

Restarting Oral Anticoagulant in Patients with Mechanical Heart Valve(s) and Intracranial Haemorrhage

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**Thesis submitted to the Faculty of Graduate and
Postdoctoral Studies in Partial fulfilment for the MSc
degree in Epidemiology**

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Dedication

To the six pillars of my life, God, my mother, my wife and my children.
Without you my life would fall apart.

I might not know where the life will take me, but knowing you are with me, Allah, through this journey has given me strength.

Mom, you have given me so much. Thanks for your faith in me since my childhood. You always taught me that success was the inevitable result of hard work.

Ghadah, you are everything for me, without your love and understanding I would not be able to make it.

Nawaf & Mishary, my angels, thanks for your love and supporting me to finish my homework. I think I deserve a sticker now.

Sarah, our future queen, we are waiting for you. October is not far and soon you will complete our family.

Acknowledgements

I would like to express sincere gratitude to my supervisor and mentor, Prof Philip Wells, whose expertise, understanding and patience tremendously enriched my graduate experience. He was always available despite his busy schedule. He consistently showed interest in my work and pushed me to pursue and develop my thesis. He provided me with all the help and tools to develop as a researcher. Thank you for providing me with the opportunity to grow under your supervision and guidance.

A special thanks goes to Dr. Charles Agbi without whose motivation and encouragement I would not have considered a graduate degree in epidemiology. He served as an external resource for my thesis. He always had time to help and advise me no matter how busy he was. I doubt that I will ever be able to convey my appreciation fully, but I owe him my eternal gratitude.

My gratitude also goes to Dr. Richard Moulton for his advice and suggestions. Thank you for taking time from your busy schedule to serve as an external resource for my thesis.

I must also acknowledge Dr. Estban Gandara from Division of Haematology, the Ottawa Hospital, for his help in conducting the systematic review. Also special thanks go to Alexandra Davis and Lee-Ann Ufholz for their tremendous help in reviewing my search strategy.

Thanks also go out to those who provided me with advice including Nicholas Cofie and Ahmed Husain. Thank you for your help.

I would like also to thank Harrison Westwick for his help with the technical aspect of the survey. Thank you all for your excellent work.

I would like also to thank the faculty staff and residents at the Department of Neurosurgery, as well as the Department of Haematology for their help and advice in the development of the study survey.

Abstract

Patients with mechanical heart valves who present with intracranial haemorrhage are initially treated by reversing their coagulopathy. However, these patients will ultimately require that their oral anticoagulant be restarted. The time at which oral anticoagulants are restarted is critical since restarting too early may increase the risk of recurrent bleeding, while withholding anticoagulants increases the patient's risk of thromboembolic events. The ideal time to restart patients on their oral anticoagulant medication is defined as the time at which all these risks are minimized.

This thesis includes a systematic review and meta-analysis of the literature. The main outcomes were recurrent haematoma, valve thrombosis, stroke and peripheral emboli. Results were stratified by types of intracranial haemorrhage. We also conducted a survey to gain insight into current practices of neurosurgeons and thrombosis experts in Canada and USA when they are faced with deciding on anticoagulant restart times in patients with ICH. Results were stratified by type of intracranial bleed and participants' characteristics and demographics.

The systematic review identified that the ideal time for restarting anticoagulant therapy in patients following an ICH is unknown. Meta-analysis was limited by the heterogeneity of the studies.

The survey results indicated that physicians had a wide range of practice and that their practice was dependent on the patient's clinical features, but many physicians would restart oral anticoagulants between 4 and 14 days after the haemorrhage. For this reason we have proposed a multi centre cohort study to investigate the safety and efficacy of restarting patients on anticoagulation therapy between day 5 and 9 post haemorrhage. A full study protocol is presented in this thesis.

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CHAPTER 1

General introduction and rationale

Valvular heart disease can be congenital or, more commonly, acquired during life. Commonly acquired causes include rheumatic heart disease, valvular calcification, and endocarditis, while less common causes include coronary artery disease, cardiomyopathy, syphilis, tumours, and radiation. Patients with significant valvular heart lesions, stenosis, or regurgitation are routinely managed by replacement or repair of the valve ¹. Generally heart valve prostheses are classified as mechanical heart valves (MHV), which have synthetic components, or bioprosthetic heart valves (BHV), which are made in part with biological components ². Of all valves implanted worldwide, approximately 55% of implanted prosthetic heart valves are mechanical ¹.

Since Starr and Edwards performed the first prosthetic valve replacement in humans in 1960 ³, it is estimated that about 45,000 MHV are implanted annually in the USA and 140,000 worldwide ⁴. The use of MHV is increasing at the rate of 3-5% per year ¹. Three designs of MHV exist, namely ball and cage valves, monoleaflet valves, and bileaflet valves ^{1,4,5}. Ball and cage valves are no longer implanted because of their noise and hemodynamic inefficiency ^{4,5}. The most important factors considered in the decision to implant MHV versus BHV include patient's age and life expectancy, patient's preference, contraindication for anticoagulation therapy, and patient's comorbidities ⁵. The criteria in favour of

using MHV include the following: (1) Patient preference and no contraindication for longterm anticoagulation; (2) the patient is already on lifelong anticoagulation; (3) the patient is <65 years of age and has a long life expectancy ⁴.

Patients with MHV implantation are at an increased risk of thromboembolic complications that include valve thrombosis and cerebral embolization. Valve thrombosis has been reported to occur in 1-13% of patients in the first year following MHV implantation, or 20% overall in patients with mechanical valves ^{6,7}. The risk of major thromboembolism has been estimated to be at least 4% per year in patients with MHV not receiving oral anticoagulation ^{6,8,9}, with the daily risk being estimated at 0.016% ¹⁰. The use of prophylactic oral anticoagulation (OAC) reduces the annual risk of thromboembolism to approximately 1% ^{6,8,9}. Although the risk of thromboembolism is present with all MHV, some studies found an increased risk with ball and cage mechanical valves and MHV in the mitral position, as well as in patients with atrial fibrillation and left ventricular dysfunction ^{6,8,9,11}. Since the risk of valve thrombosis and thromboembolism can be reduced with the use of oral anticoagulation, this medication has become the standard of care in patients with MHV implantation.

The guidelines from the American College of Cardiology, American Heart Association, European Society of Cardiology, Australasian Society of Thrombosis and Haemostasis, and Spanish Society Cardiology all indicate that

patients with MHV implantation should be on lifelong oral anticoagulation therapy ^{5, 12-15}. The most recent guidelines from the American College of Cardiology stated, “After mechanical aortic valve replacement, the goal of antithrombotic therapy is usually to achieve an international normalized ratio (INR) of 2.5 to 3.5 for the first 3 months after surgery and 2.0 to 3.0 beyond that time; and most studies have shown that the thromboembolism risk is greater for patients with mechanical mitral valve prostheses than for patients with aortic valves, even when adjusted for the presence of atrial fibrillation. Thus, anticoagulation for patients with mechanical mitral valve prostheses is maintained at an INR of 2.5 to 3.5 indefinitely” ⁵. INR is routinely used for regulating oral anticoagulation therapy and, if needed, monitoring its reversal ¹⁶⁻¹⁹.

Oral anticoagulants interfere with synthesis of vitamin K-dependent clotting factors resulting in low levels of factors VII, IX, X, and prothrombin, and therefore increase the risk of haemorrhages ¹⁹. The annual risk of haemorrhage has been estimated to be approximately 2-3% per patient-year among patients with MHV on oral anticoagulation ²⁰⁻²³. One of the life threatening major bleeding complications associated with the use of oral anticoagulation is intracranial haemorrhage (ICH).

In patients taking oral anticoagulation, 70% of ICHs are intracerebral while the remainder are subdural ^{19, 28}. Many studies have found the incidence of central nervous system haemorrhage associated with oral anticoagulation to be

0.6% to 1% per year^{10, 15, 18, 21, 24-26}, but this may represent reporting bias so the actual number could be greater. The incidence of intracerebral haemorrhage in anticoagulated patients is 7-10 times higher than in patients not taking oral anticoagulants²⁷. Over a 7 year period, as many as 23.4% of patients with intracerebral haemorrhage admitted to the Massachusetts General Hospital were taking oral anticoagulants²⁷. It becomes apparent that many intracerebral haemorrhage hospital admissions are caused by oral anticoagulation¹⁸. In another study, the annual number of patients in the USA suffering an intracerebral haemorrhage was estimated at 60,000 with approximately 7,000 of these haemorrhages being attributed to the use of oral anticoagulants²⁴.

D`Angelo et al.²⁹ found the annual probability of anticoagulated patients with MHV developing a subdural haematoma (SDH) was 0.083. The majority of ICHs occur within the therapeutic range of INR with one study estimating that with a therapeutic target INR of 2.0 to 3.0 the risk of ICH is doubled³⁰. Higher intensities of anticoagulation further increase the risk of intracranial haemorrhages^{19, 27, 31}.

Intracranial haemorrhage in anticoagulated patients is associated with high morbidity and mortality. Rosand et al.²⁷ in a study of 435 patients with intracerebral haemorrhage found the three-month mortality rate was 25.8% for those not taking OAC and 52.0% for those on an OAC. Flaherty et al.³² reported similar findings in their analysis of 1041 adult patients hospitalized for "first-ever" intracerebral haemorrhage. The increased mortality in patients with ICH on

anticoagulant therapy compared to patients not treated with anticoagulants is consistent in the literature ^{10, 18, 25, 26, 33}. OACs increase the risk of intracranial haematoma expansion beyond the first 24 hours. Such expansion has been correlated with an increased mortality rate ^{34, 35}. Oral anticoagulation is a significant predictor of fatal outcome ³⁵.

One of the most important steps in the management of patients with ICH related to oral anticoagulants is urgent reversal of the coagulopathy caused by the OAC ^{10, 18, 36-38}. Normalization of coagulation can be achieved by various methods including intravenous vitamin K₁ at a dose of 10 mg ¹⁹, intravenous fresh frozen plasma ^{16, 18, 19}, prothrombin complex concentrate ¹⁶⁻¹⁹, and recombinant factor VIIa ^{16, 18, 19}. The American Thoracic Society recommends 10 mg of intravenous vitamin K and prothrombin complex concentrates ^{19, 39}.

Patients with MHV and ICH are managed by reversing their anticoagulation and in some cases, especially subdural haematomas, surgery. However, the anticoagulation therapy is required to prevent thromboembolic events. The duration of discontinuation and the ideal time to resume OACs in patients with ICH and MHV is a major decision for neurosurgeons and thrombosis experts who are usually involved in the management of these patients. The dilemma remains unsolved in the current literature. In a report by Bertram et al. ³⁷, 10 out of 15 patients with ICH were on OAC therapy secondary to heart valve implantation, and all patients had their coagulation reversed. Two of their 15 patients experienced major thromboembolic events after

discontinuing their oral anticoagulants. Bertram et al. therefore recommended that patients receive anticoagulants after their INR is normalized as short-term discontinuation of anticoagulants places patients at high risk for cardiac embolization. Similar conclusions have been reported in other literature sources^{37, 40}.

Conversely, Wijdicks et al.³³ reported a case series of 39 patients with ICH and MHV in which 13 patients on OAC died within 2 days of admission to the hospital. The remaining patients received fresh frozen plasma and vitamin K with anticoagulant discontinuation between 2 days and 3 months. None of these patients developed systemic embolization or valve thrombosis, although 2 patients experienced clinical deterioration secondary to haematoma expansion. Wijdicks et al. concluded that early resumption of full anticoagulation therapy may be dangerous. Similar conclusions have been reported in other studies^{10, 42-45}. Butler et al.⁴¹ reviewed the records of 35 patients admitted to a neurosurgical centre between July 1994 and October 1997 with OAC related intracranial or intraspinal haemorrhage. Data was available for 13 patients who restarted OACs. With a median followup of 23.5 months, one patient had recurrent ICH and 3 patients had cerebral embolic events despite anticoagulation. They concluded that temporary cessation of OAC is safe and the risk of recurrent bleeding after restarting OAC is low. However, they did not specify the duration of this temporary cessation.

Guidelines¹⁸ published by the American Heart and Stroke Association for managing intracerebral haemorrhage in adults did not provide clear recommendations regarding when anticoagulants should be restarted after intracerebral haemorrhage. The guidelines noted that data is limited and the reversal of anticoagulation may be associated with low frequency of embolic events over a period of 7 to 10 days, after which reinstatement of oral anticoagulants appears to be safe.

Neurosurgeons and thrombosis experts frequently face the dilemma of when to reinstitute anticoagulation therapy in patients with MHV after patients present with an ICH. With such a gap in evidence, the management of ICH patients' OAC varies from one physician to another. Most decisions are based on the treating physician's personal experience accrued during his/her training or practice. For example, some neurosurgeons wait for 6 weeks before restarting OAC therapy, while others restart therapy within a few days.

Thesis objectives

This project was concerned with determining the ideal time to resume OACs in patients with MHV after patients had suffered an ICH. The main objective of this project was to identify from literature the ideal time to restart OACs in adult patients with MHV diagnosed with an ICH, and to identify current practices most neurosurgeons and thrombosis experts use when they are faced with this condition. Based on the information gathered from these two objectives

a protocol was designed to definitively answer when is the ideal time to restart OACs in adult patients with MHV and ICH. Since OACs are associated with congenital risks during pregnancy, patients must be managed differently during pregnancy^{5, 46-49} and therefore pregnancy was excluded from the current study.

To achieve our objectives this project was developed into three parts:

- 1- Systematic review of literatures related to restarting OACs in patients with MHV and ICH with the aim of identifying the ideal time based on the literature.
- 2- Surveying responses of Canadian and American neurosurgeons and thrombosis experts with the aim of identifying current practices when these physicians are faced with a decision related to OACs in adult patients presenting with MHV and ICH.
- 3- Writing a protocol for a study aiming to achieve an evidence-based answer for the ideal time to restart OAC.

CHAPTER 2

Systematic Literature Review

A comprehensive search was performed of the medical literature for contextual information dealing with the timely resumption of oral anticoagulant (OAC) medication in adult patients with mechanical heart valves (MHV) and intracranial haemorrhage (ICH). It was anticipated that a systematic review would fill the gap in the medical literature and thereby assist in the management of patients. It was also anticipated that a meta-analysis would be conducted from the data collected from the appropriate literature.

The Systematic Literature Review Question

The main question to be answered by this systematic literature review was: When should OAC therapy in adult patients with MHV and ICH be reinstated? To obtain an answer to this question all relevant available literature was used.

Objectives

The main objective of the literature review was to identify the ideal time to recommence OACs in adult patients with MHV who presented with ICH while they were on OACs. The ideal time is defined as the period of time exhibiting the

least risk of developing a valve thrombosis or stroke and when the risk of having a repeat ICH is minimized.

The secondary objective was to assess whether the ideal time to resume OACs differs between patients presenting with intracerebral haemorrhage versus subdural haemorrhage (SDH). Subdural haematomas and intracerebral haemorrhages are the most common types of ICH.

Criteria used in considering studies for this systematic literature review

The PICO framework was considered for this systematic literature review. This framework has been adopted by many associations including The Cochrane Collaboration and The Campbell Collaboration^{50, 51}.

Participants

Participants had to be adult patients (over 18 years of age) who had a MHV implanted and who presented to a hospital with ICH while they were on OACs. Since many OACs are associated with congenital risks during pregnancy, pregnant women on OAC are considered as a special group and are managed differently during pregnancy. For this reason pregnant women were excluded from our study.

Intervention

For the current study intervention is accepted as the time of anticoagulant therapy resumption in patients from the time the ICH was diagnosed. Whether patients had their OAC reversed at the time of the ICH was recorded. While all OACs were considered, we expected warfarin to be the drug of choice in most cases since it is the most widely used OAC. Dose was not regarded as relevant. We also attempted to report the INR value at the time of haemorrhage.

Comparisons

The main consideration in the literature review was the timing of OAC re-administration in patients with MHV and ICHs.

Outcome

The most important clinical events related to timing of restart OACs include valve thrombosis, thromboembolic events (including stroke, pulmonary embolism and deep venous thrombosis), and recurrent ICHs. The main issue pertains to the ideal time to restart OAC so that the physician can minimize the risk of valve thrombosis, thromboembolic events, and recurrent ICHs. Valve thrombosis, thromboembolic events, and recurrent ICHs are therefore primary outcomes. As secondary outcomes we recorded any major haemorrhages as defined by the International Society of Thrombosis and Haemostasis (ISTH)

guidelines²⁰². No specific criteria were required to confirm their development other than the outcome being diagnosed by a physician. The timing of any of these events was reported in addition to timing of OAC treatment resumption. Studies did not necessarily report all primary outcomes.

Research method and design

Types of studies

Because this was a relatively narrow research area, all of the following study designs were allowed: Randomized controlled trials (RCT), non-randomized controlled trials, longitudinal cohort studies, case series, and case reports.

Search strategy for study identification

The search strategy employed in this review aimed to identify both published and unpublished studies. The following databases were searched electronically: Medline (Ovid), Embase, Scopus, The Cochrane Library, The Cochrane Controlled Trials Register, LILACS, Web of Science, and Global Health. A senior neurosurgeon and a senior thrombosis expert (Dr. Charles Agbi and Dr. Philip Wells) were consulted in order to ensure adequate terms; also, two health sciences research librarians and information retrieval specialists (Alexandra Davis, a senior health research librarian at the Ottawa Hospital, and

Lee-Ann Ufholz, a health sciences research liaison librarian at the University of Ottawa) were consulted to ensure high study identification. The search strategy was reviewed by each librarian independently.

The search strategy (Appendix A) included the following terms:

Anticoagulants, 4-hydroxycoumarin, acenocoumarol, Sintrom, Sinthrome, dicumaro, dicoumarin, dicoumarol, vitamin k antagonist, phenprocoumon, marcumar, marcoumar, falithrom, warfarin, Coumadin, heart valve prosthesis, heart valve prosthesis implantation, prostheses, prosthetic, replacement, mechanical, artificial, mechanical heart, replacement, mitral valve, aortic valve, prosthesis implantation, heart valve diseases, intracranial haemorrhage, cerebral haemorrhage, basal ganglia haemorrhage, putaminal haemorrhage, cerebral haemorrhage, traumatic intracranial haemorrhage, brain haemorrhage, brain stem haemorrhage, haematoma, epidural, cranial, subdural, subarachnoid haemorrhage, cerebellum, bleed, brain injuries, and craniocerebral trauma. We incorporated an iterative process to refine the search by testing different search terms appropriate to each different database.

To identify all relevant studies we manually searched reference lists from included studies, previously published review articles, the guidelines from the American College of Cardiology ⁵, the guidelines from the European Society of Cardiology ¹⁴, the guidelines from the Australasian Society of Thrombosis and Haemostasis ¹⁵, and the guidelines from the Spanish Society of Cardiology ¹³.

The Gray literature search included conference proceedings of The

Congress of Neurological Surgeons, The American Association of Neurological Surgeons, The International Society of Thrombosis and Haemostasis, and The American College of Cardiology. Additional unpublished and ongoing trials were searched through clinicaltrials.gov and controlled-trials.com.

Clinical experts were contacted nationally in order to review our list of studies and to recommend any missing studies.

Data range

The search was limited to the past 62 years, i.e. 1 January 1950 to 30 April 2012 and was updated prior to submission of this thesis. Only one small case series⁵² was identified during the last update. Since it was not going to affect the results, I did not redo my analyses and tables.

Language

Although it was desirable to have the systemic review include studies in as many languages as possible, the difficulty of obtaining full articles and the cost of translations curtailed the variety of language editions included in this systematic literature review. We excluded studies written in Japanese from our analysis; detailed explanation is included at different parts of this review.

Inclusion and exclusion criteria

After completing the literature search we either included or excluded the identified studies from this review based on the following criteria:

- **Criteria for study inclusion:**
 - Studies that described MHV patients receiving OACs who presented with ICH and were restarted on their OACs.
 - Randomized controlled trials, non-randomized controlled trials, longitudinal cohort studies, case series, and case reports.
 - Human studies.

- **Criteria for study exclusion**
 - Paediatric age group (<18 years).
 - Pregnancy.
 - Reviews, guidelines, and editorial letters.

Screening and eligibility decisions

Screening and retrieval decisions

A team consisting of a neurosurgeon (Dr. Fahad Alkherayf) and a thrombosis haematologist (Dr. Esteban Gandara) reviewed the titles and

abstracts of all identified references. The reviewers were not blinded to authors or results. Each reviewer independently read the titles and abstracts to identify the citations relevant to our review based on our inclusion and exclusion criteria. Full-text articles were obtained for all the citations that either reviewer deemed to be potentially relevant. All identified references were obtained through the Ottawa Hospital library.

Eligibility decisions

The complete texts were retrieved from all identified citations throughout the initial screening. Both reviewers went through each study independently. The full text was read carefully and each reviewer decided which studies to include in the review and each reviewer documented his reasons for each inclusion or exclusion. Differences were resolved by discussion and consensus. For unresolved differences it was planned to involve a third investigator (Dr. Philip Wells, a senior thrombosis expert) who would evaluate the studies. In cases where further information from any included study was required, the reviewing team made attempts to contact the principal investigator of that study to obtain additional details before deciding to include or exclude the study. To minimize the risk of reporting bias, it was planned to include unpublished studies if they were deemed eligible based on our inclusion and exclusion criteria.

