets, stroke, prevention, older people

Introduction

Stroke is the third leading cause of death in the UK and the number one cause of long-term disability worldwide. Ischaemic stroke is a major stroke subtype contributing to ~80% of all strokes [1]. The threat of stroke recurrence is substantial, thus highly relevant and important in patients who already had a stroke in whom evidence on alternative antiplatelet regimen/procedure rather than antiplatelets for secondary prevention is limited.

Prevention is vital to reduce the disease burden and antiplatelets are one of the mainstay therapies for primary and secondary stroke prevention [2]. However, the benefit of aspirin therapy in the primary prevention of stroke remains unclear [2]. A recent study by the Antithrombotic Trialists collaboration highlighted the lack of guidance for the treatment of patients with aspirin failure, whereby they have an ischaemic stroke while receiving primary prevention [3]. A meta-analysis of primary prevention trials of aspirin showed that while aspirin is effective in reducing the risk of total
cardiovascular events and non-fatal myocardial infarction, no similar significant effect was found in stroke [4]. With regard to secondary prevention, recurrence rates of stroke are high, with ~25% experiencing a further stroke within 5 years, of which a third occurs within the first 2 years [5]. Furthermore, cardiovascular morbidity and mortality can vary widely after stroke in clopidogrel-treated patients, ranging from as low as 2% to as high as 13% at 1 year [6].

In this report, we examined the extent of pre-existing antiplatelet use in patients presenting with an incident ischaemic stroke as a proxy indicator of antiplatelet failure, or as a failure to identify and treat at risk population. We also looked at whether prior use of an antiplatelet was associated with a particular subtype of ischaemic stroke.

Methods

The study sample consists of consecutive ischaemic stroke patients admitted to a UK University Hospital with a catchment population ~750,000 between January 2004 and March 2011. The centre admits ~900 strokes per annum and all the patients were included in the stroke service register. Data were collected prospectively by trained data collectors and verified by specialist stroke nurses or doctors. For this report, we excluded all haemorrhagic strokes and those who had ischaemic stroke while on anticoagulant therapy as we are interested in usefulness of antiplatelets in primary and secondary prevention of ischaemic stroke. Secondary prevention cases were identified based on previous cardiovascular disease events (transient ischaemic attack or stroke) from clinical coding on discharge letters using Patient Administrative System held electronically. Data are presented descriptively and for meaningful comparison, the proportion (per cent) rather than absolute numbers were presented in the figures. The data on haemorrhagic stroke are also presented as Supplementary data available in Age and Ageing in an Appendix for completeness which can be assessed online. Anonymised, routinely collected, data from the stroke services data office were obtained to carry out a retrospective audit on use of antiplatelets and data were presented in anonymised and aggregated fashion. Therefore, specific ethical approval for this work was not sought.

Results

The total sample consisted of 4,307 ischaemic stroke patients (47.5% male); the mean age was 77.6 (SD 11.7) years. Figure 1 shows the proportion of patients by the prior antiplatelet status admitted over the study period by each year. The average percentage of patients for each type of antiplatelet was as follows: aspirin (35.2 ± 3.0%); aspirin and dipyridamole (4.8 ± 1.0%); clopidogrel (2.8 ± 0.6%); clopidogrel and aspirin/dipyridamole (1.5 ± 1.1%); dipyridamole (0.7 ± 0.4%). Overall, the majority (55.0 ± 2.1%) of the patients were not on any antiplatelets prior to the index ischaemic stroke. The remaining 45.0% of the sample was on an antiplatelet thus approximately half of ischaemic stroke patients sustained an ischaemic stroke despite being on an antiplatelet for either primary or secondary prevention of cardiovascular and cerebrovascular diseases.

![Figure 1](image-url)

Figure 1. Proportion of ischaemic stroke cases with or without antiplatelets admitted to the centre between January 2004 and March 2011.
Table 1 shows the sample characteristics stratified by primary or secondary prevention and prior use of antiplatelets and also presents the cross tabulation between the clinical stroke type. The proportion of patients who were on or not on antiplatelet did not change based on primary or secondary prevention status. There were no statistically significant differences between different ischaemic stroke subtypes with regard to prior antiplatelet use prior to stroke.

**Discussion**

We found that the type and pattern of antiplatelet use has not changed over the last few years in patients who presented with first-ever or a recurrent stroke. Interestingly about 50% of stroke patients in this series were not on any preventative antiplatelet medication (regardless of nature of use, i.e. primary or secondary prevention purpose) indicating that a proportion of them may potentially have benefited from risk stratification and consideration of antiplatelet therapy beforehand to reduce risk of future thrombotic events. This implies gaps in risk prediction rules or in identifying those at high risk of developing a cardiovascular event. Conversely, treatment with antiplatelet agents in some high vascular risk patients might have been considered inappropriate by the physician due to contra-indications such as gastrointestinal ulcers or haemorrhage or due to patient’s refusal. However, this is unlikely to account for all cases where patients did not receive the appropriate prevention.

