

Review Article

Oral anticoagulant therapy in patients with mechanical heart valve and intracranial haemorrhage

A systematic review

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Summary

Optimal timing for restarting anticoagulant therapy after intracranial bleeding is a critical issue. The purpose of this systematic review is to summarize published studies on the management of oral anticoagulant therapy after intracranial bleeding secondary to the use of vitamin K antagonists in patients with a mechanical heart valve. A computer-assisted search of the MEDLINE and EMBASE electronic databases till January 2008 was performed. Two investigators independently performed study selection and completed a predefined quality assessment and data extraction form. Main inclusion criterion was the enrolment of patients with a mechanical heart valve and intracranial haemorrhage during oral anticoagulant treatment. Any randomised controlled trial, observational cohort study, case series and reports was included. No randomised controlled trials were identified. Six ob-

servational cohort studies were included in the final analysis. All studies were of low quality. A total of 120 patients were enrolled. Anticoagulation was restarted within a broad time range (2 days to 3 months). Four ischaemic strokes and two recurrent cerebral haemorrhages occurred after anticoagulation was restarted after a mean follow-up of 7.9 months. Eighteen patients were described in the selected case reports. Anticoagulant therapy was restarted within four days to eight weeks. Two patients had a recurrent haemorrhagic event, and no ischaemic events were reported. In conclusion, restarting oral anticoagulant therapy few days and, indirectly, stopping anticoagulant therapy for a few days (even for 7–14 days) after the occurrence of cerebral haemorrhage are both safe. However, well-designed studies are strongly recommended to provide better evidence.

Keywords

Anticoagulant, cerebral bleeding, mechanical heart valve

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Introduction

Intracranial haemorrhage is the major fatal complication of oral anticoagulant therapy, with an estimated incidence ranging from 0.3–0.7% per year (1, 2). In the absence of antithrombotic treatment, patients with mechanical heart valves are exposed to a very high thromboembolic risk: the cumulative incidence of valve thrombosis, major and minor embolism in patients with a bileaflet valve ranges between 8.6 and 22% per year (3, 4). Thus, the optimal timing for restarting anticoagulant therapy after intracranial bleeding in patients with a mechanical heart valve is a critical issue: on the one hand, prolonged withdrawal of anticoagulants may expose patients to a high risk of systemic embolisation and valve thrombosis; on the other hand, early restarting of anticoagulation may enlarge the haematoma and predispose to bleeding recurrence.

The aim of this review is to systematically summarize all published literature on the optimal management of oral anticoagulant therapy after intracranial bleeding secondary to the use of vitamin K antagonists (VKA) in patients with a mechanical heart valve.

Methods

Study identification

A computer-assisted search of the MEDLINE and EMBASE electronic databases up to January 2008 was performed to identify published studies that evaluated the restarting of anticoagulant therapy after intracranial haemorrhage secondary to treatment with VKA in patients with a mechanical heart valve.

The following terms (MeSH and Textwords) were used for MEDLINE: Mitral Valve Prosthesis, Aortic Valve Prosthesis,

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Heart Valve Prosthesis, Mechanical Heart Valve, Valve Prosthesis, Phenprocoumon, Acenocoumarol, Warfarin, Anticoagulants, Dicumarol, 4-Hydroxycoumarins, Sintrom, Coumadin, Anticoagulation, Intracranial Hemorrhages, Cerebral Hemorrhage, Intracranial Hemorrhage, Subarachnoid Hemorrhage, Subdural Hematoma, Intracranial Hematoma, Intracranial Bleeding, Cerebral Bleeding, Basal Ganglia Hemorrhage; and the following terms (EMTREE and Textwords) were used for EMBASE: Anticoagulation, Anticoagulant Therapy, Anticoagulant Agent, Warfarin, Coumadin, Coumarin Anticoagulant, Coumarin Derivative, Acenocoumarol, Phenprocoumon, Sintrom, Heart Valve Prosthesis, Aortic Valve Prosthesis, Mitral Valve Prosthesis, Mechanical Heart Prosthesis, Brain Hemorrhage, Brain Hematoma, Subarachnoid Hemorrhage; Subdural Hematoma; Basal Ganglia Hemorrhage; Cerebral Bleeding; Intracranial Bleeding.