We endeavoured to refrain from changing any of our established inclusion and exclusion criteria. However, we were willing to refine our established criteria

if studies were found identifying concerns that were not addressed by our inclusion and exclusion criteria. We ensured that any new criterion was applied to all studies. At conclusion of the literature analysis there were no changes to our criteria apart from excluding studies in the Japanese language.

Eligibility criteria pilot test

To ensure clarity and applicability of our inclusion and exclusion criteria, 12 studies (including studies that were most likely to be included, most likely to be excluded, and those most likely needing further discussion) were tested initially where each reviewer performed an independent review. The main goal of the pilot test was to train the reviewers and ensure reviewer consistency.

Excluded studies

A list of studies that were excluded after the final screening is provided in Table 2 in the results section. The main reason for excluding each study is also provided in Table 2.

Reviewer agreement measurement

To measure the agreement between the two reviewers we calculated the kappa statistic for the eligibility criteria pilot test. The following formula was used:

$$kappa = \frac{P_0 - P_1}{1 - P_1}$$

Where:

- P0 is the proportion of studies for which there was agreement, and
- PE is the proportion of studies where one would expect there to be agreement by chance alone.

A value of -1 indicates a perfect disagreement below chance while a value of 1 indicates a perfect agreement above chance. Because reviewers were not forced to assign a fixed number of articles to certain categories, we used free marginal kappa. For calculation of the kappa statistic we used an online kappa calculator ⁵³.

Citation tracking

All steps were documented throughout the course of the systematic literature review using RefWork software ⁵⁴, Microsoft Excel, and Microsoft Word. Furthermore, the reasons for excluding certain studies were also documented.

Multiple reports

If multiple studies originated from a single study, only the latest report or the original study was considered for the analysis. If additional data or more clarification of the study methodology was required, we attempted to contact the authors of the study to procure the missing information.

Data extraction and studies quality assessment

Data extraction

An identification number was assigned to each study. The following data were collected from each study using a data collection form: Eligibility confirmation, the reason for exclusion if the study was excluded, study design, year of publication, language of publication, duration of followup, total number of participants, age and sex of participants, type of ICH, whether patients underwent cranial surgery, presence of atrial fibrillation, type of MHV, position of MHV, number of MHVs, when OAC was resumed, time and percentage of patients developing a valve thrombosis, thromboembolic events or recurrence of ICH within each group, loss of followup, and missing data.

If we were unable to extract all the required information from the study, we attempted to contact the original investigators. If a study author's contact information was not included in the study, we resorted to more recent publications, university staff listings, or conducted a World Wide Web search.

Data was extracted from the literature by the reviewers independently and then the extracted data from the two reviewers were compared. No differences were identified.

Publications were reviewed independently by each reviewer in the event that some studies were published in more than one publication. If a recent publication contained data that was not included in the original study then the

data was extracted from all publications into a single data collection form.

Collected data was managed using Microsoft Excel and Microsoft Access if needed.

Contents and categorising extracted data

Intracranial bleeding can occur into the brain parenchyma (intracerebral haemorrhage), cerebellar parenchyma (cerebellar haemorrhage), subdural space (SDH), and less often into other parts of the intracranial space (e.g. subarachnoid space and brain ventricles). Each of these types of bleeding requires different treatments. For example, surgical treatment is the main treatment for most subdural haematomas, while conservative treatment is the main treatment for most intracerebral haemorrhages. For this reason we tried to identify the types of ICH in our data extraction.

The target INR for patients with MHV should range between 2.5 and 3.5^{21, 55, 56}. For this reason we divided the INR into three ranges, namely therapeutic (2-4), sub-therapeutic (<2) and supra-therapeutic (>4). In our data extraction we collected the INR level at the time of the initial bleed, the time when patients were restarted on their OAC, and at the time of outcome if it happened.

In addition to the types of ICH and INR levels, we collected the mean age or, if available, the individual age of the patients, location of the MHV, type of MHV, number of MHVs, whether patients had a craniotomy after their initial haemorrhage, the time of restarting patients on their OACs, and whether

patients received heparin or antiplatelets after their initial haemorrhage, as well as patients with recurrent ICHs, type of recurrent ICH if it happened, timing of the most recent haemorrhage from the day of restarting OACs, any other major haemorrhages, and any thromboembolic events including valve thrombosis, brain stroke, deep venous thrombosis (DVT), and pulmonary embolism (PE).

For the timing of recurring haemorrhages, we collected data in the following time ranges in relation to restarting oral anticoagulants: 0-3, >3-7, >7-14, >14-21, >21-28, >28 days.

Studies quality assessment

Identified studies were independently assessed by the two reviewers for quality. Methodological Quality Rating Scale (MQRS) was used for randomized controlled trials (Appendix B), while the Newcastle-Ottawa Quality Assessment Scale (NOS)⁵⁷ was used for non-randomized studies. All of the included studies were also assessed according to the Oxford Centre of Evidence-Based Medicine Levels of Evidence⁵⁸.

MQRS was published in 2002 by Miller and Wilbourne and has been utilized by many systematic reviews⁵¹. MQRS scores different aspects of the study including overall design, attrition, duration of followups, types of outcome measured and intervention quality control. Each study receives a total score ranging from 0 to 17.

NOS is a system in which a study is judged on three broad perspectives: The selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. NOS has been partially validated ⁵⁷.

We did not perform any quality evaluation for the case reports. The overall quality of the studies was evaluated by each reviewer independently. Each study was evaluated based on NOS stars, type of study (RCT, prospective or retrospective), monocentric or multicentric, and duration of followup.

We included the Oxford Level of Evidence in our quality assessment because it is widely used in the literature. Also, many physicians, especially surgeons, are more familiar with the Oxford Level of Evidence than other scales.

Statistical analysis

Our initial analytic plan was to pool the data from the studies and measure the effect of restarting OAC in relation to the recurrence of ICH and other outcomes. We were planning to classify timing of restarting OAC into categorical variables and examine their relation to recurrence of ICH and other outcomes. The proposed variables were: 1- three days or less, 2- four days to seven days, 3- more than seven days to fourteen days, 4- more than fourteen days to twenty-one days, 5- more than twenty-one days to twenty-eight days, 6- more than twenty-eight days. We examined heterogeneity of the effect size using I-squared test ⁵⁹. Analysis was done using SAS 9.2 and Meta-Analysis

Package for R statistical software^{60, 61}. Furthermore, we planned to perform a meta-regression analysis using Meta-Analysis Package for R statistical software.

When data was missing from the studies regarding the participants or their outcomes we attempted to contact the authors to obtain the missing data. We would sought further help from a statistician to assist us with imputing missing data if this was applicable. For any identified RCT studies we planned to perform intention-to-treat analysis. For assessing publication bias, we utilized the funnel plot.

Results

Literature search results

An electronic database search for the period 1 January 1950 to 30 April 2012, with no language restrictions, identified a total of 763 articles (Table 1) (167 through Medline (Ovid), 350 through Embase, 49 through Scopus, 13 through Cochrane library and Cochrane controlled Trials Register, 33 through LILACS, 148 through Web of Science, and 3 through Global Health).

Another twenty studies were identified through manual searching, gray literature searching, and contacting clinical experts. A total of 783 abstracts were therefore reviewed by the investigators (Fahad Alkherayf & Esteban Gandara).

Table 1: Electronic database search results.

Database	Date of search	Number of citations
Medline (Ovid) <1950 to April 30, 2012	Limited to April 30, 2012	167
EMBASE Classic+EMBASE <1947 to 2012 Week 20>	Limited to April 30, 2012	350
Scopus	April 30, 2012	49
- Cochrane Central Register of Controlled Trial - Cochrane Database of Systematic Reviews - Database of Abstracts of Reviews	2nd Quarter 2012 Reviews 2005 to April 2012	13
LILACS	April 30, 2012	33
Web of Science	April 30, 2012	148
Global Health	April 30, 2012	3

Initial screening results

Initial screening of the abstracts identified 287 duplicated articles (articles found in more than one database) and 376 abstracts were deemed to be not relevant by both reviewers. A total of 120 studies were selected after the initial screening for a potential study.

Full-text articles of these potential studies were obtained through the Ottawa Hospital library. Only one study could not be located⁶² leaving 119 studies being fully obtained for review by the reviewers.

From the 119 studies, 20 studies were written in languages other than English (6 in Japanese, 5 in French, 4 in Spanish, 2 in German, 1 in Polish and 1 in Bulgarian). With the help of neurosurgery residents and a haematologist we were able to translate all of these articles with the exception of those written in Japanese⁶³⁻⁶⁸, which were therefore excluded. The complete texts of 113

studies were reviewed by each reviewer independently. A summary of the screening and search protocol and rationale is shown in Figure 1.

Eligibility decision results

The eligibility of studies was made by two investigators (Fahad Alkherayf & Esteban Gandara). Each reviewer assessed the full text of 113 studies with consideration of the inclusion and exclusion criteria and found 79 studies ^{6, 15,21,2,34,56,69-139} to be non relevant as they did not describe restarting oral anticoagulants after ICH in patients with MHV.

Ten articles were excluded for various reasons (Table 2). Three articles ¹⁴⁰⁻¹⁴² were letters to editors of journals or authors' comments. Owing to pregnancy being an exclusion criterion, one case report ¹⁴⁵ was excluded because it described ICH in a pregnant patient on oral anticoagulants. One article ¹⁴⁶ was a short abstract about a case which was presented at the 4th Gulf Cooperation Council Neurology Conference. It was published in the supplement issue of Neuroscience. As we were not able to obtain the details of the case after trying to contact the author, we decided to exclude the article. Four articles ^{8,148-150} were review articles about intracranial haemorrhage and anticoagulation, but because they were review articles they were excluded.

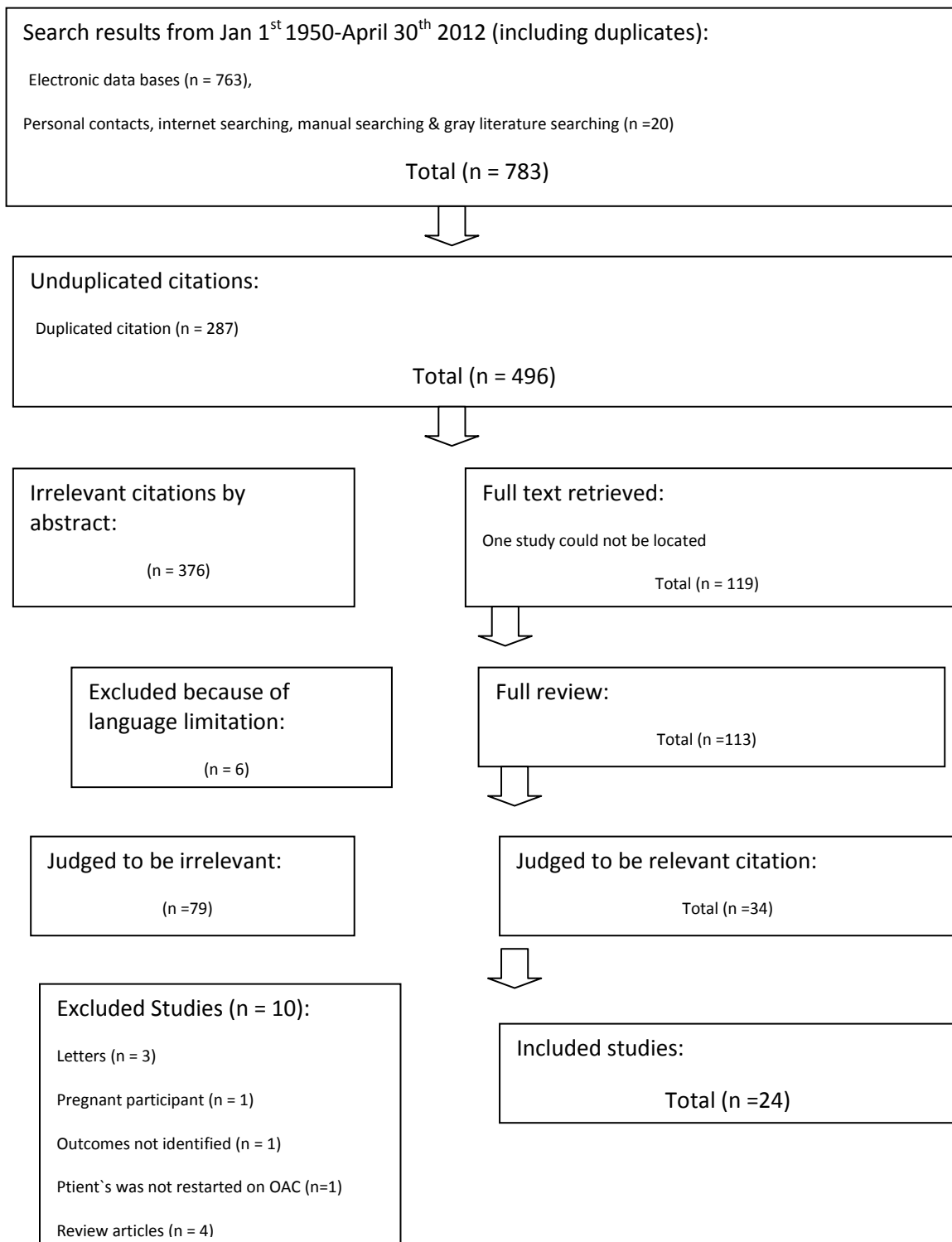


Figure 1: Literature search methodology and screening flow chart with results.

One article ¹⁴⁶ discussed the use of warfarin compared to antiplatelet agents in patients with ICH and MHV. However, the reported case was only concerned with antiplatelet therapy and the patient did not receive OAC after the ICH. This study was therefore excluded.

Table 2: Studies excluded from the systematic review.

Study	Year of publication	Reason for exclusion
Fuller et al.	2004	Letter to the editor
Phan et al.	2001	Correspondence letter
Wijdicks et al.	1999	Correspondence letter
Bagga et al.	2001	Case report of a pregnant patient
Khan et al.	2004	Outcomes were not reported
Thompson et al.	2009	Review article
Romualdi et al.	2009	Review article
Kienast et al.	1997	Review article
Al-Ahmad et al.	2001	Review article
Wong et al.	1987	Patient was not restarted on OAC

In summary, arising from our eligibility decisions we excluded 79 articles from the 113 identified for reasons of non-relevance. We excluded a further 10 studies for reasons presented in the above section, leaving us with a total of 24 articles for our literature review.

Multiple reports results

We identified two studies ^{33, 42} that shared participants. The first study ³³ (Wijdicks et al.) was a case series of 26 patients with MHV and ICHs. The second study ⁴² (Phan et al.) described a series of patients treated with OACs who had ICHs. The second study included all the patients in the first study in addition to others. The second study also included patients who were treated

with OAC for reasons other than MHV. Because the first study focussed on patients with MHV and ICHs, it provided more information about the 26 patients. The second study acknowledged that 26 patients had been previously reported in the first study. In our collected data we recognised this and avoided duplicating data from the 26 patients.

Eligibility criteria pilot test results

For the eligibility criteria pilot test we chose 12 studies ^{10, 41,66,90,110,135,138,140,145,148,149,151} from the 119 studies and each reviewer independently evaluated them. The reviewers reached the same decision in 11 studies (Table 3), while for one study ⁹⁰ the decision was reached after a discussion between the two reviewers.

Ten studies were excluded (Table 3); two studies were review articles, one was a guideline, one was a letter to the editor of a journal, three did not describe OACs after ICH in patients with MHV, one did not report the outcomes, one involved pregnant participants, and one study was excluded because of language limitations.

Reviewers' agreement was calculated using kappa statistic (Table 4). The overall agreement was 0.917; the free-marginal kappa was 0.833.

Table 3: Results from the eligibility criteria pilot test.

Study	Number of reviewer(s) agreed to include the study	Number of reviewer(s) disagreed to include the study	Reason for exclusion, if the study was excluded
Thompson et al.	0	2	Review article
Romualdi et al.	0	2	Review article
Caird et al.	0	2	Did not describe restarting OACs after ICH
Fuller et al.	0	2	Letter to journal editor
Kirazli et al.	1	1	Excluded after discussion (case report for patient with spinal epidural haematoma)
Saposnik et al.	0	2	Did not describe restarting oral anticoagulants after ICH
Bagga et al.	0	2	Study participants were pregnant
Crawley et al.	2	0	
Bertram et al.	0	2	Did not describe restarting oral anticoagulants after ICH
Butler et al.	2	0	
Hinata et al.	0	2	Language
Wong et al.	0	2	Guidelines

Table 4: Reviewers' agreement using kappa statistic.

Reviewer 2 (Esteban Gandara)	Reviewer 1 (Fahad Alkherayf)			Total
		Included studies	Excluded studies	
Included studies		2	1	3
Excluded studies		0	9	9
Total		2	10	12

Included studies

Twenty-four studies^{9, 10, 33, 41, 42, 45, 143, 147, 159, 161, 162, 165-168, 170-172, 176-181} were included in our systematic review (Figure 1 & Table 5). Most of the studies were written in English. The studies were published between 1978 and 2008. More than one third of the studies were done in the USA (Figure 2).

Table 5: Studies included in the systematic review.

Study	Year of publication	Language of publication	Country of the study
Lieberman et al.	1978	English	USA
Barra et al.	1979	French	France
Gomez et al.	1988	English	USA
Babikian et al.	1988	English	USA
Lau et al.	1991	English	Hong Kong
Nagano et al.	1991	English	Japan
Sharma et al.	1994	English	India
Kawamata et al.	1995	English	Japan
Nakagawa et al.	1995	English	Japan
Wijdicks et al.	1998	English	USA
Butler et al.	1998	English	UK
Zingale et al.	1999	English	Italy
Crawley et al.	2000	English	UK
Petrasko et al.	2000	English	USA
Phan et al.	2000	English	USA
Ananthasubramaniam et al.	2001	English	USA
Jain et al.	2002	English	India
Henderson et al.	2004	English	Australia
Conti et al.	2005	English	Italy
De Vleeschouwer et al.	2005	English	Belgium
Park et al.	2006	English	USA
McClaskey et al.	2007	English	USA
Kapisiz et al.	2007	English	Turkey
McKenzie et al.	2008	English	UK

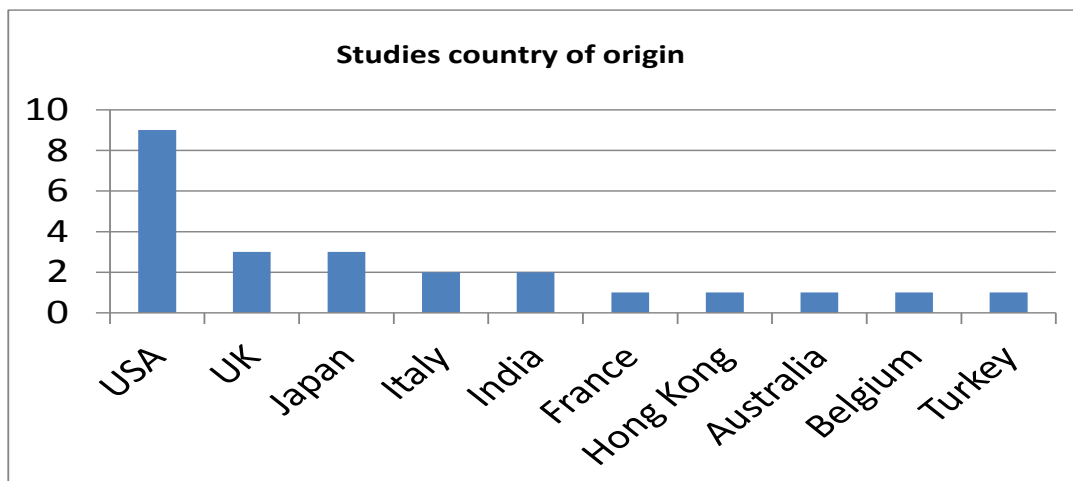


Figure 2: Country of origin of the included studies.

In summary, the articles selected to form the data of our review originated from multiple countries, with the majority originating in the USA. The year of publication of these articles ranged from 1978 through 2008, and the majority were published in English.

Types of studies

There were no randomized controlled studies, prospective cohorts, or case-control studies identified. Approximately two thirds of the studies were case reports and the remainder were case series (Figure 3).

