Antithrombotic medicines following intracerebral haemorrhage: where's the evidence?

Robert Flynn and Alexander Doney

Ther Adv Drug Saf

(2011) 2(5) 205–211

DOI: 10.1177/

2042098611415457

© The Author(s), 2011.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: The use of antithrombotic medicines in patients who have a history of intracerebral haemorrhage is widely perceived as being contraindicated. However, many patients with intracerebral haemorrhage may suffer from conditions for which antithrombotic medicines are indicated. Such scenarios represent a therapeutic dilemma whereby treating infers an increased risk of recurrent intracerebral haemorrhage, but not treating infers an increase of thrombotic complications. Despite the importance of this dilemma, there is very little guidance for prescribers. This perspective review considered previous systematic reviews that addressed this issue, together with recently published research findings from the Tayside Stroke Cohort. Systematic reviews of experimental and observational studies have concluded that there is a marked lack of data on which to judge the safety of oral anticoagulant agents following intracerebral haemorrhage. In addition, the limited data available regarding the use of antiplatelet medicines following intracerebral haemorrhage provide no evidence that they are harmful, and again further data are required. In the absence of such data, a decision analysis approach has been proposed. This considers the findings of other studies to infer the likely impact of using antithrombotic agents in patients with intracerebral haemorrhage. The success of this approach is contingent on the availability of reliable data that describe the rate of recurrent intracerebral haemorrhage; however, published data on this varies widely. There are a number of factors that conspire against researchers addressing this issue. The current paucity of evidence to guide prescribers faced with this therapeutic dilemma seems likely to remain for some time.

Keywords: anticoagulants, cerebral haemorrhage, cohort studies, hematologic agents, platelet aggregation inhibitors, recurrence

Background

The use of antithrombotic medicines in patients who have a history of intracerebral haemorrhage is widely perceived as being contraindicated [Wani *et al.* 2005]. However, many patients with intracerebral haemorrhage have comorbidities for which antithrombotic medicines are indicated. This may take different forms: for example, a patient being treated with warfarin indicated because of a prosthetic heart valve, subsequently sustaining an intracerebral haemorrhage with an international normalized ratio (INR) within the therapeutic range. Alternatively, a patient with a history of primary intracerebral haemorrhage may suffer a myocardial infarction and thus be indicated for antiplatelet medication. Both scenarios represent

a therapeutic dilemma whereby treating infers an increased risk of recurrent intracerebral haemorrhage, but not treating infers an increase of thrombotic complications. Despite this, there is very little guidance for prescribers wishing to know whether it is beneficial to prescribe long-term antithrombotic agents [Scottish Intercollegiate Guidelines Network, 2008; Broderick *et al.* 2007].

Evidence relating to antithrombotic use following intracerebral haemorrhage

Randomized controlled trials

A systematic review of randomized controlled trials revealed very little data addressing the issue of antithrombotic use following

Correspondence to:
Robert Flynn, PhD
Medicines Monitoring Unit,
University of Dundee,
Ninewells Hospital and
Medical School, Dundee
DD1 9SY, UK,
rob@memo.dundee.ac.uk

Alexander Doney, MD, PhD
Centre for Cardiovascular
& Lung Biology, University
of Dundee, Ninewells
Hospital and Medical
School, Dundee, UK

intracerebral haemorrhage [Wardlaw *et al.* 2004]. Only short-term trials were found including two in which patients with presumed cerebral infarction were 'mistakenly' prescribed aspirin with therapy stopped following diagnosis of intracerebral haemorrhage, and one smaller trial in which patients were randomized to receive a short course of heparin following hospitalisation for intracerebral haemorrhage. The authors of this systematic review concluded that the wide confidence intervals ruled out neither modest harm nor moderate benefit.

Observational studies

Antiplatelet medicines. Our systematic review of observational research considered long-term antithrombotic medication following intracerebral haemorrhage [Flynn *et al.* 2010a]. In the case of antiplatelet medicines, the only available evidence we found came from a single observational study by Viswanathan and colleagues [Viswanathan *et al.* 2006]. The risk estimates associated with post-intracerebral haemorrhage antiplatelet use in this small high-quality study had large confidence interval limits (Table 1).