No language restrictions were initially applied to the search strategy. Reference lists of all studies included in the present systematic review were manually searched for additional potentially eligible studies.

Study selection

Two investigators (ER and EM) independently performed study selection. Main inclusion criterion was the enrolment of patients with a mechanical heart valve and intracranial haemorrhage during oral anticoagulant treatment, in which restarting of anticoagulant therapy and clinical follow-up were described. If intracranial bleeding occurred after valve replacement surgery, studies were excluded. The following study designs were allowed: randomised controlled trial, observational cohort study, case series and case reports. Reviews, editorials and guidelines were excluded. Articles were subsequently also excluded if published in a language different from English, Italian, French, or Spanish.

The two investigators independently reviewed titles and/or abstracts obtained from the initial search to determine whether the inclusion criterion was satisfied. The full text of the study was retrieved when additional information was necessary. Disagreement between reviewers was solved through discussion. In case of persisting disagreement, the opinion of a third reviewer (AS) was requested. When multiple papers for a single study had been published, we decided to use the latest publication and to supplement it, if necessary, with data from the earlier publications.

Quality assessment

The same two unmasked investigators independently completed a predefined quality assessment form. Disagreement was solved by consensus and by the opinion of a third reviewer (AS), if necessary. For randomised controlled trials (RCTs), we planned quality assessment by means of a validated scale (5). For observational cohort studies, although the use of quality scoring systems or quality scales is controversial (6) study quality was assessed by the following items: type of study (prospective or retrospective); patient selection (consecutive patients without potential bias of selection); duration of follow up (more or less than 3 months); number of patients lost to follow-up (less than 5% of patients, between 5% and 20%, more than 20%); monocentric or multicentric study.

For each fulfilled item, one point was given. A scoring system was adapted to identify three quality categories as follows: a total of five points defined high quality studies; 4 points defined medium quality studies; ≤ 3 points defined low-quality studies.

Local ethics committee approval and total number of cases were also ascertained as additional quality items. The quality assessment form is available upon request from the authors.

No attempts to mask for authorship, journal name or institution were made.

Data extraction

The same two reviewers independently completed a predefined data extraction form. The following characteristics were collected: 1) total number of enrolled cases; 2) type of mechanical heart valves; 3) target therapeutic range of the International Normalized Ratio (INR); 4) INR value at the time of haemorrhage; 5) haemorrhage site; 6) interventional procedures to manage haemorrhage; 7) time of anticoagulation restarting; 8) use of heparin bridging therapy; 9) number of recurrent haemorrhagic events; 10) number of ischaemic events; 11) number of deaths

Statistical analysis

Data for qualitative variables were presented as incidence rates (N, number and percent). Continuous variables are summarised using measures of central tendency (i.e. mean, median) and dispersion (i.e. standard deviation, range).

Table 1: Observational cohort studies: quality assessment.

Author	Study type	Location	Patient selection	Follow up	Lost to follow-up	Study quality
Ananthasubramaniam et al. (77)	Retrospective	Monocentric	Not consecutive	6 months	5–20%	Low
Babikian et al. (82)	Retrospective	Monocentric	NR	6 months	<5%	Low
Butler et al. (78)	Retrospective	Monocentric	Not consecutive	23.5 months	5–20%	Low
Leker et al. (81)	Prospective	Monocentric	Consecutive	NR	NR	Low
Phan et al. (79)	Retrospective	NR	Consecutive	30 days	<5%	Low
Wijdicks et al. (80)	Retrospective	Monocentric	Consecutive	>3 months	NR	Low

NR, not reported.

Results

Two hundred fifty-nine papers were identified with the initial search strategy. Thirty-six were duplicates and 82 were considered potentially eligible based on the title and/or abstract.

Of these papers, 11 were excluded because of the language (7–17), and five were not available and could not be retrieved by

contacting the corresponding authors (i.e. no addresses available).