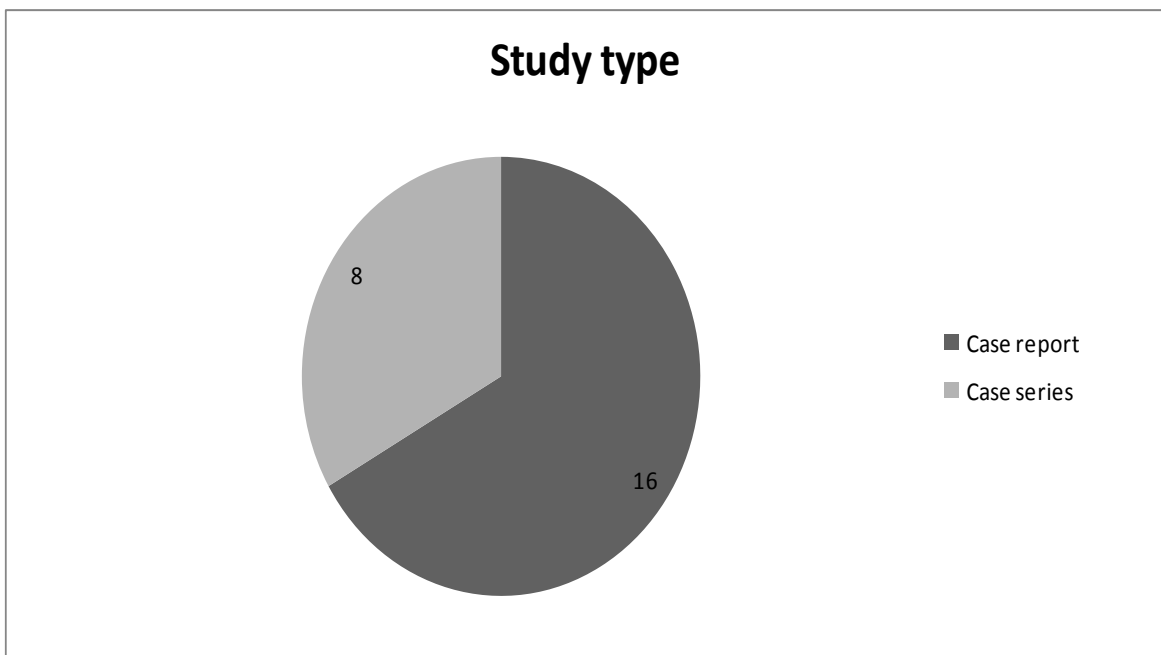


Figure 3: Types of included studies in the systematic review.

Eight case series ^{9, 33, 41, 42, 45, 161, 162, 170} were included in our review (Table 6). For these studies we only included patients with MHV and ICH who had their OAC restarted. The remaining studies in our review were case reports ^{10, 143,147, 159, 165-168, 171, 172, 176-181} (Table 7).

Table 6: Case series included in this systematic review.

Study	Study type	Number of centers	Followup	Number of included patients
Babikian et al.	Retrospective	One	6 months	6
Kawamata et al.	Retrospective	One	1 month	20
Wijdicks et al.	Retrospective	One	Up to 3 years	26
Butler et al.	Retrospective	One	Up to 28 months	16
Zingale et al.	Retrospective	One	2 months	4
Phan et al.	Retrospective	One	Up to 3 years	28 (26 reported before)
Ananthasubramaniam et al.	Retrospective	One	6 months	2
De Vleeschouwer et al.	Retrospective	One	2 months	19

Table 7: Case reports included in this systematic review.

Study	Year of publication	Language of publication	Country of the study
Lieberman et al.	1978	English	USA
Barra et al.	1979	French	France
Gomez et al.	1988	English	USA
Lau et al.	1991	English	Hong Kong
Nagano et al.	1991	English	Japan
Sharma et al.	1994	English	India
Nakagawa et al.	1995	English	Japan
Crawley et al.	2000	English	UK
Petrasko et al.	2000	English	USA
Jain et al.	2002	English	India
Henderson et al.	2004	English	Australia
Conti et al.	2005	English	Italy
Park et al.	2006	English	USA
McClaskey et al.	2007	English	USA
Kapisiz et al.	2007	English	Turkey
McKenzie et al.	2008	English	UK

Case series analysis results

Number of patients and types of intracranial haemorrhages

There were 89 patients included in the eight case series studies (Table 8). Five studies specified the type of ICH, while the remainder failed to stipulate or we were unable to deduce the type of haemorrhage. The number of patients who had ICH with MHV and were restarted on their OAC in each study ranged from 1 to 26 (Table 9). For the initial type of ICH that we were able to identify in the 49 cases, 13 were intracerebral haemorrhages, 31 were subdural haematomas, 1 was a cerebellar haemorrhage, and 4 were other types of haemorrhages (Figure 4).

Table 8: Types of ICH within the case series studies.

Study	Number of included patients	Patients with intracerebral haemorrhage	Patients with SDH	Patients with cerebellar haemorrhag	Patients with other haemorrhag
Babikiane et al.	6	3	3	0	0
Kawamata et al.	20	NA	NA	NA	NA
Wijdicks et al.	26	5	17	1	3
Butler et al.	12	4	7	0	1
Zingale et al.	4	0	4	0	0
Phan et al.	2 (26 had already been included)	NA	NA	NA	NA
Ananthasubramaniam et al.	1	1	0	0	0
De Vleeschouwer et al.	19	NA	NA	NA	NA

NA: Not ascertainable

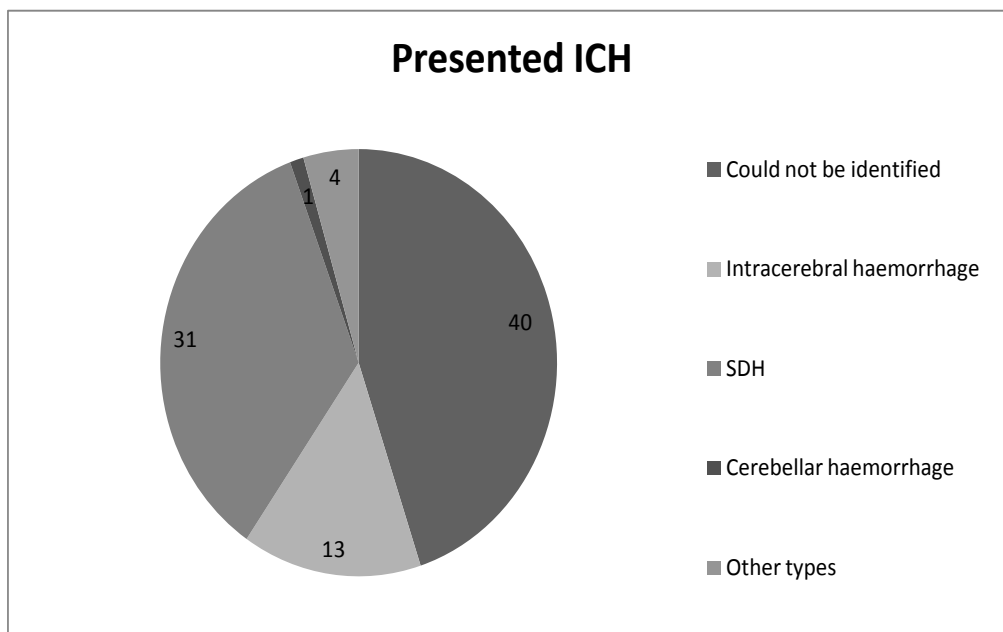


Figure 4: Types of presenting ICH identified within the case series studies.

Table 9: Extracted data from the case series studies.

	Observational studies							
	Babikiane	Kawamata	Wijdicks	Butler	Zingale	Phan	Ananthasubramaniam	De Vleeschouwer
Number of patients	6	20	26	12	4	2 (26 previously reported)	1	18
Mean age (years)	57.3	56.8	69 (median)	60.5	62	NA	NA	72
Patients with mitral MHV	2	NR	11	7	2	NA	NA	NA
Patients with aortic MHV	3	NR	12	4	2	NA	1	NA
Patients with tricuspid MHV	1	NR	0	NA	0	NA	NA	NA
Patients with multiple MHV	0	NR	3	1	0	NA	0	NA
Patients with craniotomy (after 1 st bleed)	0	13	14	NR	4	NA	1	NA

Patients taking anti-platelets	0	NR	0	NR	NR	NA	0	NR
Patients with therapeutic INR	6	NR	17	5	2	NA	NR	NA
Patients with sub-therapeutic INR	0	NR	0	0	1	NA	NR	NA
Patients with supra-therapeutic INR	0	NR	9	7	1	NA	NR	NA
Mean or median (range) for timing of restarting OAC	Mean 19 days Median 16 days (5-42 days)	NA (3 days-1month)	Median 8 days (2 days-3 months)	Median 7 days (3 -19 days)	Mean 5.2 days Median 3 days (1-14 days)	NA	21 days	Median 11 days
Target INR at restart	NR	2-4	2-4	2-3.5	NR	NA	NR	NR
Heparin after 1 st bleed	No	NR	yes	yes	yes	NA	NR	yes
Outcomes								
Patients with recurrent ICH	0	4 (20%)	1(3.8%)	1(8.3%)	2 (50%)	NA	0	1 (5.6%)
Type of recurrent ICH	0	3 SDH, 1 cerebral	cerebral	SDH	1 SDH, 1 cerebral	NA	0	SDH
Timing from restarting OAC	0	3-7 days	3 years	NR	13 days & 22 days	NA	0	4 months
INR at recurrence ICH	0	2-4	2	3.5	NR	NA	0	NR
Patients with other major haemorrhages	0	NR	0	0	0	NA	0	NR
Patients with valve thrombosis	0	1	0	2	0	NA	0	0
Timing from restarting OAC		3 days		3months & 8months		NA		
Patients with CVA	0	1	0	3	1	NA	0	0

Patients with DVT	0	0	0	0	0	NA	0	0
Patients with PE	0	0	0	0	0	NA	0	0
Patients with other thromboembolic events	0	0	0	0	0	NA	0	1
Duration of followup	6 months	1 month	3 years	2 years	2months	NA	6 months	2 months

NR: Not reported, NA: Not ascertainable

Of the eight case series studies, only three studies^{33, 41, 45} included patients with MHV and ICH. The other five studies^{9, 42, 161, 162, 170} included patients who were taking OAC for various reasons including MHV or patients with MHVs and presented with major haemorrhages. From these studies we were able to identify patients who had MHV and presented with ICH.

One of these five studies⁹ included patients with MHV and major haemorrhages. Most of the included patients had a gastrointestinal bleed and only one patient who had ICH was restarted on OAC. The other four studies^{42, 161, 162, 170} included patients who had ICH and who were taking OACs for different reasons, including MHV.

Quality assessment

All the case series studies were retrospective, the majority of them had a short followup and none were multicentre (Table 6). The largest study included only 26 patients with ICH and MHV. None of these studies had a comparison

group. All of the studies reported ICH based on CT scan or MRI. All recurrent ICH were diagnosed based on CT scan or MRI.

Using Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies, the majority of the case series studies scored only three stars out of 9 (Table 10), i.e. all of them were of low quality. Using the Oxford Centre for Evidence-based Medicine Level of Evidence all case series studies were level 4, i.e. poor quality.

Table 10: Quality assessment of the case series studies.

Study	NOS (number of stars)	Oxford Level of Evidence	Overall study quality
Babikian	2	Level 4	Low
Kawamata	3	Level 4	Low
Wijdicks	3	Level 4	Low
Butler	4	Level 4	Low
Zingale	3	Level 4	Low
Phan	4	Level 4	Low
Ananthasubramaniam	3	Level 4	Low
De Vleeschouwer	3	Level 4	Low

Baseline characteristics

The mean patient age within the included studies ranged from 57 to 72 years (Table 9). Most of the MHV were mitral or aortic in location. Among the studies in which we were able to identify the INR during the first ICH, the majority of patients had therapeutic levels (INR 2.0-4.0). In all studies OAC was stopped at the time of ICH diagnosis. In five studies it was unclear whether patients underwent surgical treatment for their ICH. In all studies patients were restarted

on their OAC at different times. Six studies reported the mean or median time of restarting OAC ranging from 3 to 21 days.

Outcomes

Seven of the eight case series studies reported recurrent ICH (Table 9). In one study⁴² the reviewers tried to obtain this information from the author, but this was unsuccessful (Table 9). All of the studies that reported recurring ICHs also specified the type of recurrent bleed. Most of the studies reported no occurrence of valve thromboses. In addition, most studies reported cerebrovascular accidents (CVA). There were no major haemorrhages, deep venous thrombosis (DVT), or pulmonary emboli (PE).

For the main outcomes of recurrent ICH, valve thrombosis and CVA, we excluded the studies of Phan et al. & Ananthasubramaniam et al. Phan et al.⁴² reported only two additional patients to the previous series (Wijdicks et al.) who had MHV and were restarted on OAC. Ananthasubramaniam et al.⁹ had only one patient out of 20 patients who had MHV and presented with ICH and who was restarted on OAC. Furthermore, these two studies did not report on most outcomes.

Overall ICH recurrent proportion and studies' heterogeneity

Eighty-six patients were included; there were eight recurrent ICHs (Figure 5). The rate of recurrence within each study ranged from zero to 50%; however,

the CI for each study was very wide (Figure 5). Two studies had very small samples; one study included 6 patients while the other one included only 4 patients.

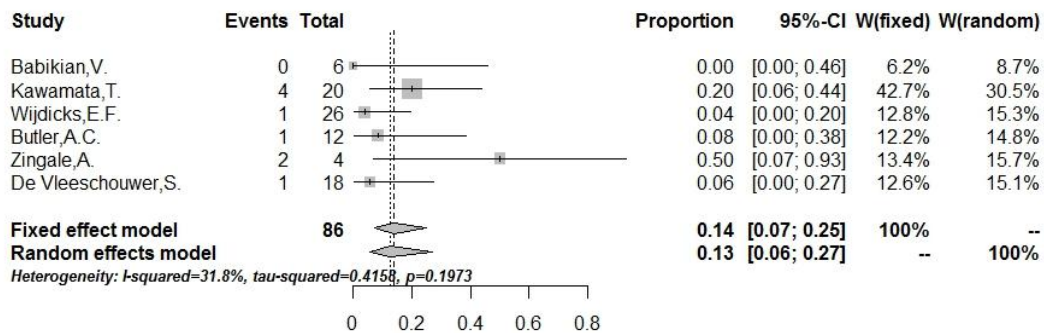


Figure 5: Forest plot for recurrent ICH.

The proportion of overall recurrence of ICH using the fixed effect model was 0.14 (CI 0.07 – 0.25), but when we looked at the amount of variation between studies, the I-squared was 31% with a *P* value of 0.20. Owing to this significant heterogeneity, we elected to not perform further meta-analysis.

Overall valve thrombosis proportion and studies' heterogeneity

Three of the eighty-six patients developed a valve thrombosis (Figure 6). The rate of valve thrombosis within each study ranged from zero to 17%. However, the same issue with very wide CI for each study was again identified (Figure 6).

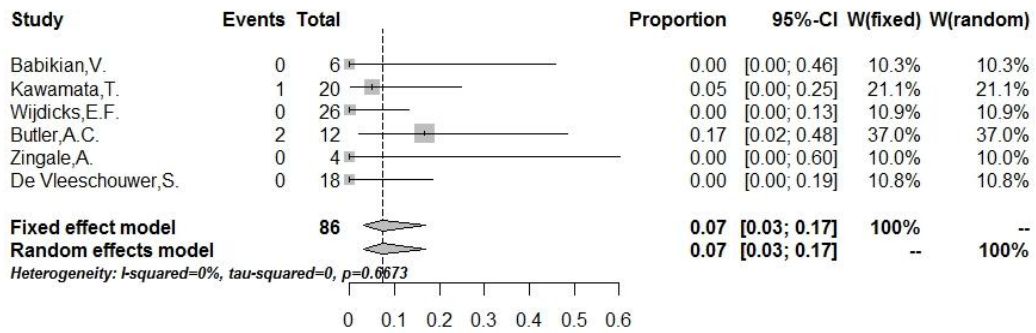


Figure 6: Forest plot for valve thrombosis.

The proportion of overall development of valve thrombosis using the fixed effect model was 0.07 (CI 0.03 – 0.17). When we looked at the amount of variation between studies the distribution of I-squared was flat because there was no valve thrombosis in 4 studies. The *P* value of the I-squared was 0.67. Because of this significant heterogeneity, we elected to not perform further meta-analysis.

Overall CVA proportion and studies' heterogeneity

Five of the eighty-six patients developed a CVA (Figure 7). The rate of CVA within each study ranged from zero to 25%; again with a very wide CI (Figure 7). The proportion of overall development of CVA using the fixed effect model was 0.12 (CI 0.05 – 0.23). Looking at the amount of variation between studies the I-squared was 24% with a *P* value of 0.25. Because of this significant heterogeneity, we elected to not perform further meta-analysis.

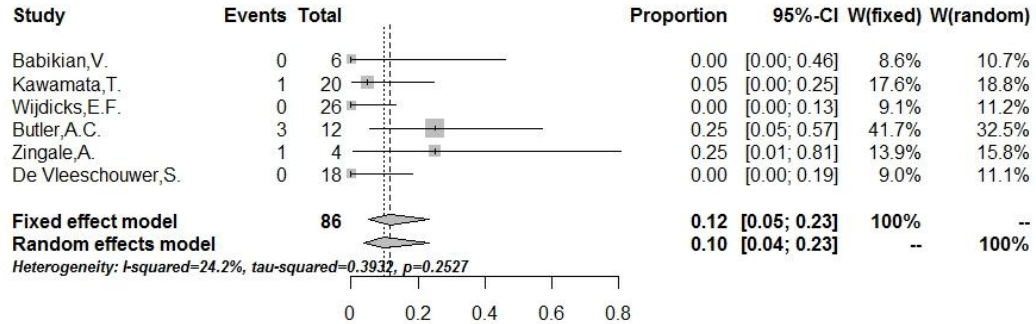


Figure 7: Forest plot for CVA occurrence.

Time of restarting OAC and recurrence of ICH

Two studies^{45, 161} reported their mean time of restarting OAC (Table 9). The first study reported a mean restart time of 5.2 days and reported a recurrence rate of 50%. The second study described a mean of 19 days and reported zero recurrence of ICH. Given the heterogeneity of the studies, sample size and the difference in followup, we could not calculate the overall recurrence rate in relation to the mean time of restarting OAC.

Meta regression analyses

We conducted a meta-regression logistic model aimed at identifying the relation between the timing of OAC restraint and the recurrence rate of ICH. We included five studies from which we were able to extract the needed data (Babikian et al., Wijdicks et al., Butler et al., Zingale et al. & De Vleeschouwer et

al.). The slope was -0.215, but the *P* value was 0.1 (Table 11). Given that our result was not statistically significant, we did not perform further analyses.

Table 11: Results of the meta-regression analysis.

	estimate	se	zval	pval	ci.lb	ci.ub
intercept	-0.3769	1.1695	-0.3223	0.7472	-2.6692	1.9153
M.restart.OAC	-0.2154	0.1290	-1.6695	0.0950	-0.4683	0.0375

INR level and recurrence of ICH

Because of the heterogeneity of the studies, we could not calculate the recurrence rate in relation to INR levels (sub-therapeutic, therapeutic, and supra-therapeutic). However, one study included 12 patients with 58% of these patients having a supra-therapeutic INR level and an ICH recurrence rate of 8.3% at a 2-year followup (Table 9).

Craniotomy and recurrence of ICH

Four case series studies included patients who had surgical intervention (craniotomy) for their ICH (Table 9). The ICH recurrence rate within these patients ranged from 3.8% to 50%. Because of the heterogeneity of the studies

and the difference in followup, we were unable to calculate the overall recurrence rate of ICHs within patients who underwent surgical intervention.

Valve location and recurrence of ICH

In five studies we were able to identify the location of the MHV (Table 9), but we were unable to identify the ICH recurrence rate in relation to the location of the MHV.

ICH recurrence and type of initial ICH

ICH recurrence in patients with intracerebral haemorrhage

Among the selected case series studies 4 studies reported patients who presented with parenchymal intracerebral haemorrhage as a subtype of ICH (Table 12). Thirteen patients were identified. They were restarted on their OAC in the time range of 2 to 27 days. None of these patients were reported to experience a recurrence of any type of ICH or develop a CVA. Only two patients developed a valve thrombosis (Figure 8).

The followup for the patients in the identified studies ranged from 6 months to 3 years. Due to the small number of patients and no report of recurrent ICH, we were unable to perform any useful statistical analyses.

Table 12: Studies with intracerebral haemorrhage as the initial ICH.