Since the publication of this review, we have conducted our own observational study also addressing this issue [Flynn *et al.* 2010b]. This study used data from the Tayside Stroke Cohort [Flynn *et al.* 2010c], a derived cohort of stroke patients with an accurate diagnosis and good case ascertainment [Flynn *et al.* 2010d] record linked to primary care prescribing data. The data from this study is also shown in Table 1. Although our study and that of Viswanathan and colleagues used different methodologies, the risk estimates for recurrent and secondary events associated with antiplatelet use were similar. However, although these relative risks were similar, the absolute risk of recurrent intracerebral haemorrhage and subsequent ischaemia differed markedly between the two studies, a finding without a clear explanation (see the further comment below). We concluded in our study that there was no conclusive evidence that antiplatelet agents are harmful in patients who had previously experienced an intracerebral haemorrhage, but that further data are required.

Oral anticoagulation. The potential use of oral anticoagulants following intracerebral haemorrhage is a more troubling issue: whilst the need for anticoagulant protection is generally much

greater than the need for antiplatelet therapy [Ohira *et al.* 2006], the risk of haemorrhage is also perceived as being much greater in anticoagulated patients [Wani *et al.* 2005]. Not treating implies a high risk of potentially fatal thromboembolism, whilst treating implies a high risk of recurrent intracerebral haemorrhage. The observational evidence addressing this issue comes from one epidemiological study and six case series with a total of just 42 patients in studies which followed up for at least 6 months [Flynn *et al.* 2010a]. Amongst these there were four recurrent intracerebral bleeds and nine thromboembolic events. We concluded that there was a marked lack of data from both randomized controlled trials and observational studies on which to judge the safety of anticoagulants following intracerebral haemorrhage.

Data taken from the Tayside Stroke Cohort added little to the available numbers for study [Flynn *et al.* 2010b]. Of 417 initial intracerebral haemorrhage long-term survivors, 15 received subsequent oral anticoagulants during a follow up of 43.2 patient years. There were no recurrent intracerebral haemorrhages (rate 0.0 per 1000 patient years; 95% confidence interval [CI] 0.0–85.4), and one subsequent ischaemic event (rate 23.1 per 1000 person years; 95% CI 0.6–128.9).

A decision analysis approach

In the absence of sufficient experimental or observational studies, a decision analysis approach in relation to anticoagulation was published by Eckman and colleagues [Eckman *et al.* 2003]. This has been widely cited and apparently influential in the formulation of practice guidelines [Scottish Intercollegiate Guidelines Network, 2008; Broderick *et al.* 2007] and expert opinions [Aguilar *et al.* 2007] on the use of warfarin following intracerebral haemorrhage. This approach used existing data to infer the likely impact of reintroducing warfarin to a patient with atrial fibrillation who has suffered an intracerebral haemorrhage. The study used a Markov state transition model to analyse decision trees and carry out sensitivity analyses. By considering the balance between the competing risks and the likely outcomes of implementing different treatment strategies, this represented a rational approach to the question 'Can a patient be anticoagulated after intracerebral haemorrhage?'. The aim is to arrive at the optimum decision by considering the possible contingencies arising

Table 1. Comparison of observational studies considering antiplatelet (AP) medicine use following ICH [Flynn *et al.* 2010b].

Study	Viswanathan <i>et al.</i> [2006]	Flynn <i>et al.</i> [2010b]
AP exposed patients (%)	46/207 (22.2)	120/417 (28.8)
Median follow up (months)	19.5	36.5
Secondary ICHs	39	14
Subsequent cerebral infarction or MI	11	40
Hazard ratio	HR (95% CI)	HR (95% CI)
All ICHs	—	1.07 [0.24–4.84]
Lobar ICHs	1.2 [0.4–3.3]	1.52 [0.31–7.39]
Deep ICHs	1.2 [0.1–14.3]	—
Ischaemic events	1.2 [0.3–4.8]	0.72 [0.25–2.02]

AP, antiplatelet; CI, confidence interval; HR, hazard ratio; ICH, intracerebral haemorrhage; MI, myocardial infarction.

when different decisions are made. This is the ‘benefits *versus* risks’ approach that is advocated in some guidelines.

