Oral anticoagulant therapy in patients with mechanical heart valve and intracranial haemorrhage: a systematic review

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CRD summary
The optimal management of oral anticoagulant therapy after intracranial bleeding secondary to vitamin K antagonist use in patients with a mechanical heart valve was investigated. The authors concluded that restarting or stopping anticoagulant therapy for a few days appeared to be safe, but the quality of evidence was low. The review was generally well conducted and the authors' conclusions appear appropriate.

Authors' objectives
To investigate the optimal management of oral anticoagulant therapy after intracranial bleeding secondary to the use of vitamin K antagonists in patients with a mechanical heart valve.

Searching
MEDLINE and EMBASE were searched (to January 2008) for studies published in English, Italian, French or Spanish. Search terms were reported. Reference lists of all studies included in the review were also searched for additional studies.

Study selection
Randomised controlled trials, observational cohort studies, case series and case reports of patients with a mechanical heart valve and intracranial haemorrhage during anticoagulant therapy were eligible for inclusion. Re-starting of anticoagulant therapy and clinical follow-up had to be described. Studies in which intracranial bleeding occurred after valve replacement therapy were excluded.

In the included studies, patients' ages ranged from 60 to 69 years (mean) in observational cohort studies and from 11 to 70 years in the case reports. Mitral and/or aortic valve sites were included. The observational cohort studies reported subdural, intracerebral, subarachnoid and intraspinal haemorrhage sites; INR (International Normalised Ratio) varied (not reported in case reports). Outcomes reported were time of oral anticoagulant restarting, cerebral ischaemic and haemorrhagic events, and deaths. The time point at which antithrombotic therapy was restarted varied. The antithrombotic therapies used were warfarin, enoxaparin, nadroparin, heparin and dipyridamole where reported.

Two reviewers independently performed study selection and disagreements resolved by a third reviewer.

Assessment of study quality
Methodological quality of observational studies was assessed in terms of study design (prospective or retrospective), patient recruitment (consecutive or non-consecutive), duration of follow-up (more or less than three months), number of patients lost to follow-up (less than 5%, 5-20%, more than 20%) and whether the study was mono- or multi-centric. Each of these items was assigned 1 point; studies given 5 points were described as high quality, 4 points as medium quality, and 3 or less points as low quality.

Quality was assessed independently by two reviewers, and disagreements resolved by a third.

Data extraction
Incidence rates (number and percentage) were extracted independently by two reviewers.

Methods of synthesis
Continuous variables were summarised using means and medians (with corresponding standard deviations or ranges). Studies were synthesised narratively by study design.
Results of the review
Six observational cohort studies (n=120 patients) and thirteen case reports (n=18 patients) were included in the review. The observational cohort studies were all reported to be low quality, only one was prospective.

Observational cohort studies: Anticoagulation therapy was stopped early after development of cerebral haemorrhage in all studies and anticoagulation was restarted at a variety of time points ranging from two days to three months. In one study, intravenous heparin was given when INR (international normalised ratio) dropped below 1.5. In two studies, some patients received heparin therapy before oral anticoagulation therapy was started. Six adverse events occurred after re-starting anticoagulation (between five days and three years after re-starting anticoagulation): four ischaemic strokes and two recurrent cerebral haemorrhages (one fatal). Forty-three patients died (most within 48 hours of the index event).

Case reports: Anticoagulation therapy was restarted within four days to eight weeks and in many cases the first therapeutic intervention after cerebral bleeding was heparin or antiplatelet drugs. Two patients had a recurrent haemorrhagic event (one fatal). No cerebral ischaemic events were reported. Overall there were three deaths; one acute myocardial infarction, one cerebral haemorrhage and one with an unreported reason.

Authors' conclusions
Restarting oral anticoagulant therapy after a few days and stopping anticoagulant therapy for a few days appeared to be safe, but the quality of available evidence was low.

CRD commentary
The research question was supported by inclusion criteria for participants, study design and intervention. Only published studies in four languages were sought, so the possibility of publication and language bias could not be ruled out. Study selection, data extraction and validity assessment were performed in duplicate, reducing the possibility of reviewer error and bias. The validity of observational studies appeared to have been assessed using relevant criteria. Narrative synthesis appeared appropriate given the heterogeneity of the included studies. The review was generally well conducted and, taking into consideration the limitations of the available evidence, the authors' cautious conclusions appear appropriate.

Implications of the review for practice and research
 Practice: The authors did not state any implications for practice.
 Research: The authors stated that well-designed, multicentre, prospective cohort studies are warranted to provide better quality evidence.

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Record Status
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