We retrieved full copies of 66 potentially appropriate studies. After excluding 46 articles not meeting the pre-specified inclusion criteria (3, 18–63), a total of 13 case reports (64–76) and six observational cohort studies (77–82) were included in the final analysis. No RCT was finally identified.

Table 2: Observational cohort studies: baseline characteristics.

Author	Patients number	Age (years)	Sex	Valve site	Haemorrhage site	INR at entry	Support therapy
Ananthasubramaniam et al. (77)	3	NR	3 males	1 mitral 1 aortic 1 mitral-aortic	1 subdural 2 intracerebral	2.5–4	3 pts surgery 1 pt vitamin K 3 pts FFP 2 pts RBC
Babikian et al. (82)	6	NR	NR	NR	NR	NR	NR
Butler et al. (78)	16*	60.23 (range 44–73)	NR	7 mitral 5 aortic 1 mitral-aortic	1 subarachnoidal 7 subdural 4 intracerebral 1 intraspinal	5.9 (3–13.4)	NR
Leker et al. (81)	4	60 ± 17.9	1 male 3 females	NR	intracerebral	5.31 ± 4.04 (1.5–9.4)	4 pts FFP, 4 pts vitamin K, 1 pt surgical evacuation
Phan et al. (79)	52	67.9 (range 23–88)	NR	14 mitral 31 aortic 7 mitral-aortic	NR	PT 31.3 sec (range 11.5– 240 sec.)	52 pts vitamin K, 52 pts FFP
Wijdicks et al. (80)	39	69 (range 41–82)	12 males 27 females	16 mitral 20 aortic 3 mitral-aortic	4 subarachnoidal 20 subdural 15 intracerebral	14 pts INR > 4 or PT > 2 times	16 pts surgery, 26 pts vitamin K 37 pts FFP

INR, international normalized ratio; PT, prothrombin time; NR, not reported; pt, patient; FFP, fresh frozen plasma; BC, red blood cell; sec, second; * data available for only 13 patients.

Table 3: Observational cohort studies: restarting of anticoagulant therapy.

Author	Oral anticoagulant therapy restarting	Other therapy	Cerebral ischaemic and haemorrhagic events	Death for any cause
Ananthasubramaniam et al. (77)	No	1 pt ASA	0	2 (1 for the acute event, 1 for unreported reason 4 months later)
Babikian et al. (82)	After mean 19 days	NR	0	1 (for bacterial endocarditis)
Butler et al. (78)	After mean 7 days (range 3–19 days)	10 pts heparin (mean 3 days after, range 1–6 days)	1 cerebral haemorrhage 3 cerebral ischaemic events (time not reported)	Cumulative death rate: 2 pts at day 2 (for the acute event) 4 pts at month 23.5
Leker et al. (81)	No	Heparin i.v. within 24 h (one pt 36 h after surgery)	0	0
Phan et al. (79)	Either heparin i.v. or warfarin: 7 pts at day 7 26 pts at day 14 28 pts at day 28		1 cerebral ischaemic event at day 5	Cumulative death rate: 18 pts at day 7 20 pts at day 14 22 pts at day 30 (causes not specified)
Wijdicks et al. (80)	median 8 days (range 2 days to 3 months) (in 3 pts with a lower INR target range)	5 pts heparin	1 fatal cerebral haemorrhage 3 years later	13 pts at day 2 (for the acute event) plus the pt who died for cerebral haemorrhage 3 years later

pt, patient; ASA, acetyl salicylic acid; INR, international normalized ratio.

Observational studies

All included observational cohort studies were of low quality; only one was prospective (81) (Table 1). A total of 120 patients were enrolled (Table 2). Mean age was 64.3 years (data available for 108 patients). The mean follow up was 7.9 months (range 1 to 23.5 months). Information on the site of the valve was available in four studies (77–80): 38 patients had the valve in the mitral position, 57 in the aortic position, and 12 had the valve in both the aortic and the mitral position. The site of haemorrhage was described in four studies (77, 78, 80, 81): 28 patients had a subdural haemorrhage, five had a subarachnoid haemorrhage, 25 had intracerebral haemorrhage, and only one had spinal haemorrhage. Information on the INR value at the time of the bleeding event is reported in Table 2.