The decision model considered a hypothetical 69-year-old man with newly diagnosed atrial fibrillation and history of intracerebral haemorrhage. The patient’s risks of thrombotic and haemorrhagic outcomes were considered both ‘on’ and ‘off’ warfarin. A range of likely outcomes were considered (for example, the patient suffers long-term morbidity post-intracerebral haemorrhage, patient suffers short-term morbidity post-intracerebral haemorrhage, patients dies following embolus, symptoms resolve, etc.), with the decision-tree structure considering 28 states of health (see Eckman *et al.* [2003] for more details). Much of the required data came from existing published systematic reviews and meta-analyses; however, many data were also extrapolated from previous studies, taken from the authors’ own prospective cohort of 435 consecutive intracerebral haemorrhage patients, or were assumed. To test the impact of assumptions made, a detailed sensitivity analysis of all of the factors was conducted by the authors. These revealed whether the findings of the study held true for a range of values and also gave ‘threshold’ values at which the decision of whether to treat would be altered. Separate consideration was given to intracerebral haemorrhages whose origins were ‘lobar’ (frontal, parietal, temporal or occipital) or ‘deep’ hemispheric (thalamus or basal ganglia) brain regions as these together account for over 80% of all haemorrhagic strokes. The authors concluded for both lobar and deep intracerebral haemorrhages, withholding anticoagulation therapy improved quality-adjusted life expectancy. However, in the case of a deep

intracerebral haemorrhage the balance could be tipped in favour of treatment where there was higher risk of thromboembolic stroke. Of particular interest are the range of sensitivities that were tested for recurrent bleeding for both deep and lobar haemorrhages, from 0 to 0.2 events per year (0 to 200 per 1000 patient years), and threshold rebleeding rate below which anticoagulation would be considered beneficial of 0.014 per year (14 per 1000 patient years). Clearly estimates of recurrent event rates taken from the literature and the nature of other assumptions can have a profound impact on the outcome and validity of the decision analysis methodology. Some specific concerns are discussed below.

Rates of recurrent haemorrhage. A major concern is related to the rate of recurrent intracerebral haemorrhage. Table 2 shows the rate of recurrent intracerebral haemorrhage from a number of published sources. This table was derived from studies identified by Bailey and colleagues [Bailey *et al.* 2001] supplemented with subsequently published studies identified in the course of our systematic review [Flynn *et al.* 2010a]. The rate of recurrent intracerebral haemorrhage in Tayside is 9.7 per 1000 patient years [Flynn *et al.* 2010b], substantially lower than found by Eckman and colleagues [Eckman *et al.* 2003]. The sensitivity analysis for the decision-tree models showed that where the rate of recurrent bleeding was below 14 per 1000 patient years, then the risk:benefit balance favours treatment. The Tayside Stroke Cohort recurrence rate is below this critical limit. As is shown in Table 2, this figure is consistent with other studies published since the systematic review of Bailey and colleagues [Hanger *et al.* 2007; Fogelholm *et al.* 2005].

Table 2. Rates of recurrent intracerebral haemorrhage (ICH) taken from a variety of difference sources.