	Case series studies			
	Babikiane.	Wijdicks.	Butler	Ananthasubramaniam.
Number of patients with intracerebral haemorrhage	3	5	4	1
Mean age (years)	55.6	69	57	NA
Patients with mitral MHV	1	2	2	0
Patients with aortic MHV	2	2	2	1
Patients with tricuspid MHV	0	0	0	0
Patients with multiple MHV	0	1	0	0
Patients with craniotomy (after 1 st haemorrhage)	0	0	NR	1
Patients taking antiplatelet	NR	0	NR	0
Patients with therapeutic INR	3	NR	1	NR
Patients with sub-therapeutic INR	0	NR	0	NR
Patients with supra-therapeutic INR	0	NR	3	NR
Mean or median (range) for timing of restarting OAC	Mean 18 day Median 19 days (8-27 days)	Median 8 days (2 days-3 months)	Median 7 days (3 -19 days)	21 days
Target INR at restart	NR	2-4	2-3.5	NR
Heparin after 1 st bleed	No	yes	yes	NR
Outcomes				
Patients with recurrent ICH	0	0	0	0
Patients with other major haemorrhages	0	0	0	0
Patients with valve thrombosis	0	0	2	0
Timing from restarting OAC			3 months & 8 months	
Patients with CVA	0	0	0	0
Patients with DVT	0	0	0	0
Patients with PE	0	0	0	0
Patients with other thromboembolic events	0	0	0	0
Duration of followup	6 months	3 years	2 years	6 months

NR: Not reported, NA: Not ascertainable

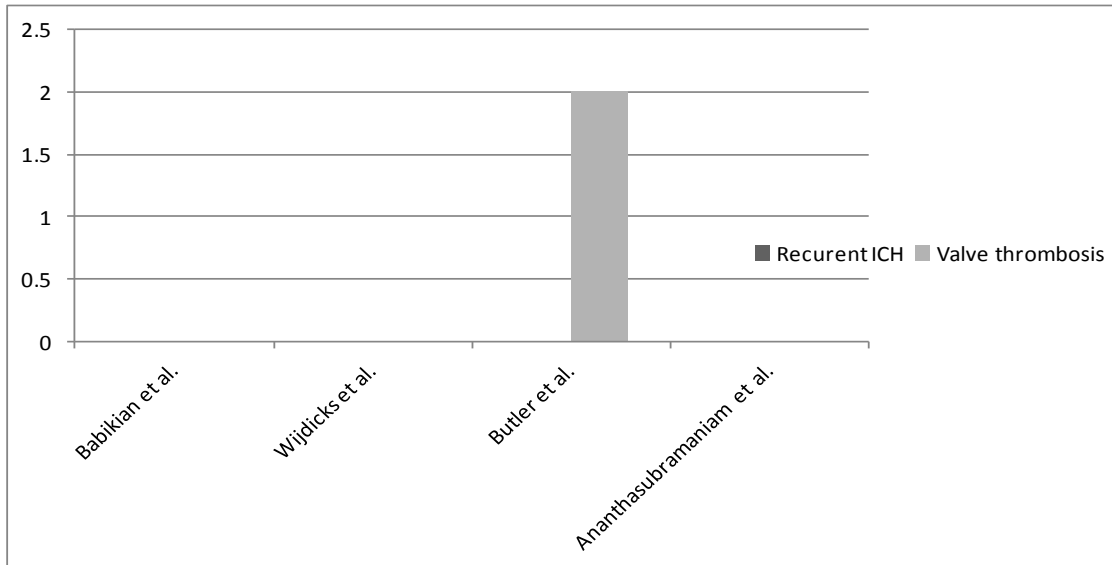


Figure 8: Recurrence of ICH versus valve thrombosis in patients with intracerebral haemorrhages.

ICH recurrence in patients with SDH

Among the selected case series studies 4 studies reported patients who presented with SDH as a subtype of ICH (Table 13). Thirty-one patients were restarted on their OAC in the range of 2 to 42 days. Four patients had a recurrence of ICH, two had recurrence of SDH, while the other two patients developed a parenchymal intracerebral haemorrhage. No patients developed valve thrombosis, while three patients developed CVA (Figure 9).

Followup for patients in the identified studies ranged from 6 months to 3 years. Due to the small number of recurrent ICHs and no report of these patients developing valve thrombosis, we were not able to perform further useful statistical analyses.

Table 13: Studies with SDH as the initial ICH.

	Case series studies			
	Babikian.	Wijdicks	Butler	Zingale
Patients with SDH	3	17	7	4
Mean age (years)	59	69	62.5	62
Patients with mitral MHV	1	7	5	2
Patients with aortic MHV	1	8	1	2
Patients with tricuspid MHV	1	0	0	0
Patients with multiple MHV	0	2	1	0
Patients with craniotomy (after 1 st bleed)	0	13	NR	4
Patients taking antiplatelet	NR	NR	NR	NR
Patients with therapeutic INR	3	NA	4	2
Patients with sub-therapeutic INR	0	NA	0	1
Patients with supra-therapeutic INR	0	NA	3	1
Mean or median (range) timing of restarting OAC (days)	Mean 20 days Median 13 days (5-42 days)	Median 8 days (2 days-3 months)	Median 7 days (3 -19 days)	Mean 5.2 days Median 3 days (1-14 days)
Target INR	NR	2-4	2-3.5	NR
Heparin after 1 st bleed	No	Yes	Yes	Yes
Outcomes				
recurrent ICH	0	1	1	2
Type of recurrent ICH		Cerebral bleed	SDH	1 SDH, 1 cerebral
Timing from restarting OAC		3 years	NR	13 days & 22 days
INR at recurrent ICH		2	3.5	NR
other major hemorrhages	0	0	0	0
Patients with valve thrombosis	0	0	0	0
Patients with CVA	0	0	2	1
Patients with DVT	0	0	0	0
Patients with PE	0	0	0	0
Duration of followup	6 months	3 years	2 years	2 months

NR: Not reported, NA: Not ascertainable

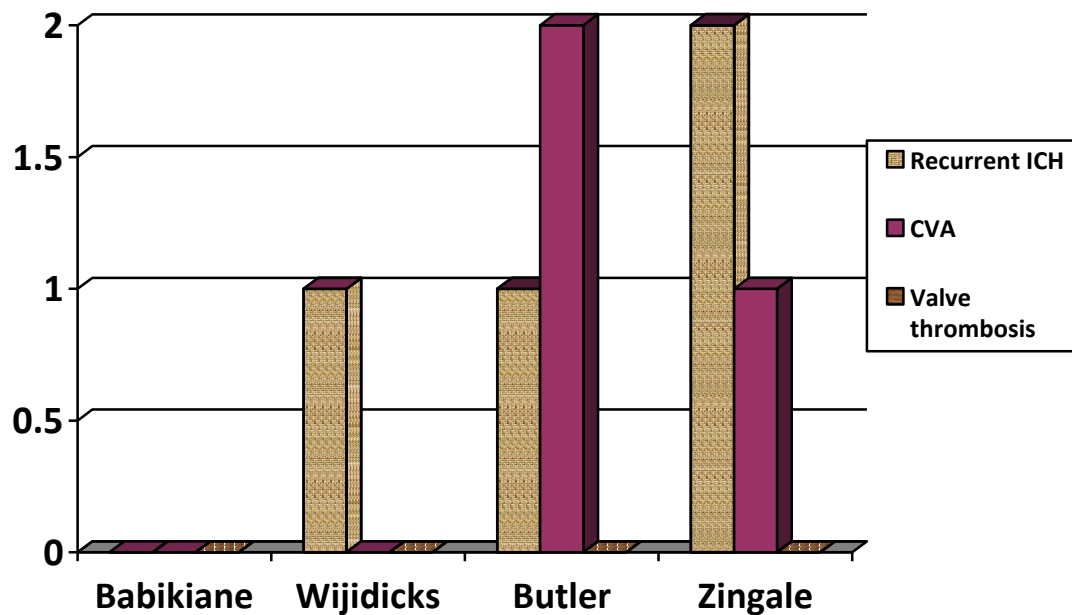


Figure 9: Recurrence of ICH versus valve thrombosis and CVA in patients with SDH.

ICH recurrence in patients with cerebellar haemorrhage

Amongst the case series studies, only one study reported a single patient who presented with cerebellar haemorrhage as a subtype of ICH (Table 14). This patient did not develop any complications. We did not perform any analysis given that only one patient was identified.

Table 14: Studies including cerebellar haemorrhage as the initial ICH.

	Case series
	Wijdicks,E.F.
Number of patients with cerebellar bleed	1
Mean age (years)	NA
Patients with mitral MHV	1
Patients with multiple MHV	0
Craniotomy (after 1 st bleed)	No
Patients taking antiplatelet	No
Patients with therapeutic INR	NA
Patients with sub- therapeutic INR	NA
Patients with supra-therapeutic INR	NA
Timing of restarting OAC	NA
Target INR at restart	2-4
Heparin after 1 st bleed	yes
Outcomes	
Recurrent ICH	No
Other major haemorrhages	No
Valve thrombosis	No
Timing from restarting OAC	NA
CVA	No
DVT	No
PE	No
Other thromboembolic events	No
Duration of followup	3 years

NA: Not ascertainable

ICH recurrence in patients with other types of ICH

Among the selected case series studies two studies reported patients who presented with ICH that was not intracerebral, subdural, or cerebellar (Table 15). Four patients were identified in one study and their OAC was restarted in the range of 2 days to 3 months. We could not tell when OACs were started in the second study. There were no recurrent ICHs or valve thrombosis reported for patients in these studies, although one patient developed a CVA. With this data we were not able to perform any useful statistical analyses.

Table 15: Studies with other types of ICH as the initial ICH.

	Case series studies	
	Wijdicks,E.F.	Butler,A.C.
Number of patients with other types of bleed	3	1
Mean age (years)	69	61
Patients with mitral MHV	1	0
Patients with aortic MHV	2	1
Patients with multiple MHV	0	0
Patients with craniotomy (after 1 st bleed)	1	NR
Patients taking antiplatelet	0	NR
Patients with therapeutic INR	NA	
Patients with sub- therapeutic INR	NA	
Patients with supra-therapeutic INR	NA	1
Mean or median (range) timing of restarting OAC	Median 8 days (2 days-3 months)	NA
Target INR at restart	2-4	2-3.5
Heparin after 1 st bleed	yes	yes
Outcomes		
Patients with recurrent ICH	0	0
Patients with other major hemorrhages	0	0
Patients with valve thrombosis	0	0
Patients with CVA	0	1
Patients with DVT	0	0
Patients with PE	0	0
Patients with other thromboembolic events	0	0
Duration of followup	3 years	2 years

NR: Not reported, NA: Not ascertainable

Publication bias

Eight studies were included in our analysis of which two had small sample sizes (Phan et al. & Ananthasubramaniam et al.). We performed a funnel plot (Figure 10) for the 6 studies with an understanding that our results may have limited value due to our small number of studies. The funnel plot showed asymmetry of the study within the funnel. This would suggest a publication bias, but this is limited by the small number of studies retrieved from the literature.

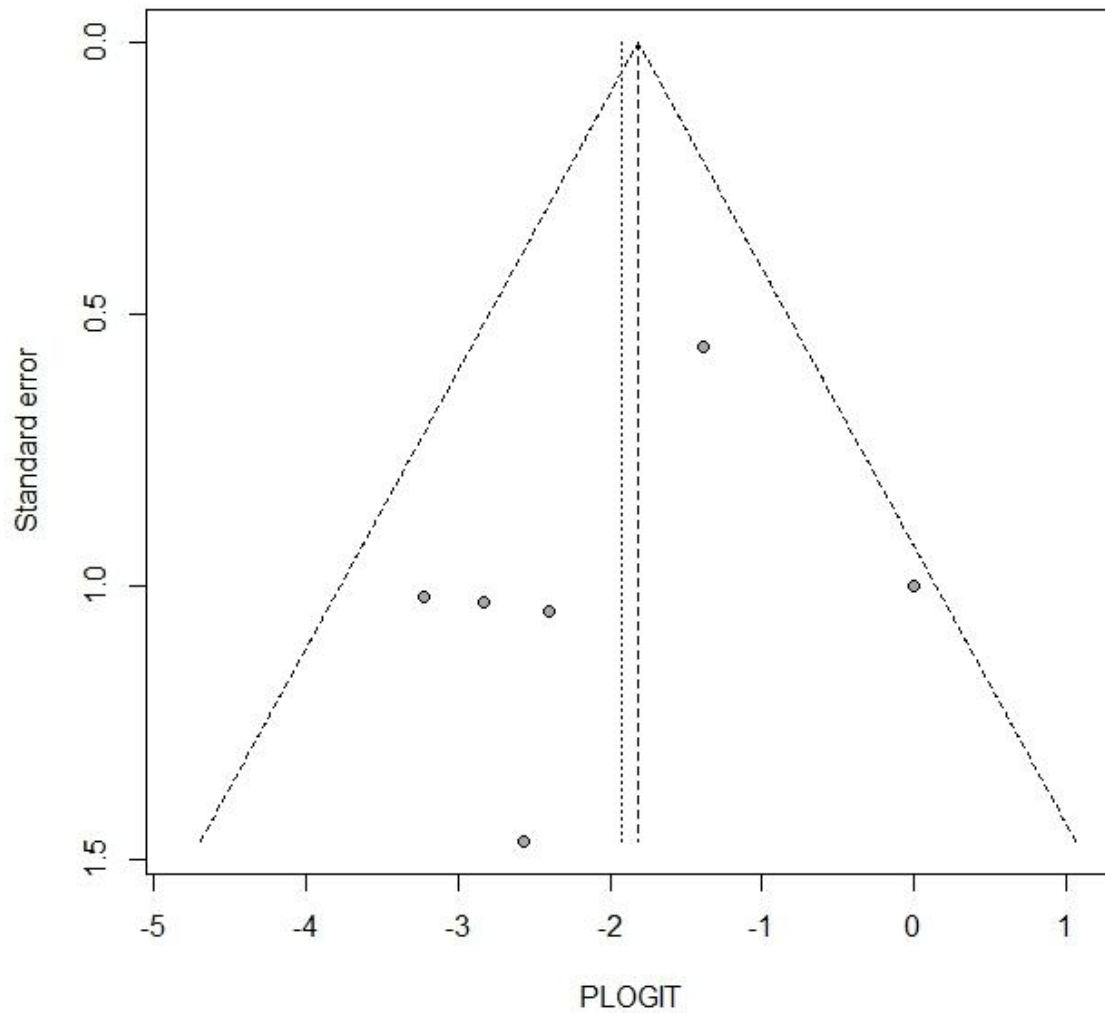


Figure 10: Funnel plot of the included case series studies.

Case report analysis results

Number of patients and types of intracranial haemorrhages

Sixteen case report articles ^{10, 143, 147, 159, 165-168, 171, 172, 176-181} were included in our analysis with a total of 20 patients with MHV who had ICH (Table 16). The

majority of the articles reported one case, while 4 articles each reported two cases. Fourteen patients presented with intracerebral haemorrhage (Figure 11), five patients presented with SDH, and one patient had a subarachnoid haemorrhage. There were no patients with a cerebellar haemorrhage. One article¹⁸⁰ was reported in French while the rest were in English (Table 7). Publication dates for these articles were between 1978 and 2008. Furthermore, the followup for these patients was short.

Table 16: Extracted data from included case reports

	Case reports						
	Lieberman	Barra	Gomez	Lau	Lau	Nagano	Nagano
Type of ICH	intracerebral	SDH	intracerebral	intracerebral	intracerebral	intracerebral	intracerebral
Age (years)	68	42	63	63	65	18	60
Location of MHV	Mitral	Mitral	Aortic	Multiple	Mitral	Aortic	Aortic
Atrial fibrillation	yes	No	No	yes	yes	No	No
Craniotomy (after 1 st bleed)	yes	yes	No	No	No	Yes	yes
Antiplatelet	No	No	No	No	NO	No	NO
INR	Therapeutic	NR	Therapeutic	Therapeutic	Therapeutic	Therapeutic	Therapeutic
Timing of restarting OAC	1 day	1 day	14 days	11 day	5 days	7 day	NR
Target INR at restart	NR	2-4	2-4	1-2	1-2	2-4	NR
Heparin after 1 st bleed	No	No	yes	yes	No	No	No
Outcomes							
Recurrent ICH	yes	No	No	No	No	yes	No
Type of recurrent ICH	Intracerebral					Intracerebral	
Timing from restarting OAC	1 day					3 months	
INR at recurrent ICH	NR					NR	
Other major haemorrhages	NO	No	No	No	No	No	No
Valve thrombosis	NO	No	No	No	No	No	No
Timing from restarting OAC							
Other thromboembolic events	NO	No	No	No	No	No	No
Duration of followup	2 days	1month	NR	3 months	36 months	4 months	4 months

Case reports (continue)							
	Sharma	Nakagawa	Nakagawa	Crawley	Petrasko	Jain	Henderson
Type of ICH	intracerebral	SDH	SDH		intracerebral	intracerebral	Subarachnoid bleed
Age (years)	45	60	53	70	77	50	38
Location of MHV	Mitral	Mitral	Aortic	Aortic	Multiple	Multiple	Aortic
Atrial fibrillation n	yes	No	No	yes	No	yes	No
Craniotomy (after 1 st bleed)	No	yes	yes	No	No	No	No
Antiplatelet	NR	No	No	NR	NO	No	NO
INR	Supra-therapeutic	Therapeutic	Therapeutic	Therapeutic	Therapeutic	Supra-therapeutic	Therapeutic
Timing of restarting OAC	20 day	4 day	90 days	1 days	28 days	42day	21 days
Target INR at restart	2	NR	NR	1-2	2-2.5	2.5-3.5	2-4
Heparin after 1 st bleed	No	No	No	No	NR	yes	No
Outcomes							
Recurrent ICH	No	No	No	yes	No	No	No
Type of recurrent ICH				Intracerebra			
Timing from restarting OAC				38 days			
INR at recurrent ICH				NR			
Other major haemorrhages	NO	No	No	No	No	No	No
Valve thrombosis	NO	No	No	No	No	No	No
Other thromboembolic events	NO	No	No	No	No	No	No
Duration of followup	3 months	8 months	18 months	3 months	12 months	Not reported	1 month

	Case reports (continued)					
	Conti.	Park	McClaskey	Kapisiz	Kapisiz	McKenzie
Type of ICH	intracerebral	intracerebral	SDH	intracerebral	SDH	intracerebral
Age (age)	53	53	57	52	73	63
Location of MHV	Multiple	Mitral	Aortic	Multiple	Mitral	Mitral
Atrial fibrillation n	No	NR	yes	No	No	yes
Craniotomy (after 1 st bleed)	No	No	yes	No	No	No
Antiplatelet	No	No	yes	No	NO	No
INR	Therapeutic	Supra-Therapeutic	Therapeutic	Supra-therapeutic	Supra-therapeutic	Therapeutic
Timing of restarting OAC	38 day	8 days	15 days	14 days	21 days	14 days
Target INR at restart	2.5	2-3	2-4	1.5-2	NR	2-3
Heparin after 1 st bleed	yes	No	No	yes	No	yes
Outcomes						
Recurrent ICH	No	No	No	No	No	No
Other major haemorrhages	NO	No	No	No	No	No
Valve thrombosis	NO	No	No	yes	No	No
Other thromboembolic events	NO	No	No	No	No	No
Duration of follow up	12 months	2 months	1 month	6 weeks	6 weeks	1 month

NR: Not reported

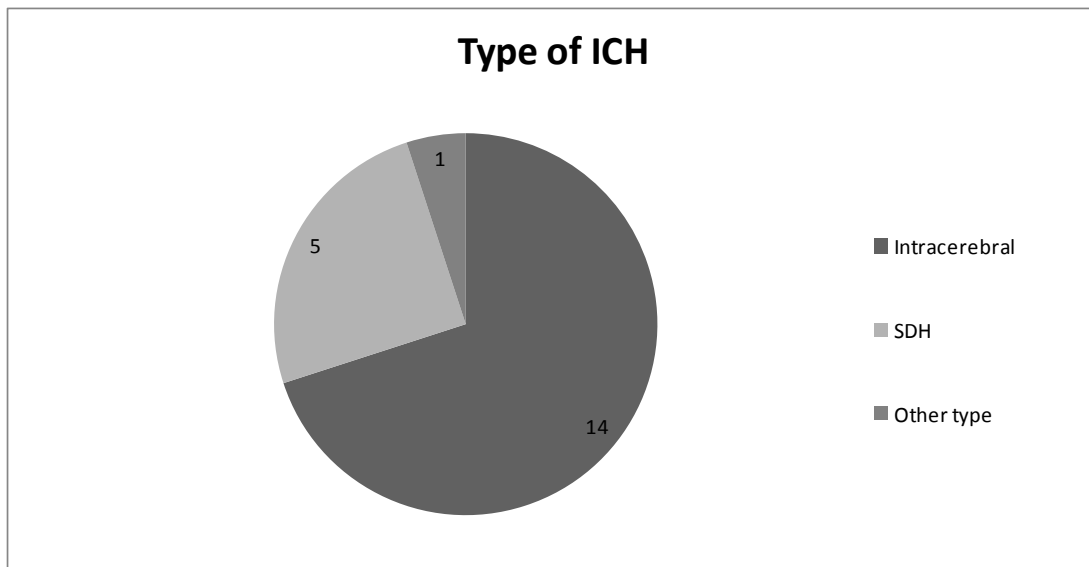


Figure 11: Types of initial ICH in the included case reports.

Baseline characteristics

The age of the reported cases ranged from 18 to 77 years. Eight patients had mitral valves, seven had aortic valves, and five had multiple valves (Figure 12).