In all observational studies (77–82), anticoagulation was stopped early after the developing of cerebral haemorrhage. In four of these studies (78–80, 82) anticoagulation was restarted and this occurred within a broad time range: from two days to three months. In one study, (81) all patients received intravenous heparin as soon as the INR dropped below 1.5. Also in other two studies (78, 80), some patients received heparin therapy before oral anticoagulant treatment was restarted (Table 3).

Overall, six adverse events (3%) occurred after anticoagulation was restarted: these were four ischaemic strokes and two

recurrent cerebral haemorrhages (only one was fatal, 3 years after the first episode) (80). Events occurred within a broad time range: between five days and three years after restarting anticoagulation. A total of 43 patients (35.8%) died, most of them early within 48 hours from the index event (Table 3).

Case reports

A total of 18 patients were described in the included case reports (63–76) (Table 4). Mean age was 50.5 years (range 11 to 60 years); males were 11 (61.1%). The INR at the time of cerebral bleeding ranged from 2.40 to 5.60 (mean 3.75) (Table 5). In all cases but one anticoagulant therapy was stopped soon after cerebral haemorrhage (64).

Anticoagulant therapy was restarted within four days to eight weeks (Table 6). In many cases, however, the first therapeutic approach following cerebral bleeding was heparin or antiplatelet drugs. Two patients had a recurrent haemorrhagic event (one was fatal, 3 months after the index event) (11.1%); no cerebral ischaemic events are reported. Overall, three patients died (16.6%): one for an acute myocardial infarction six days after cerebral bleeding, one for a recurrent cerebral haemorrhage three months later, and the last one for unreported reason after seven months (73–74, 76).

Table 4: Case reports: baseline characteristics.

Author	Age	Sex	Valve (type and site)	INR target range	Concomitant antithrombotic therapy
Anderson et al. (64)	66	F	Mitral Starr Edwards	-	-
Bagga et al. (65)	34	F (pregnant)	Aortic St Jude	2.0–3.0	-
Barra et al. (66)	38	F	Mitral Starr Aortic Starr Tricuspidal Beall	-	-
Barra et al. (66)	45	F	Mitral Starr	PT 25–30%	heparin
Conti et al. (67)	53	F	Mitral Sorin No. 29 Aortic Carbomedics No. 16	-	no
Crawley et al. (68)	70	M	Aortic St Jude	3.0–4.0	-
Gomez et al. (69)	63	F	Aortic Bjork-Shiley	-	no
Jain et al. (70)	59	M	Aortic Starr Edwards Mitralic Starr Edwards	3.5–4.5	-
Maingi et al. (71)	59	M	Aortic Bjork-Shiley	3	-
Muñoz Morente et al. (72)	60	M	Mitral Bjork-Shiley	-	-
Nagano et al. (73)	17	M	Aortic St Jude Medical	10–20%*	-
Nagano et al. (73)	60	M	Aortic St Jude Medical	10–20%*	-
Nakagawa et al. (74)	11	M	Aortic	-	-
Nakagawa et al. (74)	60	M	Mitral	-	-
Nakagawa et al. (74)	60	M	Mitral	-	-
Nakagawa et al. (74)	53	M	Aortic	-	-
Park et al. (75)	53	F	Mitral St's Jude	2.5–3.5	-
Telerman-Toppet et al. (76)	48	M	Mitral Starr	20–30% [^]	-

INR, international normalized ratio; ASA, acetyl salicylic acid; * thrombotest; [^] prothrombin time.

