Abstract:
The authors sought to determine the impact of antithrombotic therapy on emergency referrals at one neurosurgical centre. All emergency telephone referrals over a 90 day period were carefully documented with particular attention paid to current antithrombotic medications and their indication. Details regarding age, gender, diagnosis, radiological findings and treatment were also recorded. 713 emergency referrals were documented in the data collection period. 174 (24.4%) patients presented with intracranial or spinal haemorrhage and 75 (43.1%) of these were on antithrombotic therapy, ranging in age from 46-94 years (mean 71.1 years) with 43 (47.2%) on aspirin, 15 (16.4%) on clopidogrel alone or in combination with another antithrombotic agent. 17 (22.6%) had no documented indication for antithrombotic therapy (all of these were on aspirin therapy) and 9 (31%) of those on warfarin had an INR in excess of 3.5 on presentation. Almost one quarter of those on antithrombotic therapy who presented with a haemorrhagic complication had no obvious indication for such therapy. One third of those on warfarin were over anticoagulated.

Introduction
Trainees and consultants who provide acute neurosurgical services will be familiar with the terms on aspirin or warfarin which all too often accompany an emergency telephone referral. Catastrophic intracranial haemorrhage in patients on antithrombotic therapy seems to appear more and more frequently on our image-link screens (figure1). At our department, we have formed the impression that more and more patients on antithrombotic medication are being referred with haemorrhagic complications. We sought therefore, to quantify the effect of antithrombotic medication on our emergency referral load over a 3month period.

Patients and Methods
713 emergency telephone referrals were prospectively audited over a 90 day period from January to April 2004. Data was collected using a standard proforma (table 1). In particular, antithrombotic medications and indications for such therapy were documented along with international normalised ratio (INR), where applicable.

Results
713 emergency telephone referrals were documented during the data collection period. 174 (24.4%) presented with intracranial or spinal haemorrhage, 75 (43.1%) of these patients were on antithrombotic therapy at the time of referral (figure 2a,b). The age of patients ranged in age from 46 to 94 years (mean age 71.1 years). 29 (31.8%) were on warfarin, 43 (47.2%) were on aspirin, 15 (16.4%) were on clopidogrel alone or in combination with another antithrombotic agent(figure 3).

Discussion
Neurosurgeons are very aware of the risks of intracranial or spinal haemorrhage that antithrombotic therapy poses to patients. There are, however, undoubted benefits of such therapy, in terms of stroke or myocardial infarction prevention for those at risk of thrombo-embolic events. The expansion of clinical indications for warfarin therapy include non-rheumatic atrial fibrillation has increased the numbers of warfarinised patients and has raised concerns about how warfarin monitoring should be undertaken . Warfarinised patients with atrial fibrillation or previous myocardial infarction. Of those presenting with haemorrhagic complications of their antithrombotic therapy, 3 (3%) of warfarinised patients had an INR in excess of 3.5 on admission. With regard to aspirin therapy alone, 17 (39.5%) had no medical indication for aspirin therapy.

Table 1 Standard proforma for data collection

<table>
<thead>
<tr>
<th>Referral date</th>
<th>Patient name</th>
<th>Age/ DOB</th>
<th>Referring hospital</th>
<th>NSU consultant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Warfarin</td>
<td>Clopidogrel</td>
<td>Heparin</td>
<td>Streptokinase/ tPA</td>
</tr>
</tbody>
</table>

Table 2 Indications for anticoagulant/antiplatelet therapy n=91

| Atrial fibrillation | 16 |
| Ischaemic heart disease | Stroke/TIA |
| Stroke/TIA | Deep venous thrombosis/pulmonary embolism |
| Peripheral vascular disease | Hypertension |
| Multiple indications | |

Figure 1: Massive acute subdural haematoma presenting in a warfarinised patient after minor head trauma

Figure 2a: 174 of 713 referrals had CNS haemorrhage

Figure 2b: 75 (43%) of 174 patients with CNS haemorrhage were anticoagulated

Figure 3: Frequency of haemorrhage complication per anticoagulant

50 (54.4) had ischaemic heart disease, atrial fibrillation or previous myocardial infarction. Of those presenting with haemorrhagic complications of their antithrombotic therapy, 3 (3%) of warfarinised patients had an INR in excess of 3.5 on admission. With regard to aspirin therapy alone, 17 (39.5%) had no medical indication for aspirin therapy.