Study	Location	n	Patient years follow up	Recurrent events	Mean follow up	Recurrent event rate (per 1000 patient years) (95% CI)
All ICHs						
Bailey <i>et al.</i> [2009]	Various	1880	6326	147	3.4	23.2 [19.6–27.3]
Vermeer <i>et al.</i> [2002]	Netherlands	243	1337	30	5.5	22.4 [15.1–32.0]
Fogelholmet <i>et al.</i> [2005]*	Finland	203	1624	23	8.0	14.2 [9.0–21.3]
Viswanathan <i>et al.</i> [2006]	Boston, US	207	336	39	1.6	115.9 [82.4–158.5]
Hanger <i>et al.</i> [2007]	Christchurch, NZ	453	1583	19	3.5	12.0 [7.2–18.7]
Flynn <i>et al.</i> [2010b]	Tayside, UK	417	1510	14	3.6	9.7 [5.3–16.3]
Lobar ICH						
O'Donnell <i>et al.</i> [2000]	Boston, US	71	141	19	2.0	134.4 [80.9–209.8]
Bailey <i>et al.</i> [2009]	Various	192	669	30	3.5	44.8 [30.3–64.0]
Viswanathan <i>et al.</i> [2006]*	Boston, US	127	206	36	1.6	174.4 [122.2–241.5]
Flynn <i>et al.</i> [2010b]	Tayside, UK	235	801	9	3.4	11.2 [5.1–21.3]
Deep ICH						
Bailey <i>et al.</i> [2009]	Various	823	2474	52	3.0	21.0 [15.7–27.6]
Viswanathan <i>et al.</i> [2006]*	Boston, US	80	130	3	1.6	23.1 [4.8–67.4]
Flynn <i>et al.</i> [2010b]	Tayside, UK	139	469	3	3.4	6.4 [1.32–18.7]

*Assumed rates based on a total follow-up rate derived from median or presumed mean follow-up times.
CI, confidence interval; ICH, intracerebral haemorrhage.

The factors underlying the wide variation in recurrent events rates observed between different populations are not clear. This variation may be attributed to case ascertainment bias with our cohort of patients being defined by hospital admissions or deaths, and therefore comprising cases of symptomatic intracerebral haemorrhage, whilst other studies may have employed proactive follow-up imaging likely to detect asymptomatic bleeds [Wani *et al.* 2005]. As has previously been pointed out, the research group responsible for both the paper by Eckman and colleagues and the antiplatelet use following intracerebral haemorrhage study by Viswanathan and colleagues [Viswanathan *et al.* 2006] are based at the same tertiary referral centre, which has a special research interest in cerebral amyloid angiopathy [Alberts, 2006]. This condition increases risk of recurrent haemorrhage, and it could be that their study cohort is overrepresented by such patients. Differences may also be due to the different background population, with ours being a truly population-based study, whilst others have been based in secondary care referral centres. Alternatively there may be an actual difference in the underlying rates of recurrent intracerebral haemorrhage in different populations and different localities: it is well established that there is a substantial variation in the rate of first intracerebral haemorrhage amongst different ethnic groups, with higher incidences and mortality amongst non-White ethnic groups [Rosamond *et al.* 2007],

and intracerebral haemorrhages accounting for a higher proportion of all strokes in Asian populations [Sacco *et al.* 1994].

Finally, other clinical factors may be involved. Blood pressure is the principal modifiable risk factor for intracerebral haemorrhage and blood pressure management varies between localities and across time [Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, and National High Blood Pressure Eradication Program Coordinating Committee, 1997; Colhoun *et al.* 1998]. This could have an impact on rates of recurrence in populations with different levels or management of hypertension.

Other issues with the decision analysis approach. Other concerns regarding the decision analysis approach have been raised [Stollberger and Finsterer, 2003]. Secondary causes of intracerebral haemorrhage are not accounted for, such as vascular malformations, vasculitis, amyloid angiopathy, haemorrhages secondary to cerebral infarctions and traumas. Where such secondary causes have been identified and rectified, it would be quite rational to assume that the underlying problem no longer exists and that treatment with either oral anticoagulants or antiplatelet medicines could be started with impunity. It was also assumed that the site of the index event was predictive of the site of subsequent event. This also