Author	GCS	Site	INR	Withdrawal of anticoagulation	Support therapy
Anderson et al. (64)	-	Right frontoparietal subdural	-	No	Dexamethasone
Bagga et al. (65)	-	Right parieto occipital	2.40	Yes	Mannitol
Barra et al. (66)	-	Right frontal subdural	<10% ^	Yes	Surgery evacuation, replace with biological valve after 3 months
Barra et al. (66)	-	Left subdural	-	Yes	Surgery evacuation, replace with biological valve after 3 months
Conti et al. (67)	15	Right parietal with ventricular invasion	3.22	Yes	rFVIIa Vit K 10 mg i.v.
Crawley et al. (68)	-	Left sided intracerebral	3.60	Yes	-
Gomez et al. (69)	-	Left thalamous third ventricle internal capsule caudate nucleus	-	Yes	-
Jain et al. (70)	-	Intracerebellar	5.60	Yes	Vit K 10 mg i.v., FFP
Maingi et al. (71)	-	Epidural hematoma	2.80	Yes	FFP, evacuation of epidural haematoma
Muñoz Morente et al. (72)	-	Temporo parietal and occipital (bilatereral)	2.45	Yes	Antibiotics (endocarditis)
Nagano et al. (73)	-	Intracerebral (right parieto-occipital)	-	Yes	Vit K, FFP, craniotomy
Nagano et al. (73)	-	Right temporo-parietal haematoma	-	Yes	Vit K, FFP, craniotomy
Nakagawa et al. (74)	-	Left intracerebellar	27%*	Yes	Surgical removal
Nakagawa et al. (74)	-	Right intracerebral haematoma	56%*	Yes	Surgical removal
Nakagawa et al. (74)	-	Left subdural	28.1%*	Yes	Irrigation and drainage 1 week later
Nakagawa et al. (74)	-	Bilateral subdural haematoma	-	Yes	Irrigation and drainage
Park et al. (75)	-	Left occipital	6.23	Yes	Vit K, FFP, rFVIIa
Telerman-Toppet et al. (76)	-	Epidural haematoma L3-L4	25%^	Yes	Laminectomy D12-L4 with evacuation of the haematoma 3 days after

GCS, Glasgow coma scale; INR, international normalized ratio; rFVIIa, recombinant activated factor VII; vit K, vitamin K; i.v., intravenous; FFP, fresh frozen plasma; L, lumbar; D, dorsal; * trombotest; ^ PT.

Table 5: Case reports: haemorrhagic events.

Discussion

The results of this systematic review of the literature on the management of oral anticoagulant therapy after a cerebral bleeding in patients with a mechanical heart valve show that restarting oral anticoagulant therapy few days and, indirectly, stopping anticoagulant therapy for few days (even for 7–14 days) after the occurrence of cerebral haemorrhage are both safe. However, published evidence is poor: only low-quality observational cohort studies and case reports are available.

Restarting antithrombotic therapy after a major bleeding is a critical issue, in particular in patients with a mechanical heart valve after an intracranial bleeding. Life-long oral anticoagulant therapy is recommended in all patients with a mechanical heart valve to prevent thromboembolic events (4). However, this treat-

ment places patients at an increased risk of severe or fatal bleeding. Cerebral bleeding is certainly the most threatening complication of oral anticoagulant therapy, with an estimated six-month mortality of 67% (83). Moreover, it is a seriously disabling illness, with as many as 80–90% of survivors left with persistent neurological deficits (84). The estimated incidence of cerebral bleeding during anticoagulation is 0.3–0.7%/year (1–2). Risk factors for cerebral bleeding are age, hypertension, previous stroke, INR levels, concomitant use of antiplatelet drugs, and cerebral amyloid angiopathy (83). Although INR values exceeding 3.5 are associated with an increased risk of cerebral bleeding, haemorrhages may also occur when the INR is within the therapeutic range (85, 86).

We performed this systematic review with the aim to identify published literature on the optimal management of oral anti-

Table 6: Case reports: restarting therapy.