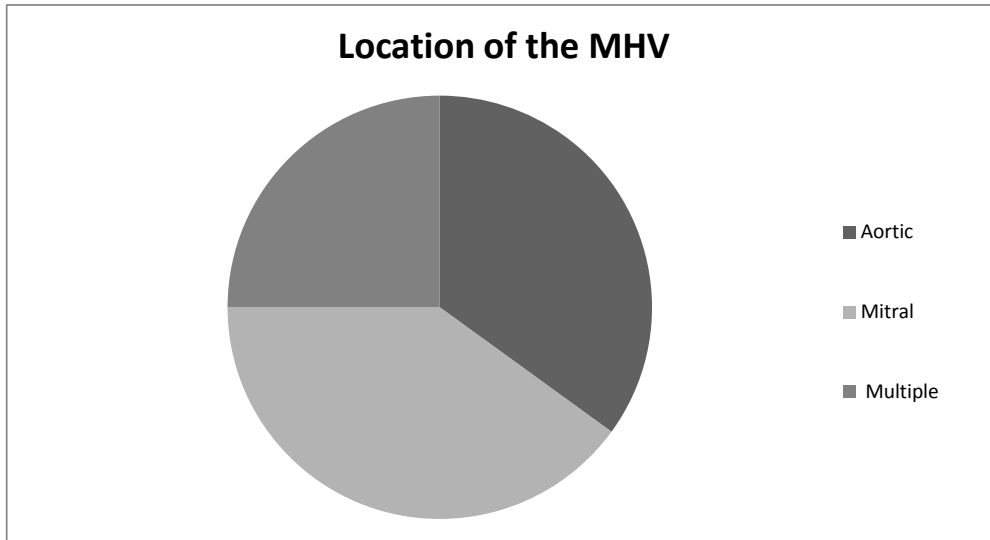


Figure 12: Location of MHV in the included case reports

The majority of patients had therapeutic INR levels at the time of their initial haemorrhage. The timing for restarting these patients on their OAC ranged from 1 day to 42 days.

Outcomes

Three patients had a recurrent ICH (Table 16) and all of them had an intracerebral haemorrhage as their initial presentation. Their recurrent ICH was

intracerebral as well. OAC was restarted on day 1 for two of these patients, while OAC for the third patient was restarted on the 7th day after the first bleed. One of the recurrent ICH occurred within one day of restarting OAC, while the other two occurred approximately one month from the day of restarting OAC.

One patient developed a valve thrombosis while the other 19 patients did not develop any valve thrombosis during their followup. The patient who developed a valve thrombosis was restarted on OAC on day 14 after their initial ICH. None of the patients developed PE, CVA, or major haemorrhages during their followup.

Discussion

Search strategy and included studies

We obtained assistance from two experienced health librarians who reviewed our literature search strategy. We searched the most common electronic databases, manually reviewed citations, and contacted experts in our study field. By performing our search strategy as explained earlier in detail, we believe the likelihood of missing important studies is improbable.

We were able to obtain full text articles of all published potential studies from our literature search except for one study⁶². We tried to obtain this article through the Ottawa Hospital library, but the article could not be located. We also tried to contact the author of the study, but we were not successful in retrieving the full text article.

Exclusion criteria

In our exclusion criteria we decided to exclude studies that encompassed the two population groups of pregnant participants and paediatric participants. Anticoagulation treatment during pregnancy usually requires special consideration as warfarin, the most commonly used oral anticoagulant, is associated with fetal risk mainly during 6 to 12 weeks of gestation⁹. A common practice during pregnancy is to use heparin instead of OAC during the first trimester and the last month of pregnancy.

Paediatric participants were excluded because causes of ICH in children differ to the adult population. For example, most paediatric intracerebral haemorrhages are caused by arteriovenous malformation¹⁸⁴. Further, the need for MHVs and their management is different within the paediatric group.

We excluded review articles and letters, but we manually reviewed their citations to identify any additional potential studies. Such an approach reassured us that we did not miss any prospective study.

Initially we did not set language as an exclusion criterion. However, we identified six articles written in Japanese. None of these articles described randomized controlled trials or prospective trials. Five of these articles were case reports and only one⁶³ article described followup in patients receiving anticoagulation therapy. This latter study included 37 patients with MHV, but the abstract suggested that the main focus of the article was complications related

to OAC and did not describe restarting OAC in these patients. As these articles were unlikely to affect the result of our review and due to the difficulty of finding help with translating the Japanese language, we elected to exclude these articles from our analyses.

Collected data and missing data

In our data collection we aimed to collect the following information:

Sample size, mean patient age, location of the MHV, presence of atrial fibrillation, type of MHV, number of MHV, patient history of thromboembolisms, surgical intervention after initial ICH, antiplatelet therapy, INR level at initial ICH, type of ICH, timing of restarting OAC, heparin administration after the initial bleed, antiplatelet therapy after the initial bleed, target INR after restarting OAC, recurrence of ICH, timing of recurrence of ICH, occurrence of valve thrombosis, development of any major haemorrhage, CVA, DVT, and PE.

In patients with MHV many factors affect the risk of valve thrombosis^{185,186}. Some of these factors are related to the valve itself such as valve type, location, and number of prostheses. Other risk factors are patient related such as atrial fibrillation, age, history of thromboembolisms, and INR levels¹⁸⁵.

The risk of haemorrhaging in patients on OAC therapy may increase in relation to elevation of the INR and also use of antiplatelet drugs^{4,187}. Many studies have found a direct relationship between the intensity and risk of an ICH^{4,187}.

Because of the diversity in the mechanism and treatment of different types of ICH, we tried to identify types of ICH from the included studies. For example, many SDHs require surgical treatment, while most intracerebral haemorrhages are treated without surgical intervention.

Since elevated INR levels might be a risk factor for the initial ICH, we tried to identify the target INR level after restarting the OAC and the level of INR during any recurring ICH.

Many of the articles included in this review were missing some of the abovementioned data. Three out of the eight case series articles (Phan et al., Ananthasubramaniam et al. & De Vleeschouwer et al.) included many patients taking OAC. The majority of these patients were being treated with OAC for reasons other than MHV. We were not able to identify the specific data for the patients with MHV. Although we tried to contact the authors to get this data, we were unfortunately not successful. This limitation in the available data restricted our ability to perform many statistical analyses.

Reviewers' agreement and eligibility criteria pilot test

The reviewers reached matching decisions for all the included studies in the eligibility criteria pilot test apart from one article. The disagreement arose when one reviewer included a case report⁹⁰ that described a spinal epidural haematoma in a patient taking OAC. Following a discussion between the

reviewers the study was excluded owing to knowledge that the spinal cord is not part of the intracranial central nervous system.

Many studies^{189, 190} suggest using free marginal kappa statistic when reviewers are not forced to assign a certain number of articles to each category. This was the same situation encountered in our study. The kappa statistic obtained in this study suggested adequate agreement between the reviewers.

A pilot eligibility criteria test was performed by both reviewers before the study articles were fully reviewed. We found performing this pilot test to be extremely helpful for training the reviewers. An additional advantage of performing the pilot test was to let the reviewers become familiar with the data collection sheet. After completing the pilot test we updated our data collection sheet to enhance its clarity.

Studies quality

No RCT or prospective cohort studies were identified. All included studies were case series or case reports. We did not do any quality assessment for case reports because we did not include them in our statistical analyses. All of the included studies scored three to four stars using the Newcastle-Ottawa Quality Assessment Scale (NOS) and all of them were level 4 when we applied the Oxford Centre for Evidence-Based Medicine Level of Evidence, i.e. all studies were low quality.

The use of scoring systems in observational studies may not demonstrate the validity of the included studies and the use of quality scoring in meta-analysis of observational studies remains controversial ¹⁸⁷. However, the MOOSE group ¹⁹¹ recommended reporting quality scoring.

NOS is a system that evaluates studies based on selection of study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest ⁵⁷. The face/content validity of the NOS has been established ⁵⁷. One limitation of the NOS is that it does not have a threshold to distinguish between good and poor quality. However, we found NOS easy to use and self explanatory, making it useful for us to evaluate the quality of articles.

In addition, we included reports on the quality of studies using the Oxford Centre for Evidence-Based Medicine Level of Evidence because many neurosurgeons are more familiar with this than many other quality scoring systems.

Participant characteristics

All patients with MHV need lifelong OAC. The target INR ranges from 2.5 to 3.5 depending on the type and location of the MHV ⁵⁷. All patients in our included studies were receiving OAC and the majority had a therapeutic INR at their initial ICH. All patients in the included studies were restarted on their OAC.

In reviewing the literature we did not come across a study where patients were not restarted on anticoagulants.

The mean age of patients ranged from 57.3 to 72 years and the majority of included patients had a single MHV. The majority of patients received heparin after their initial ICH.

From the baseline characteristics of patients included in the case series studies, we believe these patients are representative of the majority of patients with MHV who present with ICH.

Risk of ICH and re-bleed

The risk of first time ICH in middle-aged and older populations is about 0.4%⁵ and this includes mostly intracerebral haemorrhage. OAC increases the risk of having ICH and the risk of ICH in patients taking OAC ranges from 0.25% to 1.1% per year.

The recurrent rate of ICH in the general population might be less than that in patients with MHV. In a retrospective study Vermeer et al.¹⁹⁴ included 243 patients with intracerebral haemorrhage; more than 90% of these patients were not taking OAC. These authors reported an ICH recurrence rate of 2.1% per year. A similar rate for ICH recurrence has been reported in other studies^{4, 16, 187}. The recurrence rate of ICH in the population with SDH who are not on OAC has been reported to range from 3.7% to 12%¹⁹⁷. The recurrence rate of ICH after restarting OAC in patients with MHV has clearly not been established.

Our included case series studies reported a recurrence rate of zero to 50% (Table 17). Unfortunately all of the included studies had a relatively small sample size and are liable to publication bias.

Table 17: Summary of outcomes from the case series studies.

	Number of patients	Cranio-tomy	Timing of restarting OAC	Recurrent ICH	Valve thrombosis	CVA	Follow up
Babikian	6	0	Median 16 days	0	0	0	6 months
Kawamata	20	13	NA	4 (20%)	1 (5%)	1(5%)	1 month
Wijdicks	26	14	Median 8 days	1 (3.8%)	0	0	3 years
Butler	12	NR	Median 7 days	1 (8.3%)	2 (16.7%)	3(25%)	2 years
Zingale	4	4	Median 3 days	2 (50%)	0	1(25%)	2 months
De Vleeschouwer	18	NA	Median 11 days	1 (5.5%)	0	0	2 months

NR: Not reported, NA: Not ascertainable

Babikian et al.⁴⁵ reported 6 patients with MHV who had an ICH (3 intracerebral haemorrhages and 3 SDH). The patients' OACs were stopped at the time of ICH diagnosis, but then was resumed after a mean interval of 19 days. None of their patients developed recurrent haemorrhages at a 6-month followup.

Wijdicks et al.³³ reported 26 patients with MHV who had ICH (5 intracerebral haemorrhages, 17 SDH, and 1 with another intracranial bleed). OAC therapy was stopped for all of them following ICH diagnosis. Fourteen patients required surgical treatment. OACs were resumed after a median of 8 days. A single patient developed a recurrent bleed (3.8%) over 3-years followup.

Butler et al.⁴¹ reported 12 patients with MHV who had an ICH (4 intracerebral haemorrhages, 7 SDH, and 1 with another intracranial bleed). OAC therapy was stopped in all of these patients, but was resumed after a median of 7 days. A single patient developed a recurrent bleed (8.3%) over a 2-year followup.

De Vleeschouwer et al.¹⁷⁰ included 18 patients with MHV and ICH who were restarted on their OAC. Oral anticoagulants were resumed after a median of 11 days. Only one patient developed a recurrent bleed (5.5%) over 2-month followup.

Kawamata et al.¹⁶² analyzed patients with ICH resulting from OAC. They included 20 patients with MHV. The range of restarting OAC was less than 3 days to more than 1 month, with more than 50% of these patients being restarted on their OAC within 3 days or less. They had 4 patients with recurrent ICH (20%) and their followup was at one month.

Zingale et al.¹⁶¹ reported 7 patients with SDH while taking OAC. Four of these patients had MHVs. OACs were resumed after a mean of 5.2 days. Two of the four patients had recurrent bleed (50%) over a 2-month followup.

Because of the heterogeneity and different followup times between studies, we could not calculate the recurrence rate of ICHs. However, it appears that the reported rates are higher in patients with MHV than those without MHV.

Most included case reports stated no recurrence of ICH. Given that those were only case reports, we were unable to obtain any useful analysis regarding

the rate of ICH recurrence. Furthermore, case reports are prone to publication bias.

Risk of valve thrombosis

While thrombosis associated with MHV is generally rare, it is associated with serious morbidity and mortality^{195, 196, 199}. Valve thrombosis in patients with MHV is usually caused by inadequate anticoagulation therapy^{195, 196}. The incidence of valve thrombosis is about 4% per patient-year without OAC¹⁹⁹. This risk is typically less with OAC where incidence of valve thrombosis ranges between 0.3% and 2.3% per patient-year¹⁹⁹.

The case series studies (Table 17) included 89 patients for which there were three reported valve thromboses. Kawamata et al.¹⁶² reported 20 patients of which one patient had developed a valve thrombosis within a one-month followup. Butler et al.⁴¹ reported 12 patients of which two patients developed valve thrombosis within 2-years followup. The two patients developed a valve thrombosis after 3 and 8 months of restarting their OAC. The median time for restarting OAC in the series of Butler et al. was 7 days.

On the other hand, Wijdicks et al.³³ reported 26 patients with the longest available followup (three years), during which none developed a valve thrombosis. The median time for restarting OAC in Wijdicks et al. series was 8 days.

Because of the heterogeneity among studies, we were not able to perform comparisons between studies. In addition, all studies had small sample sizes. This factor may explain the zero occurrence of valve thrombosis.

Within the case reports only one article reported occurrence of valve thrombosis and the involved patient was restarted on OAC on day 14 after the initial ICH. In many of the reported cases patients were restarted on their OAC at 14 days or after and did not report valve thrombosis.

From the case series and the case reports it seems that development of a valve thrombosis is generally a rare outcome. It also appears that the risk is small even if the OAC is started three weeks after the initial haemorrhage. At the same time we acknowledge that there are many limitations to making any definitive conclusion from the included studies.

Risk of CVA

One of the feared complications of withholding OAC is development of CVA. This includes ischemic stroke and transient ischemic attack (TIA). The rate of development of CVA in the included studies vary among the studies.

Babikian et al.⁴⁵ reported 6 patients with MHV who had an ICH; OACs were stopped and heparin instituted. OACs were resumed after a mean interval of 19 days. None of their patients developed CVA after 6-months followup. Also, Wijdicks et al.³³ reported 26 patients with MHV who had an ICH; OACs were

stopped for all of them and were resumed after a median of 8 days. None of their patients developed CVA over 3-years followup.

On the other side Butler et al.⁴¹ reported 12 patients with MHV who had ICHs. All patients received heparin after the initial haemorrhage and OACs were resumed after a median of 7 days. Three patients (25%) developed a CVA.

From our included case series studies it is difficult to make any conclusion given the small sample size and heterogeneity of data. Publication bias may also overestimate the real incidence of CVA in relation to timing of restarting OAC.

Initial INR level and recurrence of ICH

The majority of patients included in the identified studies had a therapeutic INR at their initial ICH (Table 9). Two studies reported a large percentage of their patients had supra-therapeutic INR levels. Wijdicks et al.³³ included 9 patients (34%) with supra-therapeutic INR. With their study the recurrence rate was 3.8% over 3-years followup. Butler et al.⁴¹ included 7 patients (58%) out of 12 patients who had supra-therapeutic INR. Only one patient had a recurrent ICH. From the included case reports 3 patients had recurrent ICHs. All of these patients had therapeutic INR levels at their initial ICH.

It is difficult to draw any conclusions between INR levels and risk of recurrent ICH. The initial INR may have no role in increasing the recurrent risk of ICH. This is most likely related to the fact that all patients with ICH in the included studies had their INR corrected at the time of diagnosis of their ICH.

Craniotomy and recurrence of ICH

Many neurosurgeons are reluctant to restart patients on OAC immediately after surgery. A common practice is to wait 2 to 4 weeks after surgery before resuming OAC treatment. However, in patients with MHV there is a concern of thromboembolic complications. In the included case series studies (Table 17), Wijdicks et al.³³ reported that in 26 patients 14 underwent surgical treatment for their ICH and over the subsequent 3 years only one patient had recurrent ICH. Kawamata et al.¹⁶² included 20 patients with ICH, of which 13 had surgical intervention for their ICH. These patients demonstrated a recurrent rate of 20% within one month. Zingale et al.¹⁶¹ included 4 patients in their study, all of whom had surgical intervention and 2 experienced recurrent ICH.

It therefore appears that surgical intervention may play a limited role in the recurrence rate of ICHs, especially when we consider the timing of resuming OAC therapy. Kawamata et al.¹⁶² reported a recurrence rate of 20% and more than half of the included patients were restarted on their OAC within the first 3 days after their initial bleed. Zingale et al. had a median of 3 days of restarting OAC. Wijdicks et al. on the other hand only reported recurrence of 3.8% over 3 years and the median of starting OAC was 8 days.

We were not able to perform any useful statistical analysis because of the heterogeneity in data and different followup periods. However, it seems that

surgical intervention may play a limited role in increasing the risk of recurrent ICH in patients with MHV.

Time of restarting OAC and recurrence of ICH

Utilizing data from the included case series, we conducted a meta-regression logistic model with the aim of identifying the relation between the timing of OAC restraint and recurrence rate of ICH. The following covariates were included: Timing of restarting OAC, patient age, location of the valves, presence of surgical intervention after initial ICH, INR level at initial bleed (sub-therapeutic, therapeutic, supra-therapeutic), and use of heparin after initial ICH. We excluded three studies.

The slope of the meta-regression was -0.215, but the *P* value was 0.1 (Table 11). This result suggests a negative relation between the timing of restarting the OAC and the recurrence of ICH. This result was statistically insignificant (*P* value 0.1).

These results are most likely affected by the small number of patients included in our meta-regression, especially with the relatively small incidence of recurrent ICH. Also, this analysis was affected by the fact that the followup was short for most of the studies.

By observing the case series (Table 17) it appears that the longer the restart time of OAC is, the less likely there will be a recurrence of an ICH. Butler et al. reported a recurrence rate of 50% with a median time of restarting OAC of

3 days. On the other hand, Babikian et al. reported zero recurrence of ICH with a median time of restarting OAC of 16 days.

Within the case reports there were three reported cases with recurrent ICH. In two of them the OAC was restarted within one day after the initial bleed. In the third case report the OAC was restarted on day 7. However, there were also three case reports where OAC was restarted within the first week with no recurrence of ICH.

We did not obtain any significant statistical analysis because of data heterogeneity and the difference in followup times. However, it seems that restarting OAC within the first 3 days is associated with a higher chance of ICH recurrence.

Risk of re-bleed in patients with different types of ICH

About two thirds of ICHs in patients taking OAC are intracerebral while the remainder are subdural ¹⁹. When we considered the type of the initial ICH in our included studies we were able to identify the initial type of ICH in less than half of the included patients. This is most likely caused by the fact that many physicians use the term intracranial bleed to describe intracerebral haemorrhage. Given that this is an assumption, we only considered patients where the type of ICH was clearly identified.

There was no recurrence of ICH in 13 patients that presented with intracerebral haemorrhage. Four recurrent ICHs occurred in 31 patients who had

SDH. Wijdicks et al.³³ included 5 patients with intracerebral haemorrhages and 17 patients with SDH. There was one recurrence of ICH in the patient population with the SDH. We could not identify whether there was a difference in the timing of restarting OAC between these two groups of intracerebral and subdural haemorrhages. Also, Butler et al.⁴¹ reported recurrent ICH within the SDH group, but not in patients who presented with intracerebral haemorrhage.

Most of SDH are caused by trauma while most intracerebral haemorrhages are spontaneous. Owing to the small number of patients in each study, it is difficult to draw conclusions, although the SDH group might have a higher risk of ICH recurrence considering the mechanism of the initial ICH.

Potential biases and limitations

Our study was subject to many limitations and biases. One of the main limitations of this study was that it was based on small patient numbers. This led to a lack of data to show a meaningful conclusion. Another limitation affecting our review was that our analyses included mixed studies as not all of the included studies were designed to establish the relationship between restarting time of OAC and recurrence of ICH or development of valve thrombosis.

Our review might also have been subjected to outcome reporting bias. It is likely that many studies where no recurrence of ICH occurs are not published. Also, publication bias is one of the main sources of biases that affected our study. Our planned assessment of publication bias was by using the funnel plot.

However, as we only had six studies, this limited the interpretation of the funnel plot. In addition to the limited number of studies, each of the included studies had a very small sample size. In our funnel plot there was asymmetry with four studies in one side, suggesting a possible bias. However, at least ten studies should be included to be able to obtain a useful interpretation of the funnel plot.

Our review was not able to provide any statistically significant data regarding timing of restarted OAC and recurrence of ICH. This was caused by many factors including lack of good quality studies with large sample sizes to include in the meta-analyses. Another factor contributing to the limited statistical analyses was the presence of significant heterogeneity between published studies. Despite our effort we could not find any unpublished study addressing restarting OAC in patients with MHV and ICH.

