Management of intracranial bleeding in anticoagulated patients

Intracranial haemorrhage is a life-threatening complication of anticoagulation. When the anticoagulation is for a mechanical heart valve the risks of further bleeding on warfarin need to be balanced against the risks of thromboembolism from an unprotected valve.

Since the development of the first aortic valve in 1960 by Harken the clinical dilemma of what to do with patients who suffer an intracranial bleed while on warfarin for a mechanical valve has existed. There are no clear guidelines to follow because of the heterogeneous nature of heart valve replacements, ranging from the thrombogenic ball and cage valve in the mitral region to the less thrombogenic third generation tilting disc valve in the aortic region, and the heterogeneous nature of intracranial bleeds.

The aim of this article is to collate the available data to help clinicians make an informed decision about when to stop and restart anticoagulation. To conduct this review Medline and EMBASE were searched from 1998 to 2008 using the search terms 'Heart valve prosthesis, cerebral or brain haemorrhage, anticoagulants or warfarin'. The term intracranial haemorrhage includes subdural haematomas and subarachnoid haemorrhage and intracerebral haemorrhage. Intracerebral haemorrhage is also divided into lobar intracerebral haemorrhage, which refers to frontal, parietal, temporal or occipital haemorrhage, and deep hemispheric intracerebral haemorrhage which includes thalamic and basal ganglia regions, as these are the two most common sites for haemorrhagic strokes. Much of the data are for intracerebral haemorrhage alone.

Table 1. Rates of intracranial haemorrhage during long-term anticoagulation with warfarin

Source	Patients	INR	Intracranial haemorrhage (%/year)
Fihn et al (1993)	Atrial fibrillation (n=1236)	Control	0.1
Fihn et al (1993)	Atrial fibrillation (n=1225)	< 3.0	0.3
Stroke Prevention in Atrial Fibrillation Investigators (1994)	Atrial fibrillation (n=1236)	2.0–4.5	0.9
	≤75 years (n=358)		0.5
	>75 years (n=197)		1.8
Ezekowitz and Levine (1999)	Atrial fibrillation (n=523)	2.0–3.0	0.5
Turpie et al (1993)	Prosthetic valves (n=184)	3.0–4.5	1.4
Pengo et al (1997)	Prosthetic valves (n=104)	2.5–3.5	0.3

INR = international normalized ratio. Adapted from Levine et al (2001)

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The effect of anticoagulation on an intracranial haemorrhage

The annual risk of a spontaneous intracranial haemorrhage is 0.1% a year. Anticoagulation increases this risk 8–10 times to an annual risk of around 1% (*Table 1*) and carries a higher mortality than spontaneously occurring haemorrhages; the 3-month mortality was 25.8% for patients not taking warfarin compared to 52% for those on warfarin (Rosand et al, 2004).

The short-term mortality for intracerebral haemorrhage is strongly related to the level of consciousness on presentation, as participants unconscious on arrival have a 96% mortality (Sjöblom et al, 2001). The 30-day (in-hospital) mortality is dependent on the volume of haematoma measured on computed tomography scan, and location of the haemorrhage in the posterior fossa or extension of the haemorrhage into the ventricular system are also poor prognostic factors (Rådberg et al, 1991; Broderick et al, 1993; Berwaerts et al 2000). The intensity of anticoagulation independently predicts 3-month mortality for intracerebral haemorrhage, and the risk rises further as the international normalized ratio (INR) increases (Rosand et al, 2004). Additional risk factors for intracerebral haemorrhage are shown in *Table 2*.

Haematoma expansion occurs in up to 35% of patients with spontaneous intracerebral haemorrhage within the first 3 hours, and early haematoma growth is associated with a poor outcome (Huttner et al, 2006). Anticoagulated patients have a higher rate of early clinical deterioration in the first 24–48 hours of 47% compared to 33%, and although the cause of the deterioration could not be assessed as recurrent computed tomography scans were not performed, the most likely reason was haematoma enlargement (Sjöblom et al, 2001). Some, although not all, studies support a link between increased haematoma volume at presentation and anticoagulation (Rådberg et al, 1991; Berwaerts et al, 2000). The link between the intensity of anticoagulation and clinical outcome supports the rationale for the rapid reversal of warfarin.