has been questioned [Stollberger and Finsterer, 2003], with one study of 243 patients finding that the site of initial event was not predictive of recurrence [Vermeer *et al.* 2002]. Further data are required to address this issue, particularly in view of the fact that differences in recurrence rate seem to be much greater between *geographic* regions than between *brain* regions (see Table 2). Similarly, little consideration was given in the decision analysis to the effect of other risk factors for thromboembolism. Factors such as hypertension, diabetes, hypercholesterolaemia and history of stroke or transient ischaemic attack could significantly impact on secondary events of this nature [Stollberger and Finsterer, 2003]. The decision-tree analysis made no account of these assuming a fixed rate of thromboembolism of 4.5% per year; however, in practice this could vary from 1.0% to 8.9% depending on the presence and management of these risk factors [Stollberger and Finsterer, 2003]. The results of the sensitivity analysis suggested that this could be an important consideration with treatment being preferred where the annual risk was above 7%. The analysis therefore fails to take into account the extent to which effective management of these additional risk factors impacts on thromboembolism. Given that hypertension is a risk factor for both intracerebral haemorrhage and cerebral infarction, it is hard to judge exactly how this would affect the risk-benefit balance. As can be seen in Table 1, for patients in Tayside, following an initial intracerebral haemorrhage there is a greater risk of cerebral infarction and myocardial infarction than recurrent intracranial haemorrhage.

In general, these criticisms are based around the fact that intracerebral haemorrhage is a multifactorial disease which is, through necessity, represented in simplistic terms in the analysis used. However, because of these criticisms and the uncertainty relating to the rates or recurrent intracerebral haemorrhage, the conclusions of the decision-tree analysis by Eckman and colleagues are questionable. This, however, does not invalidate the approach used. As has been stated above, the approach used by Eckman and colleagues is intuitive and represents a rationalisation of the process that is undertaken when physicians follow the much offered, but not precisely defined, advice of balancing the 'risks' against the 'benefits' of treatment [Broderick *et al.* 2007].

It is clear from the literature that there is a heterogeneity of expert opinion as to how such dilemmas should be addressed [Aguilar *et al.* 2007; Estol and Kase, 2003]. The underlying issue is that there is a marked paucity of randomized and observational data addressing the safety of antithrombotic medication following intracerebral haemorrhage and that there are issues with the intuitive inferred decision analysis approach.

Challenges when researching intracerebral haemorrhage

There are a number of factors that conspire against researchers addressing this particular issue. In our cohort a large number (52.4%) of the 979 patients with radiologically confirmed intracerebral haemorrhage did not survive to discharge [Flynn *et al.* 2010c]. Of the 417 patients who did survive to discharge, 5.9% were deceased within 3 months and a further 8.4% within 6 months. A smaller proportion of patients are either prematurely censored or suffer events which would bring about the completion of their follow up within a short period of time (5.5% within 3 months, 8.6% within 6 months). Such an attrition rate reduces the opportunity for patient exposure to antiplatelet medicines. This is even more true of the less widely used anticoagulant drug, warfarin. Patients with cogent indications for warfarin therapy will likely have been receiving it prior to the index event. These patients, already anticoagulated on admission, will have a high rate of short-term (predischARGE) mortality [Sjalander *et al.* 2003], further depleting the pool of potential study subjects. The resulting cohort is then unlikely to be exposed to the medicines of interest because physicians are often reluctant to prescribe antiplatelet medication and warfarin to those patients that do survive [Aguilar *et al.* 2007]. The net result is that the number of surviving intracerebral haemorrhage patients exposed to antiplatelet medication is small and the number receiving anticoagulation is even smaller. To fully address this area of outstanding uncertainty using observational data, multiple data are required from multiple sources in multiple regions using different methodologies. Clearly the gold standard approach would be a well-designed randomized study, however obtaining ethical approval for such a study is likely to be challenging, especially without clear evidence of safety from observational studies. If this is forthcoming, the scarcity of suitable subjects combined with the practical challenges of consenting and following up such patients

means it will be a long time before this question is adequately addressed in a randomized study, if ever. Approaches that balance the benefits and risk of therapy may need to be developed further.