Conclusion

When should oral anticoagulation therapy in adult patients with MHV and intracranial haemorrhage be reinstated?

Most MHV are used in young populations with long life expectancies. All patients with MHV will need lifelong OAC therapy to reduce their risk of valve thrombosis and stroke. This preventative management exposes them to iatrogenic risk of ICH. It is very important to balance these two major issues. While the protective effect of OAC is clear, it is not clear when the ideal time is to

restart patients on their OAC after they develop an ICH. In addition, the natural history of recurrent ICH in this group has not been identified in the literature.

Unfortunately we could not conduct a meaningful meta-analysis because of the small sample size of the available studies and the significant heterogeneity among them. In addition, all of the available studies were low quality studies and not many of them had a comparison group.

Despite all of the limitations imposed on the current review, it appears from literature that the risk of recurrent ICH is higher when OAC is restarted within the first 4 days following diagnosis of the haemorrhage. At the same time the risk of valve thrombosis may not be influenced if OAC therapy is resumed later than the first week. Further, it appears that patients who present with SDH might be at a higher risk of experiencing a recurrence of their ICH than patients presenting with an intracerebral haemorrhage. Also, a higher INR seems to be associated with a higher rate of ICH.

In conclusion, withholding the OAC for 4 days after the initial ICH might be safe for patients with intracerebral haematomas, while in patients with SDH it might be safe to withhold their OAC for about a week after their initial haemorrhage.

CHAPTER 3

The Survey

Introduction and rationale

The standard management of patients with mechanical heart valve (MHV) is lifelong anticoagulation with oral anticoagulant (OAC), with most guidelines recommending that the INR for patients with MHV should be kept between 2.5 and 3.5^{4, 12-15, 199}.

One of the life threatening complications associated with the use of OAC is intracranial haemorrhage (ICH). While the guidelines for management of intracerebral haemorrhage associated with OAC suggest rapid reversal of the coagulopathy caused by OACs^{5,19, 28}, not all physicians will do this in patients with MHV¹³⁹ due to fear of stroke and valve thrombosis. Furthermore, physicians have diverse practices for reversing the effect of OAC⁵.

However, it appears that most patients with MHV and ICH are managed by correcting their coagulopathy, in addition to surgical intervention in some situations. Most patients will resume their OAC at some point after the ICH. In our systematic review we noted that the time physicians restart their patients with MHV on OAC after ICH is variable and controversial. As previously discussed, the literature does not support a specific time; some studies

suggested restarting OAC within a short time from correction of the patient's INR, while other studies recommended waiting for a few weeks before recommencing OAC therapy.

This controversy in the literature has created different practices among neurosurgeons and thrombosis experts during management of patients with MHV and ICH. Most decisions are based on a treating physician's personal experience. To identify the current practice of physicians with respect to the time to restart OAC, we conducted a survey that included North American members of the American Association of Neurological Surgeons (AANS) and International Society of Thrombosis and Haemostasis (ISTH) who practice in North America.

Survey Objectives

The main goal of the survey was to identify the current practice of neurosurgeons and thrombosis specialists in Canada and USA regarding the time to restart OAC in adult patients with MHV who present with ICHs.

The survey aimed to identify whether physicians differ in the timing of restarting OAC according to the type of ICH. Further, since some patient related factors may affect the decision, this survey also intended to identify if certain risk factors affect the decision on time to restart OAC.

We endeavoured to test whether a physician's speciality, country of practice, type of practice, average number of cases they managed annually, and years of practice influenced their decisions.

Another objective of this survey was to identify whether neurosurgeons and thrombosis experts would be willing to participate in future studies, either a randomized controlled trial (RCT) or a cohort study.

The survey was started in October 2011. Consequently our objectives were related to the information available at the time of the survey.

Methods

Population of interest and sample selection

The population of interest were neurosurgeons and thrombosis experts who manage patients with MHV and ICH in the USA and Canada. The sampling frame was the neurosurgeons and thrombosis experts who were active members of the American Association of Neurological Surgeons (AANS) or International Society of Thrombosis and Haemostasis (ISTH) during the year 2010.

Active members of the AANS include neurosurgeons with special interests in paediatrics, spine, functional neurosurgery, epilepsy, general, peripheral nerves, oncology, and cerebrovascular neurosurgery ²⁰¹.

Members of ISTH include physicians and non-physicians who are mostly scientists ²⁰².

We had access to the membership directory of both organisations. Dr. Alkherayf had access to neurosurgeons' e-mail addresses through his membership with the AANS and Dr. Wells had access to thrombosis experts' e-mail addresses through his membership with the ISTH.

We manually reviewed both directories; given our population of interest we excluded paediatric, spine, functional, epilepsy and peripheral nerves neurosurgeons. We also excluded neurosurgeons that practiced in Mexico. For the ISTH members, we excluded paediatric haematologists, basic scientists and members who practiced outside USA or Canada.

All active members of AANS and members of ISTH with valid e-mail addresses who met our abovementioned criteria were included in our survey sample.

Survey design

Our survey was an observational cross-sectional survey, but also aimed to examine the relationship among physician specialities, country of practice, type of practice, average number of cases they managed annually, years of practice, and timing of restarting OAC in patients with MHV and ICH. The survey was a self-administrated internet-based survey.

In our systematic review the majority of ICHs were identified as either intracerebral or subdural. Therefore in our survey we included two clinical scenarios, one was a patient with an intracerebral haemorrhage and the other

was a patient with a SDH. The two key questions asked were, 1) if physicians would reverse their patient's coagulopathy, and 2) when would physicians restart their patients on OACs for each scenario?

Survey key questions

The first question in our survey addressed whether physicians would reverse coagulopathy in their patients at time of ICH diagnosis. As we discussed in our systematic review, most authors recommend correcting coagulopathy in patients with MHV and ICH. Despite this, some physicians may not correct the coagulopathy¹³⁹. Although we did not specify how coagulopathy would be corrected, we did ask participants whether they would correct the coagulopathy in patients with MHV and ICH.

The second key question was about timing of restarting OAC. Our systematic review did not demonstrate a consistency with regard to timing of restarting OAC in patients with MHV and ICH. OAC therapy was usually resumed between 3 days and 3 months with the majority being between 3 and 42 days. Kawamata et al.¹⁶² reported restarting OAC in a time range from 3 days to 1 month. Butler et al.⁴¹ reported restarting OAC in a time range of 3 to 19 days, while Babikian et al.⁴⁵ described restarting OAC in the range of 5 to 42 days. It seems that the first week after diagnosis of ICH is more critical than the rest for successfully choosing the time to reinitiate OAC. Some authors reported the occurrence of rebleeding or thromboembolic complications within the first

three days of discontinuing OAC. Given that the first seven days might present different critical time points, we divided the first week into three time intervals. Our survey included seven options of time intervals to reinitiate OAC. These options were: First 72 hours (first 3 days), 73 hours to 120 hours (4 days to 5 days), 121 hours to 168 hours (6 days to 7 days), 8 days to 14 days, 15 days to 21 days, 22 days to 28 days, and more than 28 days.

Several clinical risk factors may influence the response to restart time and reversal of coagulopathy, specifically patient age, presence of surgical intervention, haematoma size, patient's CHADS2 score, recent PE, recent DVT, MHV type, MHV location and multiplicity. These factors were chosen because some increase the risk of thromboembolic complication and others may increase rebleeding risk.

Justification of inclusion of the clinical risk factors

Management of ICH may include surgical intervention^{19, 24}. Many neurosurgeons are reluctant to restart OAC after surgical intervention. Participants were therefore asked about time of restarting OACs in patients with MHV who presented with ICH and underwent a surgical intervention.

Another factor that may contribute to when OACs are restarted is the size of the initial intracranial haematoma. Given that large sized intracranial haematomas are associated with higher morbidity and mortality^{86, 203, 204}, treating physicians might consider this in deciding the time to restart OAC. Many

literatures^{205, 206} consider large intracerebral haematomas as being more than 30 cm³. To determine whether haematoma size affected a treating physician's decision of when to resume OAC therapy, this survey considered haematomas in two size groups, namely small haematomas (less than 30 cm³) and large haematomas (more than 30 cm³).

Patients with atrial fibrillation in addition to MHV might be at a higher risk of thromboembolic complications^{207, 208}. The risk of thromboembolic complications is higher in patients with a CHADS2 score of 2 or more^{207, 208}. CHADS2 is an acronym for Congestive heart failure, Hypertension, Age>75, Diabetes mellitus and prior Stroke or transient ischemic attack^{207, 208}. Different CHADS2 schemes were considered in our survey since they may affect timing of restarting OAC.

Another factor that may contribute to a physician's decision of restarting OAC in patients with MHV and ICH is a recent history of pulmonary embolism (PE) or deep venous thrombosis (DVT)²⁰⁹⁻²¹¹. These factors were therefore included in our survey.

A patient's age may affect timing of restarting OAC. Advanced age is associated with higher mortality in patients with ICH secondary to OAC^{212, 213}. Many literature articles consider 75 years as an advanced age^{212, 213}. In our survey we included a young age (less than 30 years) and an old age (more than 75 years) as two different variables that may affect timing of restarting OAC.

There are factors related to the MHV that may also affect timing of restarting OAC. One of those factors is the type of MHV. For example, caged-ball valves have a higher risk of thromboembolic complications¹²⁻¹⁴ than newer generations of MHVs. Caged-ball valves have a thromboembolic complication rate of 2.5% per year, while newer generation MHV have 0.5% to 0.9% events per year. Other factors include the location and number of MHV¹²⁻¹⁵. For example, mitral valves showed an incidence of thromboembolism of 0.9% per year, while aortic valves had only 0.5% per year. The incidence of thromboembolism was 1.2% for multiple valves¹²⁻¹⁵. Given that valve-related factors may therefore influence the timing of restarting OAC, we included these factors in our survey.

In addition, our questionnaire collected the following variables that may influence physician responses to the clinical scenarios:

1- Respondent`s speciality

Our goal was to identify the current practice of neurosurgeons and thrombosis experts in Canada and USA. Thrombosis experts are mostly haematologists, but sometimes internal medicine as well. In our first question respondents had to choose one of three options as their speciality, namely Neurosurgery, Hematology, or Other. For the third option we provided a space for the respondent to identify their speciality.

2- Respondent's medical position

Our target participants were staff neurosurgeons and thrombosis experts. To ensure that we did not include neurosurgeons or thrombosis experts who were under training, we added the question where respondents had one of four choices, namely staff physician, fellow, senior resident, or junior resident. By including this question in our survey we ensured that all of our participants were staff physicians.

3- Participant's years of practice

Given that years of practice may influence a physician's management ²¹⁵, participants were asked to identify how many years they had been in practice. We categorised years of practice into 0-5, 6-10, 11-15, 16-20, 21-25, and more than 25 years.

4- Participant's country of practice

We collected whether the physician's practice was located in Canada or USA. We added a third option where participants could select "Others" to ensure that we did not include physicians practicing outside our countries of interest.

5- Participant's practice setting

In the USA most physicians practice in either an academic or private practice ^{216,217}, while in Canada it is mostly an academic or community-based practice ²¹⁸. Therefore, participants were given a choice of the following settings of practice to select: University hospital, hospital with university affiliation, community hospital, or private.

Finally, participants were asked through two separate questions whether they would be willing to have their patients participate in a RCT or a cohort study. The first question asked about their willingness for their patients to participate in a RCT and the second question enquired about their willingness for their patients to participate in a cohort study. The last question asked whether participants wished to receive the results of the survey.

Survey questions and questionnaire development

In our questions and questionnaire development we tried to adopt most of Dillman's principles²¹⁹. The survey questions (Appendix C) were designed to be focussed, precise, short, and clear. The questionnaire was designed to take less than ten minutes. Questions were written in the English language using simple and clear words to avoid leading respondents in their responses. We did not use any abbreviations in our questions. The readability and grammar of the questions were checked using Microsoft Word 2007. We tried to make the questions short without affecting question validity and reliability.

Closed-ended questions using vertical response format were used throughout the survey. Options were given for each question. For the main questions of the survey, since there was a small chance that the list of possible answers may not include an answer acceptable to the respondents, we added an additional option where the participant could enter their own answer.

We assigned a number to each question. The questionnaire was three pages in length and was constructed using Hypertext Mark-up Language (HTML) using SurveyMonkey.com. We limited colour use to encourage consistency in appearance. We used drop-down boxes for answering most questions. At the end of the questionnaire participants received a thank you message. The questionnaire included ten questions that covered three main categories.

The first six questions mainly addressed the baseline characteristics of the participants. These baseline characteristics included the participant's speciality, current position of the participant, years of practice, country of practice, type of practice, and the average number of patients with MHV and ICH treated annually by the participant.

The seventh question was the main part of the questionnaire. It included two scenarios of a patient with MHV on OAC who presented with an ICH. In the first scenario the type of ICH was an intracerebral haemorrhage, while in the second it was a SDH. For each scenario we considered 14 different situations that may affect the treating physician's decision of reversing a patient's coagulopathy or the timing of restarting their OAC. The same 14 clinical situations were considered for each haemorrhage scenario. Participants were asked to answer yes or no regarding correcting the coagulopathy, and when they would restart the patient on OAC.

The last three questions were about the participant's willingness to participate in future studies and if they wished to receive the survey results.

The questionnaire's clarity, balance, and length were evaluated during our evaluation of the survey validity and reliability. We also tested our ability to extract the data during a trial of the questionnaire.

Reliability and validity

Face and content validity

Before sending the survey to eligible participants, the survey was sent to ten neurosurgeons and thrombosis experts at the the Ottawa Hospital. This testing aimed to evaluate the clinical sensibility of the survey, face validity, content validity, clarity, utility, and redundancy. Each expert participating in this survey validity trial was interviewed to ensure that the questions were clear and interpreted in the same way.

Our initial survey included four clinical scenarios; most of the participants in our initial testing found that the survey was very long and that they were unable to complete the survey in 10 minutes. A few of the survey questions also needed to be clarified. After considering the feedback from our participants, we included only the two relevant clinical scenarios (the intracerebral haemorrhage and the SDH scenarios) to shorten the time needed to complete the survey. The final questionnaire (Appendix C) was completed and was used for the actual study.

Test-retest reliability

To ensure that any given question in the survey produced consistent results at different times, we conducted a test-retest evaluation. We selected one of the two scenarios (patient with intracerebral haemorrhage and MHV) and sent it to four neurosurgery residents. To minimize the possibility of real or random changes affecting participants' answers, we re-sent the survey to the same four participants 10 days after they completed the first survey. We calculated the correlation coefficient for the respondents' answers. We wanted to ensure that our test-retest correlation coefficients were at least 0.7.

Inter-rater reliability

Our survey was an online self-administrated survey and was conducted using Hypertext Mark-up Language (HTML) using SurveyMonkey.com. All data from the survey was stored electronically through the website. The website also provided the ability to transfer the data to the analysing software electronically. Given these advantages we did not conduct an inter-rater reliability analysis.

Internal and external validity

Cross-sectional surveys are limited in determining causation^{220, 221}. In our analysis we controlled for some factors that may influence the timing of

restarting oral anticoagulants. The goal of our survey was not to determine any causations regarding timing of restarting OACs.

We conducted the survey hoping it will be representative of the practice of thrombosis specialists and neurosurgeons in Canada and USA. Given that our survey was a cross-sectional study, our results' external validity are limited to the survey time. We acknowledge that our external validity is also greatly related to our response rate ^{222,223}.

Survey execution and monitoring

During our survey we tried to follow Dillman's principles ^{219,222,244,245}. All participants were contacted via e-mail with a pre-notification message (Appendix D) that included a short introduction about the survey and notifying them that the survey would be sent within the following few days. A second e-mail was sent within 3 days from the first one and contained a letter with a link that took the participant directly to the survey webpage. We sent the pre-notification e-mail on a Monday and the e-mail with the link to the survey on Wednesday of the same week. We indicated in our pre-notification letter the reason we thought our survey was important and the value of participation in our survey. We also clearly indicated that participation was voluntary and whom to contact if the participant had any questions concerning the survey.

To maximize our response rate non-respondents received three reminder e-mails. The first reminder e-mail was sent one week after the survey was first

sent, the second reminder was sent after one week from the first reminder e-mail, and the last e-mail was sent four weeks from the day of the original e-mail. The survey was closed after four weeks from the last e-mail.

The reminder e-mails were automatically sent through the SurveyMonkey.com website. Participants were given the option to opt out from receiving reminder e-mails. The SurveyMonkey.com website provided monitoring of participants who opted out, responded, or did not respond.

The survey website also provided the ability to identify missing information and link them to the e-mail of the participant. We planned to contact respondents to ask them to complete the survey if 50% or more of the survey was missing. Given our limited budget, we did not provide any incentives to respondents, but offered to share the survey results with respondents who completed the survey.

Data collection

All data was initially collected and stored by the SurveyMonkey website. All data was protected through the website. Only the survey administrator had access to the results. Before closing the survey we evaluated it for missing data. As discussed earlier, we planned to contact respondents who had completed 50% or less of the survey to request them to complete the survey. If respondents only opened the website without completing any part of the survey,

this was regarded as a non-respondent. Data was then transferred from the website for analyses.

Data analysis

Our outcome variables were timing of restarting OAC and answering yes or no for correcting coagulopathy (the two key questions). As described previously, timing of restarting OAC was divided into 7 categories. The answer to correcting coagulopathy was analysed as a nominal variable. We considered participant characteristics and demographic data as covariates. These covariates were categorical and were measured at the nominal level.

For descriptive analysis, univariate analysis was done to calculate variable frequencies, percentage, and medians. For measurement of dispersion we planned to calculate standard deviation when needed. Also, the percentage distributions of the outcome variables were obtained. These results were then stratified by the covariates (physician's speciality, country of practice, years in practice, type of practice, and annual average number of ICH cases physicians managed).

We also performed bivariate and multivariate analysis to examine the relationship of participant characteristics and demographics in response to the clinical scenarios. Also, we examined if there was a difference in physicians answers to the key questions between the two clinical scenarios. Analyses were done to examine if participant responses to OAC restarting time (one of the key

questions) where different for patients with different clinical risk factors. These risk factors included age, presence of surgical intervention, haematoma size, patient`s CHADS2 score, recent PE, recent DVT, MHV type, MHV location and multiplicity. We examined the existence and strength of relationships in the bivariate analyses using the Chi-square test, Fisher Exact test (when responses for one cell were less than 5) and student t-test. All analyses were performed at the conventional alpha value of 0.05. For the multivariate analysis we performed Poisson regression model to examine the effect of participant characteristics and demographics on the time of restarting OAC for each clinical scenario. We also calculated Poisson regression coefficients along with the standard errors, z-scores and *P*-values for the coefficient at 5% significant level.

We conducted multinomial logistic regression for the clinical risk factors with thrombosis experts who chose less than 72 hours to restart OACs as the reference group. The multinomial logit or logistic regression is appropriate when the outcome variable has more than two categories and cannot be ranked in order. For a more intuitive interpretation, the coefficients were transformed into relative risk ratios (RRR). All analyses were performed using STATA 11, SPSS, R2.15.1 and Microsoft Excel.

For missing data the following strategy was planned for every variable: If the missing data was 10% or less, we would not take any action. If the missing data was 35% or more we would exclude the variable. If the missing data was

between 11 and 34% we would consider multiple imputations for the missing data.

Ethics

The survey was approved by the Ottawa Hospital Research Ethics Board (OHREB). Participation was voluntary. No physician names or addresses were collected.

The transferred data is housed in a database using Microsoft Excel 2007 and is protected by a password. The database is stored on the hospital server under the principle investigator account, which is protected by a password. Only the research team had access to the database under direct supervision of the principle investigator. OHREB has access to the database, if required. The Ottawa Hospital Research Institute has the right to audit the study record at any time if required.

Records will be kept and stored for the next 15 years by the principle investigator (Fahad Alkherayf), as required by the OHREB.

Results

Test-retest reliability

The calculated correlation coefficient was 0.91 and when we calculated it only for the questions that asked about timing of restarting OAC, it was 0.85.

Participation and response rate

A total of 1469 potential participants were identified to be candidates for the survey. This included 1267 neurosurgeons and 202 thrombosis experts. A total of 504 physicians responded to our survey (Table 18). One respondent did not provide his/her speciality. The total response rate was 34.31%.

Table 18: Number of respondents and their speciality.

Candidate speciality	Number of survey candidates	Number of respondents (%)
Neurosurgery	1267	428 (33.86%)
Thrombosis experts	202	75 (37.13%)
Total	1469	504 (34.31%) One did not provide speciality

Approximately 15% of the respondents were thrombosis experts and the remainder were neurosurgeons (Figure 13). The majority of the thrombosis experts were haematologists while the remainder were internal medicine specialists with an interest in thrombosis (Figure 14).