Author	Antithrombotic restarting therapy	Antithrombotic restarting therapy time	Follow-up	Haemorrhagic event	Thrombotic event	Death
Anderson et al. (64)	Warfarin was not stopped	4 months	No	No	No	
Bagga et al. (65)	Enoxaparin 20 mg twice a day Acenocumarol	Day 14 Day 42 (20th post-operative day)	10 weeks	No	No	No
Barra et al. (66)	Only ASA after biological valve replacement	No	9 months	No	No	No
Barra et al. (66)	Anticoagulation	Yes	-	No	No	No
Conti et al. (67)	Nadroparin 50 U/kg b.i.d Warfarin (target INR, 2.5)	Day 18 Day 38	1 year	No	No	No
Crawley et al. (68)	Heparin i.v.	Day 0	90 days	2 new intracranial haematomas at day 38	No	No
Gomez et al. (69)	Antiplatelet drug Heparin i.v. then warfarin	Day 0 Day 10	-	No	No	No
Jain et al. (70)	Enoxaparin at increasing doses Anticoagulation	Day 14 1.5 months after	-	-	-	-
Maingi et al. (71)	ASA 325 mg, then warfarin plus dipyridamole	8 weeks after	18 months	No	No	No
Muñoz Morente et al. (72)	Heparin i.v. for 6 weeks, then bemiparina s.c. for 3 months, then acenocumarol	Day 4	-	-	-	-
Nagano et al. (73)	Warfarin (range PT, 50–60%)	Day 7	3 months	Massive intracranial haemorrhage after 3 month	Ischaemic stroke 2 months later	death of intracranial haemorrhage
Nagano et al. (73)	Warfarin (range PT, 30–40%)	NR	6 months	No	No	No
Nakagawa et al. (74)	Heparin i.v. Wafarin	After surgery 3 days after surgery	3 years	No	No	No
Nakagawa et al. (74)	Not restarted		6 days	No	AMI	Death for AMI at 6 days
Nakagawa et al. (74)	Warfarin	4 days after surgery	8 months	No	No	No
Nakagawa et al. (74)	Warfarin	1 month after surgery	20 months	No	No	No
Park et al. (75)	Warfarin (INR range, 2–3)	Day 8	2 months	No	No	No
Telerman-Toppet et al. (76)	Dipyridamole Anticoagulation	Soon after surgery 10 days after surgery	7 months	No	No	Death after 7 months

NR, not reported; ASA, acetyl salicylic acid; i.v., intravenous; PT, prothrombin time; AMI, acute myocardial infarction.

coagulant therapy after intracranial bleeding secondary to the use of VKA in patients with a mechanical heart valve. Unfortunately, available evidence is of low quality. No RCTs have ever been published. Retrieved observational cohort studies have several methodological drawbacks. Available data are poor because only few of the patients described in these cohorts were receiving oral anticoagulant drugs for a mechanical heart valve, and several patients were followed up for a short period of time. Moreover, most extracted data was heterogeneous: for example, INR values were not available in older studies. The most important limitation was in the different approach in the management of cerebral bleeding and in the restarting of antithrombotic therapy: for example physicians often administer antiplatelet drugs or he-

parin as bridging therapy. Finally, 11 articles were excluded because of language as described in the Methods section, but retrieved abstracts suggest that neither RCTs nor prospective studies have been missed.

Available evidence – even if of low quality – suggests that restarting oral anticoagulant after few days and, indirectly, stopping oral anticoagulant therapy for few days are apparently safe. Oral vitamin K was restarted after a broad range of time (2 days to 3 months): the heterogeneity of data do not allowed a statistical analysis but many physicians stopped therapy for 7–14 days. In the worst-clinical-case scenario, the incidence of thromboembolic events in the absence of anticoagulant therapy in patients with a mechanical bileaflet valve is 22 per 100 patient-years (1). Although

this is a high risk on a yearly basis, this corresponds to a 0.06% daily risk (i.e. 6 in 10,000 patients). Therefore, short interruption of anticoagulation may not be as dangerous as is often presumed. The risk of severe damage to organs by bleeding when anticoagulation is not fully interrupted is probably much higher in these situations.

In conclusion, well-designed studies are strongly recommended to provide better evidence. On the one hand, RCTs may be unfeasible, but on the other hand, multicenter prospective observational cohort studies are certainly warranted.

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