Reversing anticoagulation

The British Society of Haematology recommends administration of factor concentrates in preference to fresh frozen plasma to rapidly reverse the effects of anticoagulation in major bleeding, and administration of intravenous vitamin K to sustain the effect (Baglin et al, 2005). The amounts of vitamin K-dependent coagulation factors vary in each unit of fresh frozen plasma, so the efficacy of fresh frozen plasma in reversing INR is unpredictable and incomplete. In non-randomized cases of intracerebral haemorrhage where factor concentrate has been compared to fresh frozen plasma, factor concentrate was associated with a lower incidence of haematoma enlargement (Yasaka et al, 2003). Patients with INR levels completely reversed after 2 hours did not fare worse on fresh frozen plasma compared to prothrombin complex concentrates, suggesting it is the time taken to achieve sustained reversal of the anticoagulation that is important (Huttner et al, 2006).

The effect of stopping anticoagulation on mechanical heart valves

Patients with mechanical heart valves are anticoagulated to prevent the risk of thrombosis forming on the artificial valve and subsequent embolization. Unfortunately little data exist on the risks and benefits of oral anticoagulation, and the reported risks vary considerably. The most comprehensive review is still that of Cannegieter et al (1994) which reviewed 13 088 patients over 53 647 patient-years, and found the annual risks of embolization to be 4% off anticoagulation, reduced to 2% with antiplatelet therapy, and 1% with anticoagulation. This demonstrates the risk:benefit of anticoagulation, with 1.4% risk of major bleeding *vs* a 4% risk of thromboembolism (*Table 3*).

However, the risk can be further stratified by including information such as the position, number and type of valves, and considering traditional risk factors including atrial fibrillation, left ventricular dysfunction and a history of thromboembolism. The old caged ball valves such as Starr–Edwards are more thrombogenic than the tilting disc valves, e.g. Björk–Shiley, which are more thrombogenic than the bileaflet valves, e.g. St Jude, with a relative risk ratio of total embolism of 2:1.4:1 respectively while on anticoagulation. Valves in the mitral position have a 2.4 increased relative risk of total embolism compared to those in the aortic position (Cannegieter et al, 1994).

The risk of valve thrombosis and major embolism is therefore often overestimated. A rate of 1.8% and 4% a year off anticoagulation would confer a daily risk of valve thrombosis and major embolism of 0.016% ((1.8+4)/365) and only 0.1% per week.

Table 2. Risk factors for 3-month mortality

Patient characteristics		Odds ratio (95% confidence interval)
Age >70 years		2.4 (1.4–4.0)
Male sex		1.4 (0.9–2.2)
Coronary artery disease		1.2 (0.7–2.0)
Diabetes mellitus		1.8 (1.1–3.3)
Antiplatelet agent		1.1 (0.6–1.7)
Lobar intracranial haemorrhage		1.3 (0.8–2.1)
Warfarin, INR	All INRs	2.2 (1.3–3.8)
	< 2.0	1.5 (0.6–3.7)
	2.0–3.0	2.0 (1.0–4.1)
	>3.0	3.7 (1.6–8.4)

INR = international normalized ratio. Adapted from Rosand et al (2004)