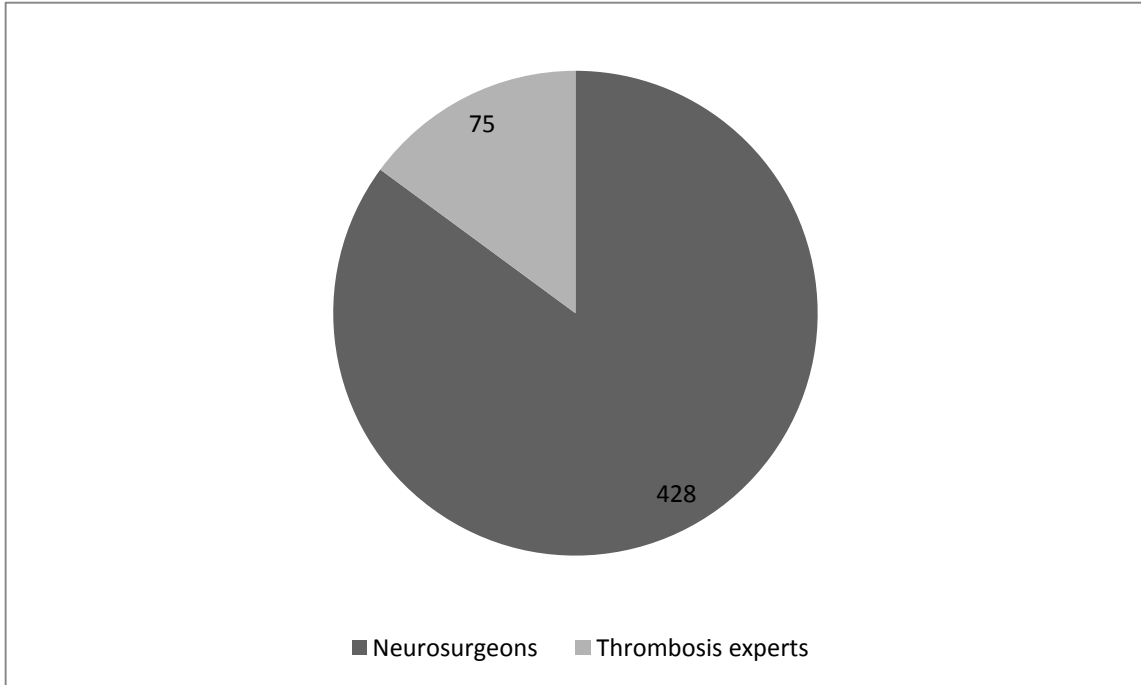


Figure 13: Number of respondents and their specialities.

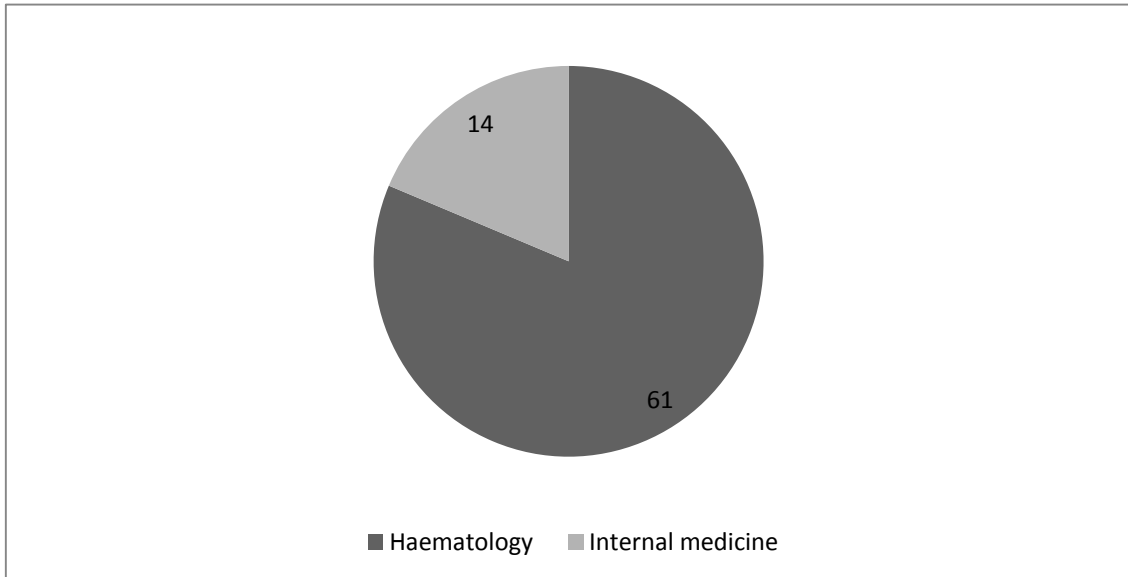


Figure 14: Thrombosis experts' subspecialties.

In summary, there were more neurosurgeons who responded to our survey than thrombosis experts. However, of the total possible thrombosis experts who could reply, there was a higher response rate from this specialty than from the neurosurgeon group. The overall response rate for both groups was 34.31%.

Respondents' characteristics

The majority of the neurosurgeons who participated in the survey were practicing in the USA (Figure 15), whereas the distribution of thrombosis experts between USA and Canada were almost equal.

There were more physicians within the group of thrombosis experts than the group of neurosurgeons who had been practicing for a longer period of time.

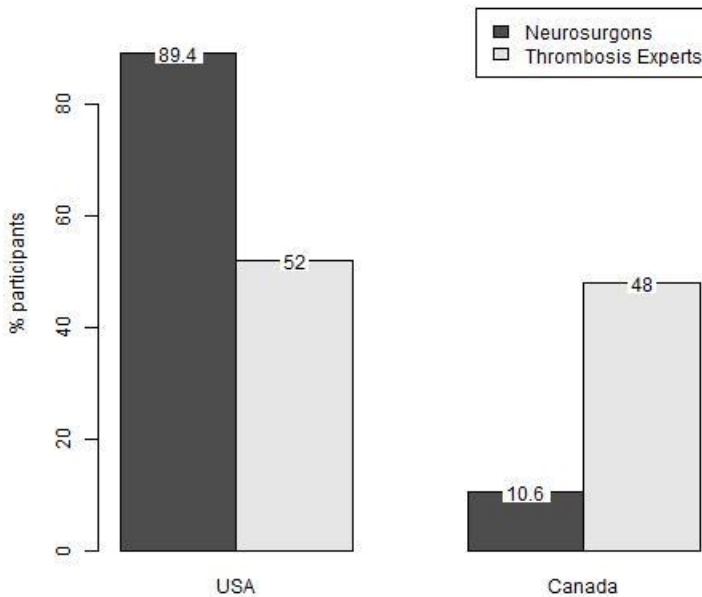


Figure 15: Participants' country of practice and their speciality.

About one third of the thrombosis experts had more than 25 years of practice (Figure 16). On the other hand, close to one third of the neurosurgeons had five years or less of practice.

There were more physicians who practiced either in an academic setting or were affiliated to university hospitals within both the thrombosis experts and neurosurgeons compared to other settings (Figure 17). While neurosurgeons were found to practice in private settings, no thrombosis experts were found in this sector.

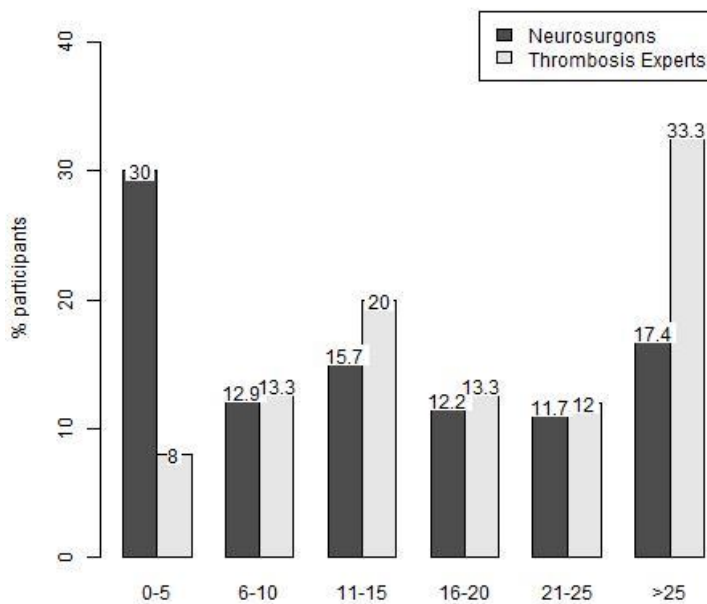


Figure 16: Participants' years of practice and their speciality.

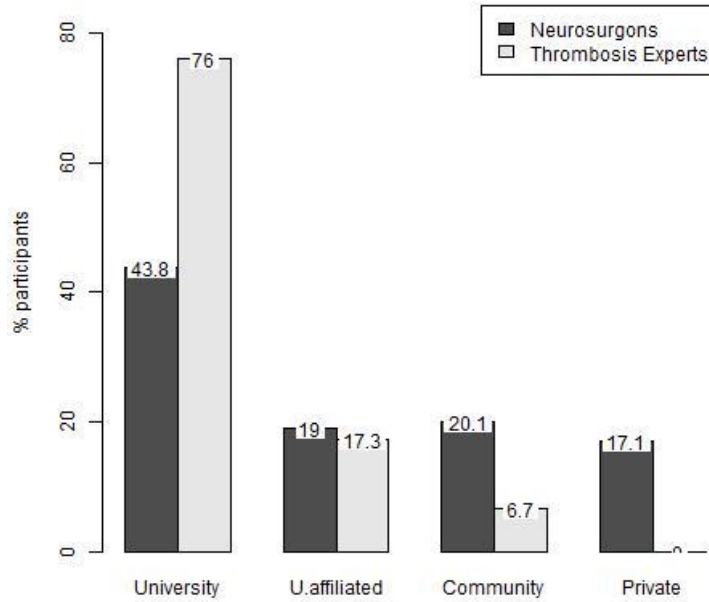


Figure 17: Participants' setting of practice and their speciality.

The majority of the thrombosis experts managed five or fewer patients with both MHV and ICH annually (Figure 18), whereas the majority of the neurosurgeons managed more than 5 patients annually.

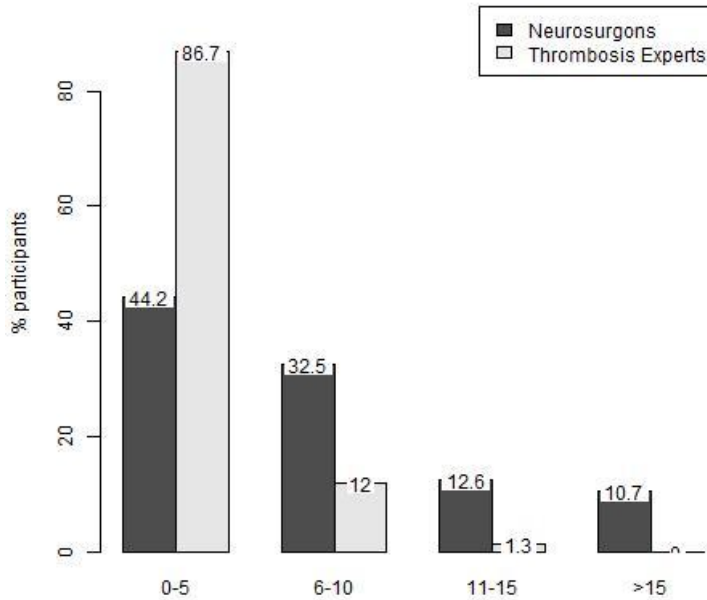


Figure 18: Average annual number of patients managed by participants.

Respondents' characteristics therefore demonstrate a variety of work settings and variable experience both in terms of number of years in practice as well as the number of patients they treated annually who had both MHV and ICH.

Restarting oral anticoagulants in patients with intracerebral haemorrhage

Intracerebral haemorrhage in patients with no risk factors

When participants were asked about 50-year-old patients with MHV on an OAC regimen who presented with ICH without any other accompanying risk factors, the majority of participants said they would correct the patient's coagulopathy (Figure 19). This question was not answered by 4.8% of the

participants. There was no statistical significant difference between the neurosurgeons and thrombosis experts' answers using Fisher`s Exact test (P value 0.23).

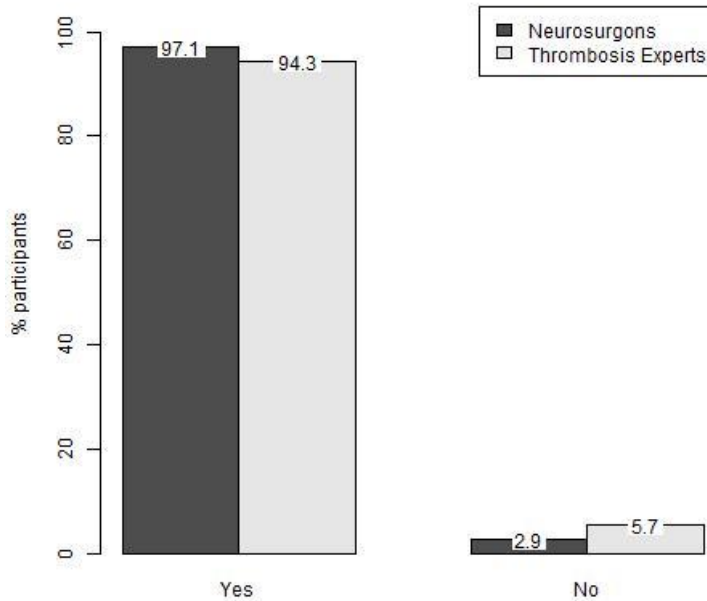


Figure 19: Physicians' decisions in correcting coagulopathy in patients with intracerebral haemorrhage and no risk factors.

Regarding what timing would be chosen for reinstating OAC, 5.2% of the respondents did not answer this question. There was no clear agreement between physicians about the timing (Figure 20). There was no statistical significant difference between the answers provided by the neurosurgeons and the thrombosis experts using Pearson Chi-Square test (P value 0.33).

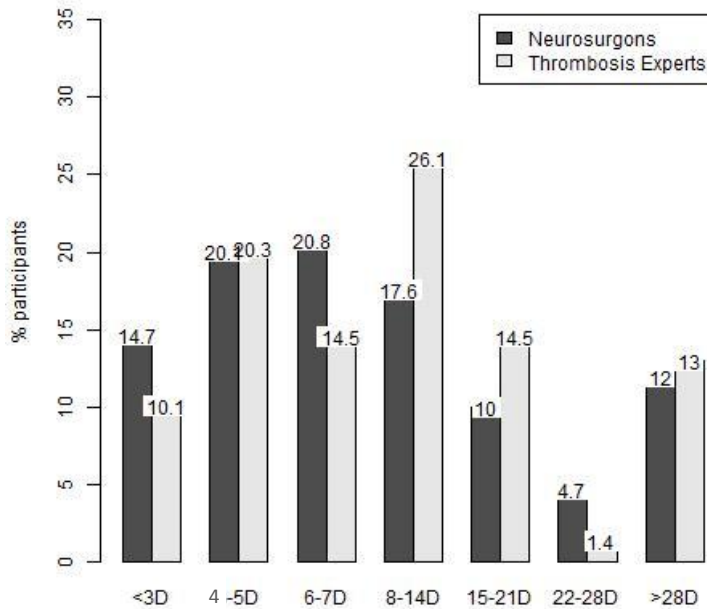


Figure 20: Timing restarting OAC in patients with intracerebral haematoma and no risk factors.

In summary, the responses provided by participants did not elicit clear differences in time for restarting OAC therapy in patients without risk factors. However, about 60% of participants restarted OAC in 4 to 14 days.

Intracerebral haematoma and surgical intervention

When participants were asked about their management of patients who undergo surgical treatment for their intracerebral haematoma, almost all of the physicians said that they would correct the patient's coagulopathy (Figure 21). Only 0.8% did not answer this question. We did not find any statistical significant difference between the responses of the two physician specialities using Fisher's Exact test (P value 0.73).

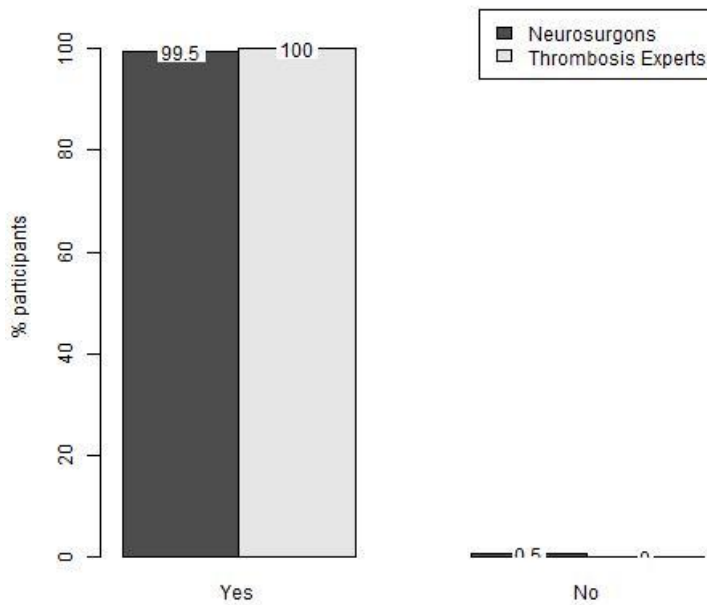


Figure 21: Physicians' decision in correcting coagulopathy in patients with intracerebral haematoma after surgical intervention.

While only 1% of the respondents did not provide what timing they would re-institute the OAC after surgical intervention, there was no clear agreement between physicians about the timing they would choose for restarting OAC (Figure 22). There was no statistical significant difference between the responses of the two physician specialities using Pearson Chi-Square test (P value 0.14).

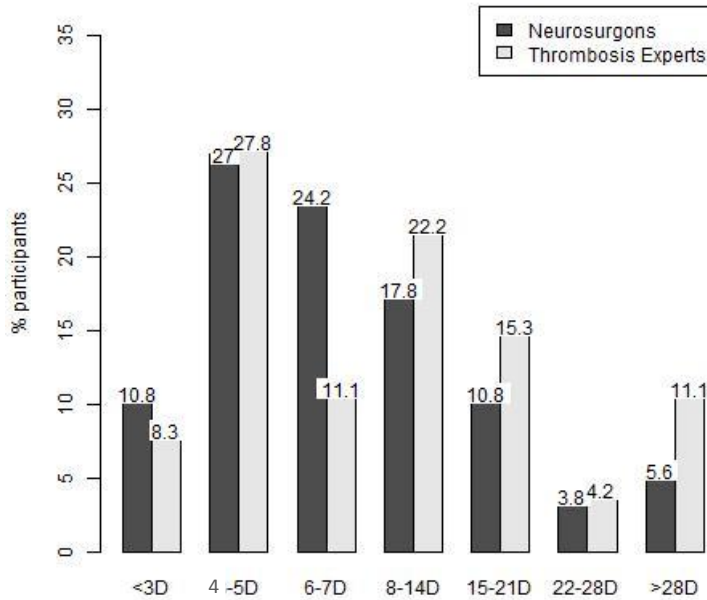


Figure 22: Timing of restarting OAC in patients with intracerebral haematoma who had surgical intervention.

The lack of statistical significance between the responses provided by the two physician specialities indicate that patients would be treated similarly regarding restarting OAC if treated by a neurosurgeon or a thrombosis expert following surgical intervention for ICH.

Intracerebral haematoma and haematoma size

When participants were asked whether they would correct for coagulopathy if the size of the haematoma was small (less than 30 cm³), the majority answered affirming they would correct the coagulopathy (Figure 23). Similarly for patients presenting with a large haematoma (more than 30 cm³), almost all of the respondents indicated that they would correct the coagulopathy

(Figure 24). We only had 0.8% missing data for each haematoma size scenario and we found that there were no statistical differences in responses between the two physician specialities for the two scenarios of haematoma size using Pearson Chi-Square and Fisher`s Exact tests (P value 0.31 & 0.62 respectively).

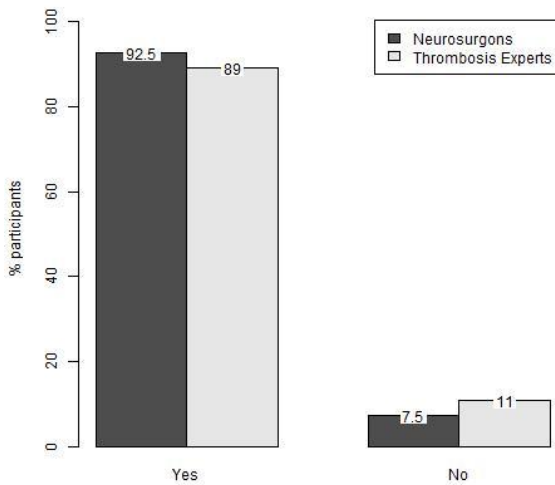


Figure 23: Physicians' decisions in correcting coagulopathy in patients with a small intracerebral haematoma.