Further development in the understanding of the pathophysiology of cerebral haemorrhage is also required to inform decision making. For example, there has been recent interest in the ability to detect cerebral microbleeds with associated efforts to determine their clinical implications. The concern is that the use of antithrombotic agents could be predictive of cerebral microbleeds, and that this in turn could increase risk of overt cerebral haemorrhage (with or without the presence of antithrombotics). Currently, there is a lack of consistent evidence as to whether the presence of cerebral microbleeds does predispose individuals to intracerebral haemorrhage [Cordonnier, 2011]. Some studies have found that lobar microbleeds are associated with subsequent intracerebral haemorrhage whilst others have found a greater risk of subsequent cerebral infarction [Thijs *et al.* 2010]. Further well-designed studies are required to address this issue. A previous reviewer concluded that observed associations between antithrombotic drugs and the presence of microbleeds are likely to be confounded, and that there is currently no evidence to contraindicate the use of antithrombotics in patient with microbleeds [Cordonnier, 2011].

Conclusions

Until there is better evidence to guide prescribers, should patients with a history of intracerebral haemorrhage be given antithrombotic medicines? Not if they have unaddressed risk factors, for example uncontrolled hypertension. Not if they have anything other than an absolutely cogent indication for antiplatelet treatment (for example, a history of myocardial infarction) or anticoagulation (for example, the presence of a prosthetic heart valve). However, what is the advice in respect of a patient with such indications for whom other risk factors have been controlled? Our opinion, based on the limited information available at this time and on the knowledge gained whilst researching this issue, is that it would not be unreasonable to introduce such agents following recovery from the initial haemorrhage. In the meantime, the current paucity of evidence to guide those faced with this therapeutic dilemma seems likely to continue for some time. Prescribers will have to continue

to balance the 'benefits' of treatment against the 'risks'.

Funding

Robert Flynn's fellowship was funded by Chief Scientist Office, Scottish Executive Health Department (fellowship grant number CZF/1/41).

Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

References

- Aguilar, M.I., Hart, R.G., Kase, C.S., Freeman, W.D., Hoeben, B.J., Garcia, R.C. *et al.* (2007) Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. *Mayo Clinic Proc* 82: 82–92.
- Alberts, M.J. (2006) Do antiplatelet agents increase the risk of recurrent intracerebral hemorrhage? *Nat Clin Pract Neurol* 2: 480–481.
- Bailey, R.D., Hart, R.G., Benavente, O. and Pearce, L.A. (2001) Recurrent brain hemorrhage is more frequent than ischemic stroke after intracranial hemorrhage. *Neurology* 56: 773–777.
- Broderick, J., Connolly, S., Feldmann, E., Hanley, D., Kase, C., Krieger, D. *et al.* (2007) Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults. 2007 Update. Guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Stroke* 38: 2001–2023.
- Colhoun, H.M., Dong, W. and Poulter, N.R. (1998) Blood pressure screening, management and control in England: results from the health survey for England 1994. *J Hypertension* 16: 747–752.
- Cordonnier, C. (2011) Brain microbleeds: more evidence, but still a clinical dilemma. *Curr Opin Neurol* 24: 69–74.
- Eckman, M.H., Rosand, J., Knudsen, K.A., Singer, D.E. and Greenberg, S.M. (2003) Can patients be anticoagulated after intracerebral hemorrhage? A decision analysis. *Stroke* 34: 1710–1716.
- Estol, C.J. and Kase, C.S. (2003) Need for continued use of anticoagulants after intracerebral hemorrhage. *Curr Treatment Options Cardiovasc Med* 5: 201–209.
- Flynn, R.W., MacDonald, T.M., Murray, G.D. and Doney, A.S. (2010a) Systematic review of observational research studying the long-term use of antithrombotic medicines following intracerebral hemorrhage. *Cardiovasc Therapeut* 28: 177–184.