Restarting anticoagulation

Once a patient has survived an intracranial bleed, it is unclear at what stage the risks of further bleeding from resuming anticoagulation are outweighed by risks of preventing thromboembolism. There are small series of patients with metallic heart valves remaining off warfarin long term (Anderson and Alstrup, 1992). A history of an intracerebral haemorrhage is a strong risk factor for a repeat intracerebral haemorrhage, although the chances of recurrence depend on the underlying aetiology and published reports of recurrence vary significantly for lobar intracerebral haemorrhage. The annual risk of rebleeding is 2.1% for deep hemispheric intracerebral haemorrhage and 0.03% for subdural haematoma, but for lobar intracerebral haemorrhage it varied from 4.4% to 15% (O'Donnell et al, 2000; Bailey et al, 2001; Vermeer et al, 2002). Assuming an annual risk of rebleeding at 2–3% and a 5.8% risk of thromboembolism from a mechanical valve without anticoagulation it is beneficial to restart anticoagulation. However, it is not clear if anticoagulation after an intracranial haemorrhage confers an additional risk – in one series of 21 patients restarted on warfarin it increased the incidence of recurrent intracerebral haemorrhage threefold (Vermeer et al, 2002).

There is no consensus on when to reintroduce warfarin. In a case series of 13 patients with 2 years' follow up, warfarin was reintroduced after a median of 7 days

Table 3. Incidence of valve thrombosis, major embolism and total embolism per 100 patient years (95% confidence intervals)

	Valve thrombosis	Major embolism*	Total embolism†
No anticoagulation	1.8 (0.9–3.0)	4.0 (2.9–5.2)	8.6 (7.0–10.4)
Antiplatelet treatment	1.6 (1.0–2.5)	2.2 (1.4–3.1)	8.2 (6.6–10.0)
Coumarin	0.2 (0.2–0.2)	1.0 (1.0–1.1)	1.8 (1.7–1.9)

Adapted from Cannegieter et al (1994). *Major embolism (causing death, residual neurological defect or peripheral ischaemia requiring surgery); † total embolism (valve thrombosis, major and minor embolism – transient cerebral or peripheral ischaemia)

(INR<2.0 for 0–19 days). The target INR was lowered in nine patients, and there was only one case of recurrent (non-fatal) haemorrhage (Butler and Tait, 1998). Other series have withheld warfarin for 1–2 weeks without complication, and for most patients this should be sufficient to observe a parenchymal haematoma, coil or clip an aneurysm or evacuate an acute subdural haematoma (Wijdicks et al, 1998; Ananthasubramaniam et al, 2001).

When warfarin is reintroduced, at what INR should the patient be maintained? Original guidelines for anticoagulation were based on retrospective studies on first and second generation mechanical heart valves and may have been overcautious setting a high INR. The GELIA study compared three regimens of anticoagulation for the St. Jude valve in both aortic and mitral regions, with an INR 3–4.5, INR 2.5–4 or INR 2–3.5, and found a linearized incidence of moderate or severe thromboembolic events at 0.43% per patient year and a severe bleeding risk of 0.56% per patient year (Hering et al, 2005). There was no significant difference in bleeding or thromboembolic events between the different INR regimens, although in this study 90% of all INR measurements were in the therapeutic range, whereas many of the cases of intracerebral haemorrhage occurred when the INR was well outside the prescribed range. There is no role for the use of aspirin in isolation as it does not significantly reduce the rate of thromboembolism, and trials have only used it in conjunction with warfarin as an additional agent rather than with a sub-therapeutic INR.

Conclusions

Intracerebral bleeding on anticoagulation is a life-threatening complication for which rapid reversal of anticoagulation is required. If possible the cause of the bleeding should be identified and corrected, e.g. coiling an aneurysm. The cautious reintroduction of anticoagulation to protect a mechanical heart valve is usually considered after 1–2 weeks. **BJHM**

Conflict of interest: none.

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KEY POINTS

- The 3-month mortality from an intracranial haemorrhage is 52% for patients taking warfarin compared to 25% mortality off warfarin, with mortality linked to the level of anticoagulation.
- Rapid reversal of warfarin is recommended with factor concentrates, as the daily risk of thrombosis and embolism from an un-anticoagulated valve is low.
- The patients will need to be managed with neurosurgical and cardiology input, and the reintroduction of anticoagulation is usually considered after 1–2 weeks.