It is equally alarming that remaining ~50% of stroke patients in this series were on one or more antiplatelets in an attempt to prevent a CV event, and yet this failed to prevent a stroke. This raises the issue that antiplatelet ‘failure’/antiplatelet resistance may be a significant issue in this patient group with regard to considering the secondary prevention. We found that previous antiplatelet use prior to stroke did not influence subtype of ischaemic stroke. Similarly, a large international stroke trial that examined prior aspirin use and baseline stroke severity concluded that there was no evidence of an association between the two [7] which is in keeping with our results. While the dose of antiplatelet agent may have some impact on antiplatelet resistance, the majority of patients were on aspirin and on a standard dosage of 75 mg o.d.

While the study was retrospective, the prospective nature of the data collection limited the effect of recall bias. The aims of the study were best addressed by adopting an observational study using registry data, as this included all patients admitted with an ischaemic stroke (no selection bias). It should be noted that the sample did not include those patients in the population on the primary prevention who did not experience...
a stroke. Such information may have been useful in gauging the proportion of which patients are still experiencing stroke despite primary or secondary prevention. Nevertheless, our study highlights the need for better identification of at risk populations, perhaps using emerging novel risk factors [8, 9].

Patient concordance with prescribed therapy is also worth considering as some of the patients on antiplatelet drugs may not be taking their medication and this may explain why some patients with previous CVD were not on antiplatelets (see Table 1). Recent small-scale studies suggest that incomplete adherence to antiplatelet therapy may be responsible for up to 50% of such cases [10, 11]. Another limitation of study involves the lack of information recorded regarding the reliability of the obtained drug history and what the indications were for prior antiplatelet therapy. Finally, atrial fibrillation (which accounts for ~15% of ischaemic stroke) may contribute to apparent antiplatelet failure. We excluded those on warfarin/anticoagulant for AF in this study and therefore ischaemic stroke due to undiagnosed AF accounting for apparent failure in this cohort was likely to be much <15%.

Despite these limitations, there are two issues which are of our concerns in terms of primary or secondary stroke prevention. First, our findings support current evidence regarding the limited effectiveness of risk assessment tools in primary prevention of ischaemic stroke. Recent research regarding the external validity of QRISK2 and other scoring systems demonstrated that current systems are concerned with a high-risk approach, focusing particularly on identifying those who will benefit the most [12]. Although more contemporary assessment tools have aimed to account for interaction among a number of risk factors, this has yet to result in substantial improvements in the discriminative ability of the tools [12].

It is apparent that while these prognostic tools are targeted at identifying the people at the greatest risk of a major cardiovascular event such as stroke, there is a proportion of the population that will not be detected. Recent research regarding patterns of risk within different ethnic groups has indicated that tailor-made prevention programmes may be more appropriate at targeting different groups within a population [13]. While there are several additional risk factors and interactions that assessment tools account for, the issue of antiplatelet resistance is important to consider. Evidence to date suggests that antiplatelet resistance is not uncommon in patients with coronary artery disease, e.g. those who underwent coronary angioplasty; reported prevalence varies between 15 and 30% [14].

Although reduced platelet responsiveness to clopidogrel, currently recommended first line antiplatelet in secondary stroke prevention, and its inter- and intra-individual variability referred as clopidogrel resistance has been investigated widely in patients with ischaemic heart disease [15], there is a dearth of information on the prevalence of antiplatelet resistance in stroke. There are only a few small studies conducted in Japanese stroke patients where the prevalence of clopidogrel resistance was reported up to 29% depending on the methods used [16, 17]. However, in both studies the sample sizes were small and conducted in one ethnic group making it difficult to imply generalisability (n < 80 in both). There is a wide variation in the estimated prevalence of aspirin and clopidogrel resistance, which is attributed to the lack of a consensus regarding diagnostic criteria [3, 18]. In addition, there are numerous factors within aspirin resistance including: comorbidities; drug interactions and poor/lack of treatment concordance [3, 19].

In summary, future studies to improve risk prediction rules are clearly needed to guide effective primary and secondary prevention of cardiovascular diseases including stroke. Additionally, it is also important to better understand the factors that may contribute to failure of antiplatelet therapy including antiplatele resistance so as to provide more individually tailored approach in the future. The findings also indicate that control of multiple risk factors may be very important in stroke prevention.

**Key points**

- Half of the patients sustained a stroke despite being prescribed antiplatelets agents; this did not differ between primary and secondary prevention.
- It is important to better understand failure of antiplatelet therapy including antiplatelet resistance.

**Conflicts of interest**

None declared.

**Ethical approval**

Anonymised data from routinely collected hospital stroke services data office were obtained to carry out a retrospective audit on use of antiplatelets and data were presented in anonymised and aggregated fashion in line with the National Information Governance Board guidance and according to the Caldicott Principles. Therefore, specific ethical approval for this work was not sought.

**Supplementary data**

Supplementary data mentioned in the text is available to subscribers in Age and Ageing online.

**References**

Could more than three million older people in England be at risk of alcohol-related harm? A cross-sectional analysis of proposed age-specific drinking limits

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