- Flynn, R.W., MacDonald, T.M., Murray, G.D., Ferguson, C., Shah, K. and Doney, A.S. (2010c) The Tayside Stroke Cohort: exploiting advanced regional medical informatics to create a region-wide database for studying the pharmacoepidemiology of stroke. *Pharmacoepidemiol Drug Safety* 19: 737–744.
- Flynn, R.W., MacDonald, T.M., Murray, G.D., MacWalter, R.S. and Doney, A.S. (2010b) Prescribing antiplatelet medicine and subsequent events after intracerebral hemorrhage. *Stroke* 41: 2606–2611.
- Flynn, R.W., Macdonald, T.M., Schembri, N., Murray, G.D. and Doney, A.S. (2010d) Automated data capture from free-text radiology reports to enhance accuracy of hospital inpatient stroke codes. *Pharmacoepidemiol Drug Safety* 19: 843–847.
- Fogelholm, R., Murros, K., Rissanen, A. and Avikainen, S. (2005) Long term survival after primary intracerebral haemorrhage: a retrospective population based study. *J Neurol Neurosurg Psychiatry* 76: 1534–1538.
- Hanger, H.C., Wilkinson, T.J., Fayed-Iskander, N. and Sainsbury, R. (2007) The risk of recurrent stroke after intracerebral haemorrhage. *J Neurol Neurosurg Psychiatry* 78: 836–840.
- Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure, National High Blood Pressure Eradication Program Coordinating Committee. (1997) The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Internal Med* 157: 2413–2446.
- O'Donnell, H.C., Rosand, J., Knudsen, K.A., Furie, K.L., Segal, A.Z., Chiu, R.I. *et al.* (2000) Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. *N Engl J Med* 342: 240–245.
- Ohira, T., Shahar, E., Chambless, L.E., Rosamond, W.D., Mosley Jr, T.H. and Folsom, A.R. (2006) Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities Study. *Stroke* 37: 2493–2498.
- Rosamond, W., Flegal, K., Friday, G., Furie, K., Go, A., Greenlund, K. *et al.* (2007) Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 115: e69–e171.
- Sacco, R.L., Mayer, S.A. and Feldmann, E. (1994) Epidemiology of intracerebral hemorrhage. In *Intracerebral Hemorrhage*, Futura Publishing Company: New York, pp. 3–23.
- Scottish Intercollegiate Guidelines Network. (2008) SIGN 108. Management of Patients with Stroke or TIA: Assessment, Investigation, Immediate Management and Secondary Prevention. A National Clinical Guideline, Scottish Intercollegiate Guidelines Network: Edinburgh.
- Sjalander, A., Engstrom, G., Berntorp, E. and Svensson, P. (2003) Risk of haemorrhagic stroke in patients with oral anticoagulation compared with the general population. *J Internal Med* 254: 434–438.
- Stollberger, C. and Finsterer, J. (2003) Antithrombotic therapy after cerebral hemorrhages. *Stroke* 34: e217–e218.
- Thijs, V., Lemmens, R., Schoofs, C., Gerner, A., Van Damme, P., Schrooten, M. *et al.* (2010) Microbleeds and the risk of recurrent stroke. *Stroke* 41: 2005–2009.
- Vermeer, S.E., Algra, A., Franke, C.L., Koudstaal, P.J. and Rinkel, G.J. (2002) Long-term prognosis after recovery from primary intracerebral hemorrhage. *Neurology* 59: 205–209.
- Viswanathan, A., Rakich, S.M., Engel, C., Snider, R., Rosand, J., Greenberg, S.M. *et al.* (2006) Antiplatelet use after intracerebral hemorrhage. *Neurology* 66: 206–209.
- Wani, M., Nga, E. and Navaratnasingham, R. (2005) Should a patient with primary intracerebral haemorrhage receive antiplatelet or anticoagulant therapy? *Br Med J* 331: 439–442.
- Wardlaw, J.M., Keir, S.L., Seymour, J., Lewis, S., Sandercock, P.A., Dennis, M.S. *et al.* (2004) What is the best imaging strategy for acute stroke? *Health Technol Assessm*, 8(1).

Visit SAGE journals online
<http://taw.sagepub.com>

SAGE JOURNALS
 Online