Discussion
Neurosurgeons are very aware of the risks of intracranial or spinal haemorrhage that antithrombotic therapy poses to patients. There are, however, undoubted benefits of such therapy, in terms of stroke or myocardial infarction prevention for those at risk of thrombo-embolic events. The expansion of clinical indications for warfarin therapy include non-rheumatic atrial fibrillation has increased the numbers of warfarinised patients and has raised concerns about how warfarin monitoring should be undertaken . Warfarinised patients with atrial fibrillation are reported to be at significantly reduced risk of ischaemic stroke when the INR is 2.0 or greater; furthermore, the same study demonstrated no marked absolute increase in the rate of intracranial haemorrhage for INR values less than 4.0 . Others report a significant increase in haemorrhagic complications of warfarin therapy in patients with an INR in excess of 4.5. In our series, the majority (69%) of patients who developed haemorrhagic complications of warfarin therapy had an INR of 3.5 or less (figure 4a).

Figure 4a: Warfarin therapy

Figure 4b: Aspirin therapy

In the UK an estimated 470,000 people currently take warfarin; 60% of patients with atrial fibrillation remain unidentified and thus outside the antithrombotic net, raising the potential for a significant increase in the number of warfarinised patients .

Table 2 Indications for anticoagulant/antiplatelet therapy n=91

Comments: John Caird. Royal Victoria Hospital Belfast, BT12 6BA (Ward 4F).

The warfarin clinic at our institution is attended by approximately 2000 people from a catchment population of approximately 250,000. Extrapolating this figure to the population of the Republic of Ireland (4,000,000), an estimated 0.4% of the population of Ireland is warfarinised; this figure corresponds well with U.K. figures where 470,000 of the 60,000,000 population (0.78%) are warfarinised.

The catchment population of our neurosurgical unit is approximately 3,000,000 including an estimated 24,000 warfarinised individuals; with roughly 120 warfarinised patients being referred to our centre in 1 year (29 in 90 days) we estimate that 1 in every 200 warfarinised patients annually will be referred with a neurosurgical emergency. Almost 1/3 of warfarinised patients in our series had an INR in excess of 3.5.

For patients presenting with subdural haematoma, significantly worse outcomes have been demonstrated in those on antithrombotic agents, with such agents implicated in the pathogenesis of the majority of spontaneous subdural haemorrhage. The STICH trial has reported an unfavourable outcome for 82.6% of patients on antithrombolytic therapy presenting with spontaneous supratentorial intracerebral haemorrhage who were randomised to the initial conservative treatment arm, compared with 75.5% for patients also treated conservatively but not on antithrombotic therapy. Antithrombotic treatment-related intracranial haemorrhage has been reported to be less frequent with clopidogrel than aspirin. While numbers of clopidogrel treated patients in our study were too small to determine statistical significance, there is a growing perception amongst neurosurgeons that clopidogrel-treated patients may be at risk of intraoperative and post-operative haemorrhage.

Patients who undergo interventional endovascular procedures are also at risk of antithrombotic therapy related intracranial haemorrhage in the postprocedure period, particularly if ventriculostomy is required in patients with aneurysmal subarachnoid haemorrhage. Combination therapy of more than one antithrombotic agent as secondary prevention of cardiovascular deaths in high risk patients has been proposed as standard treatment. Combination therapy with aspirin and clopidogrel for secondary prevention of stroke has been found to increase the incidence of haemorrhagic complications over clopidogrel treatment alone and is potentially harmful. The use of aspirin therapy as primary prevention of ischaemic events in hypertension has been found by meta-analysis of published data to be potentially harmful.

In our series 8 (19%) patients were on aspirin therapy for primary prevention in hypertension; a further 17 had no documented reason for aspirin therapy, giving a total of 59% of patients on aspirin with no firm medical indication for such therapy (figure 4b).

While there are undoubted benefits of antithrombotic therapy for patients at risk of thrombo-embolic events, the haemorrhagic complications of such therapy outside the domain of randomised, prospective trials may be underestimated.

In particular the practice of prescribing aspirin as primary prevention in hypertensive patients remains contentious and has not been supported by a randomised, prospective trial.

7. The international stroke trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International stroke trial collaborative group. Lancet 1997;349:1359-81