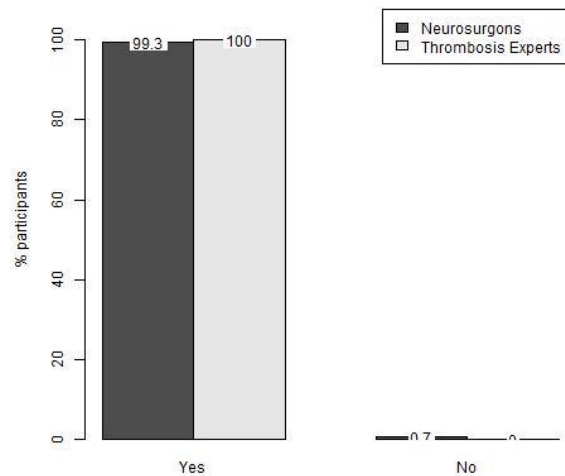


Figure 24: Physicians' decisions in correcting coagulopathy in patients with a large intracerebral haematoma.

When physicians were asked to consider the size of the haematoma when deciding on times to restart their patients on OAC therapy, it would appear that physicians were more reluctant to restart OAC in the first 3 days when the haematoma was large (Figures 25 & 26). There were 3.6% of the participants who did not provide timing in the case of small haematomas, while 1% did not provide timing in the case of large haematomas. We found no statistical

differences between the responses of the two physician specialties for the two scenarios of haematoma size using Pearson Chi-Square test (P value 0.85 & 0.69 respectively).

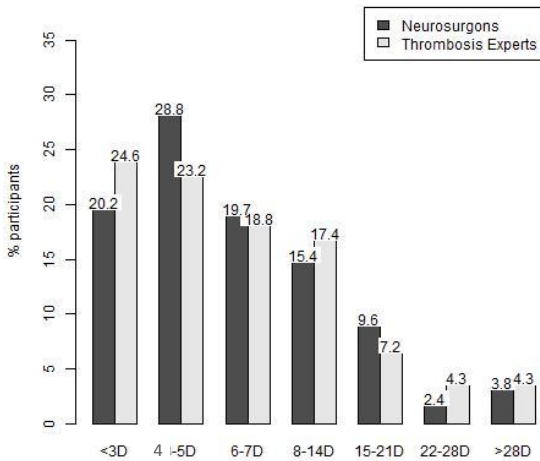


Figure 25: Timing of restarting OAC in patients with small intracerebral haematomas.

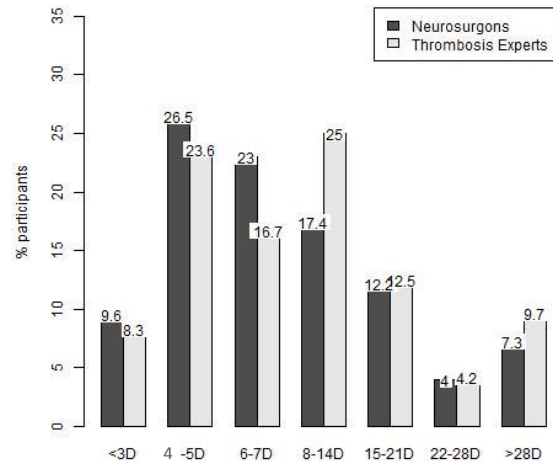


Figure 26: Timing of restarting OAC in patients with large intracerebral haematomas.

We examined whether the numbers of respondents and their choices differed between the two scenarios of haematoma size using goodness of fit test. We found that there was a statistical significant difference between the two scenarios (P value 0.001) with physicians restarting OAC earlier when patients had a smaller haematoma compared to when patients presented with larger haematomas. Also, we found the majority of physicians restarted their patients on OAC between 4 to 14 days.

Intracerebral haematoma and atrial fibrillation

When participants were asked to consider their patient's stage of atrial fibrillation, there were slightly more participants who would not correct a patient's coagulopathy if the patient scored 2 or more in the CHADS2 scoring system (Figures 27 & 28). We only had 1% missing data or less for each CHADS2 scenario and we found that there were no statistical differences between the responses of the two physician specialities for the two scenarios using Fisher's Exact test (P value 0.42 & 0.62 respectively).

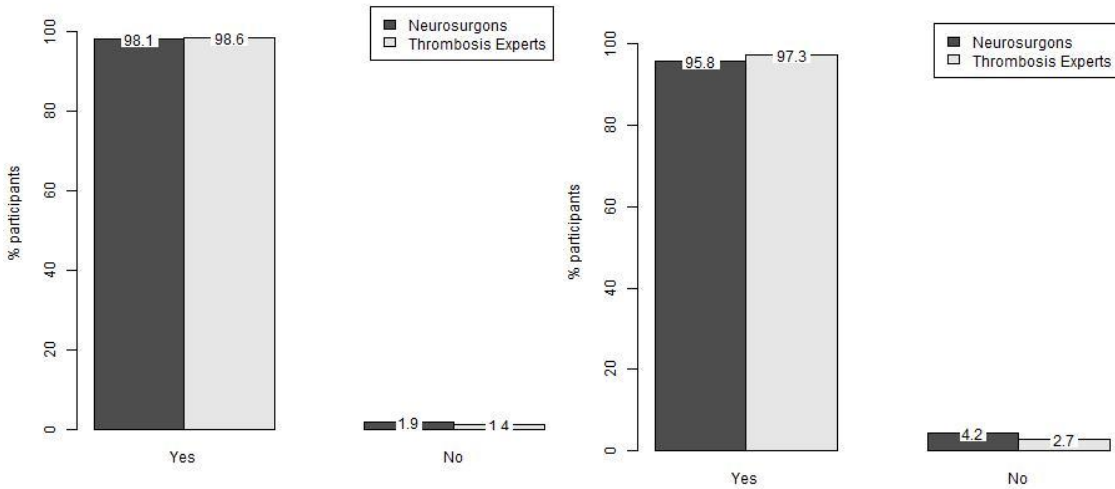


Figure 27: Physicians' decisions in correcting coagulopathy in patients with intracerebral haematoma and CHADS2 0-1.

Figure 28: Physician's decisions in correcting coagulopathy in patients with intracerebral haematoma and CHADS2 2 or more.

There were more physicians who restarted OAC earlier (within the first 5 days) in patients who had a CHADS2 score of 2 or more compared to patients with a CHADS2 of 0-1 (Figures 29 & 30). While 3.4% of the participants did not provide the timing in the case of CHADS2 2 or more, 1.6% did not provide the timing in the case of CHADS2 0-1. We found that there were no statistical differences between the two physician specialities for the two CHADS2 scenarios using Pearson Chi-Square test (P value 0.71 & 0.1 respectively).

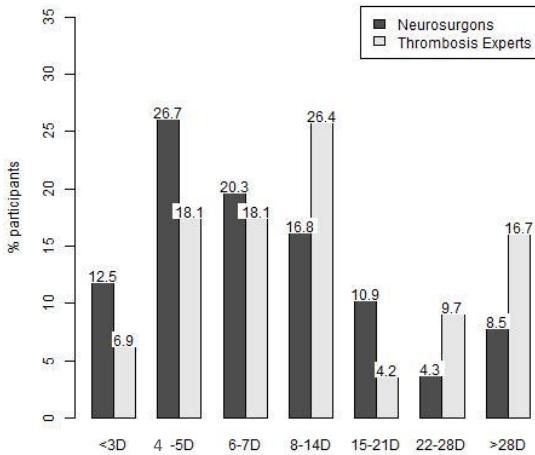


Figure 29: Timing of restarting OAC in patients with intracerebral haematoma and CHADS2 0-1.

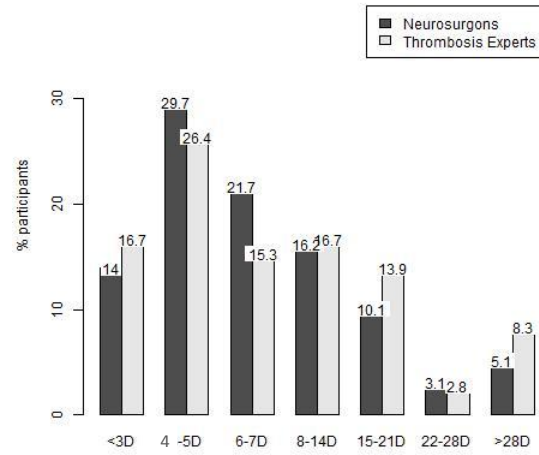


Figure 30: Timing of restarting OAC in patients with intracerebral haematoma and CHADS2 2 or more.

We examined whether the number of respondents and their choices differed between the two CHADS2 scenarios using goodness of fit test. We found that there was a statistical significant difference between the two scenarios (P value 0.001) with physicians restarting OAC earlier for patients who

had a CHADS2 score of 2 or more. Additionally we found close to two thirds of the respondents restarted patients on OAC between 4 and 14 days in both scenarios.

Intracerebral haematoma and deep venous thrombosis

When participants were asked about their management of patients who had experienced a DVT in the last month before the intracerebral haematoma, the majority of participants indicated that they would correct the coagulopathy (Figure 31). Only 0.8% did not answer this question. We did not find any statistical significant difference in the responses between the two physician specialities using Fisher`s Exact test (P value 0.11).

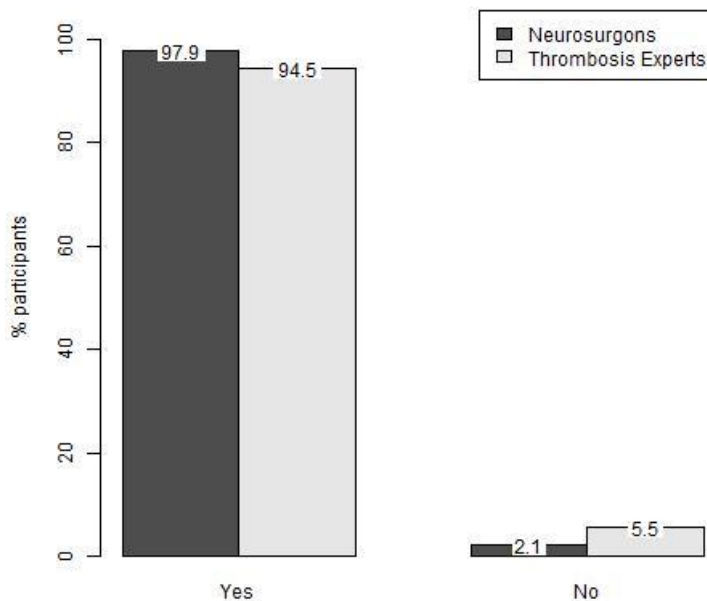


Figure 31: Physicians' decisions in correcting coagulopathy in patients with intracerebral haematoma and DVT.

A total of 2% of the respondents did not provide what timing they would re-institute the OAC in patients who had a DVT. There was no clear agreement between physicians about the timing of OAC restart in patients presenting with a DVT (Figure 32). Further, there was no statistical significant difference between the responses provided by the two physician specialities using Pearson Chi-Square (P value 0.41).

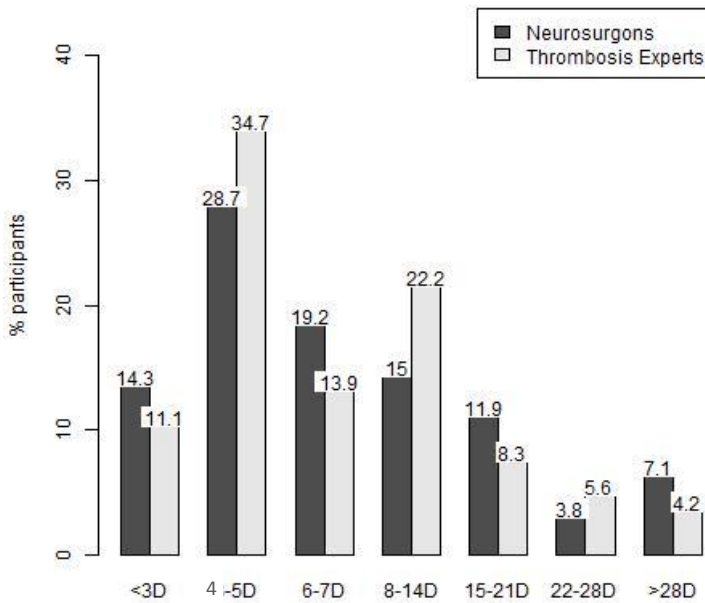


Figure 32: Timing of restarting OAC in patients with intracerebral haematoma and DVT.

In summary, participants indicated that they would correct the coagulopathy in patients presenting with an intracerebral haematoma and who had also suffered a DVT in the month preceding the haemorrhage. Again, about two thirds of the physicians restarted OAC in their patients between 4 and 14 days.

Intracerebral haematoma and pulmonary embolism

When patients had a PE in the last month before the intracerebral haematoma, most physicians chose to correct the patient's coagulopathy (Figure 33). Only 1% of the participants did not answer this question. We did not find any statistical significant difference between the responses of the two physician specialities using Fisher's Exact test (P value 0.45).

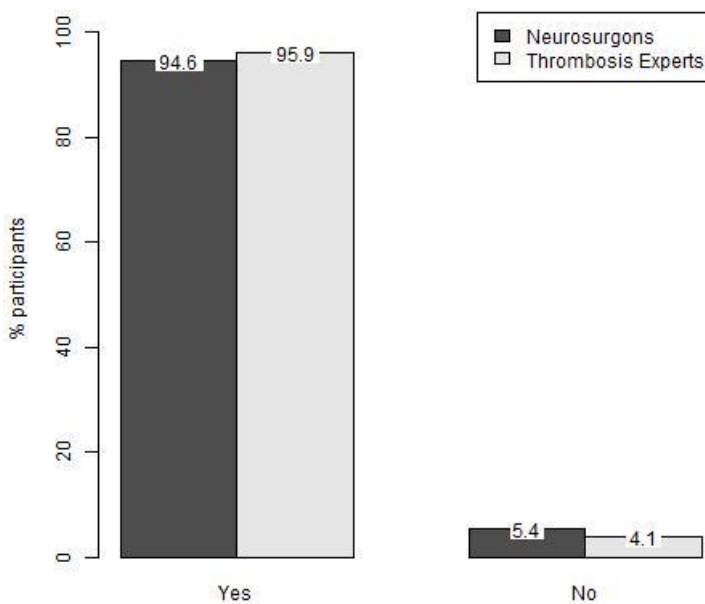


Figure 33: Physicians' decisions in correcting coagulopathy in patients with an intracerebral haematoma and PE.

Of the respondents 3.2% did not provide what timing they would reinstitute the OAC. There was no clear agreement between physicians about the timing (Figure 34). Also, there was no statistical significant difference between the two physician specialities using Pearson Chi-Square (P value 0.45).

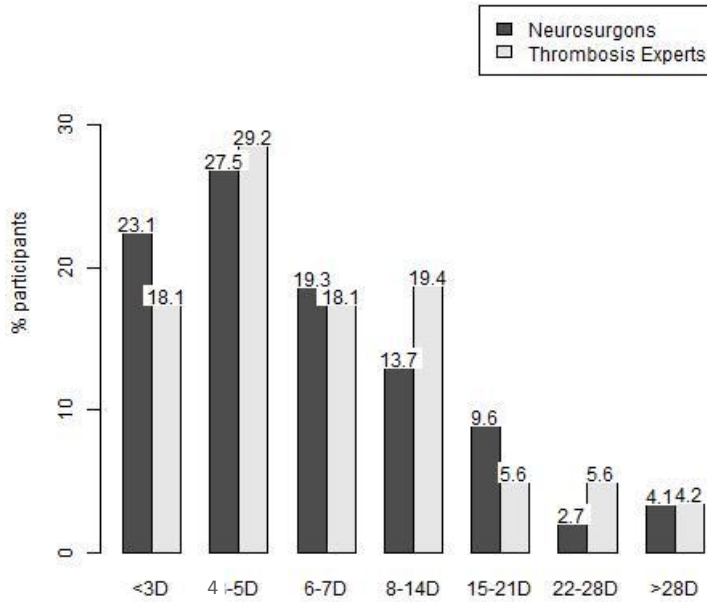


Figure 34: Timing of restarting OAC in patients with intracerebral haematoma and PE.

In summary, both neurosurgeon and thrombosis expert participants again indicated that they choose to correct coagulopathy in patients presenting with an ICH as well as a PE, but the timing at which OAC is reinstated remained in disagreement.

Intracerebral haematoma and patient’s age

When participants were asked to consider the patient’s age when they were deciding on correcting the patient’s coagulopathy, the majority of physicians indicated that they would correct the patient’s coagulopathy irrespective of whether the patient was young (less than 30 years) or older

(more than 75 years) (Figure 36). We only had 1% missing data for each scenario and we found that there were no statistical differences in the responses between the two physician specialties for the two age-related scenarios using Fisher`s Exact test (P value 0.44 & 0.61 respectively).

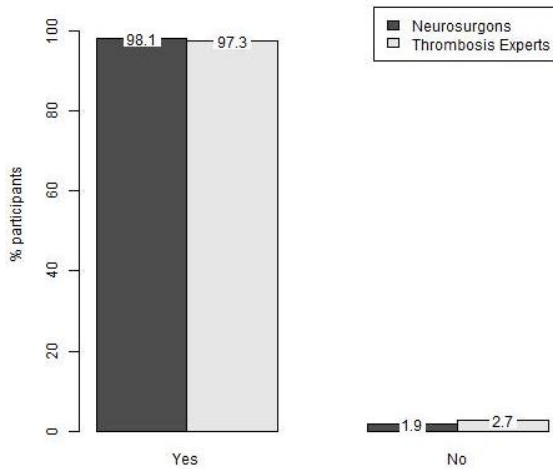


Figure 35: Physicians' decisions in correcting coagulopathy in young-age patients with intracerebral haematoma.

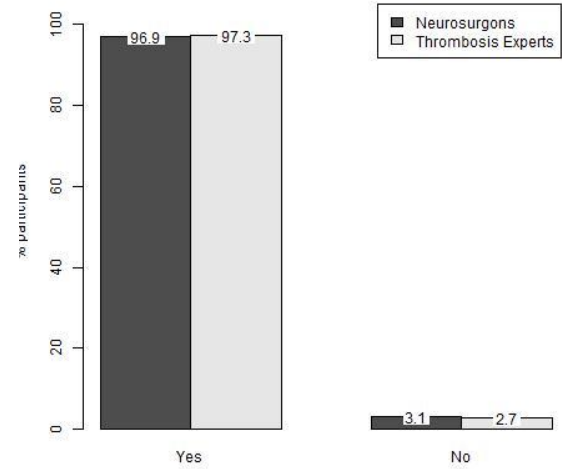


Figure 36: Physician's decisions in correcting coagulopathy in old-age patients with intracerebral haematoma.

Physicians had very similar responses to the timing of restarting OAC when considering the younger and older patient scenarios (Figures 37 & 38). A total of 2.2 % of the participants did not provide the timing of OAC reinstatement in the young age scenario, while 2.8% did not provide timing for patients in the older age group. We found that there were no statistical differences between the two physician specialties for restarting OAC therapy in the two scenarios of

younger and older patients using Pearson Chi-Square test (P value 0.78 & 0.61 respectively).

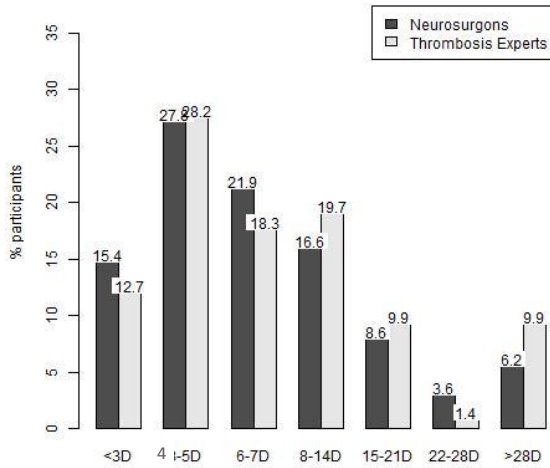


Figure 37: Timing of restarting OAC in young-age patients with intracerebral haematoma.

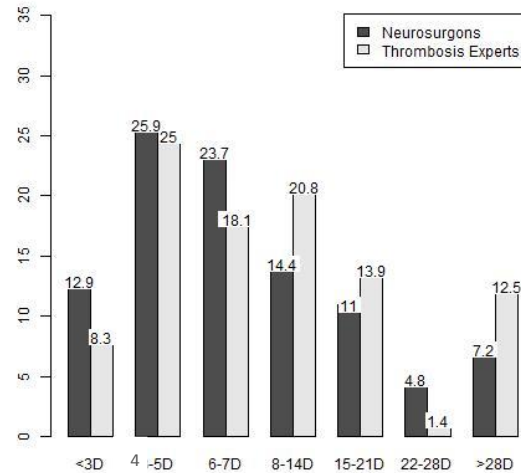


Figure 38: Timing of restarting OAC in old-age patients with intracerebral haematoma.

We examined whether the number of respondents and their choices were different between the scenarios of younger versus older patients using goodness of fit test. We found that there was no statistical significant difference between the two scenarios (P value 0.001) with physicians restarting OAC earlier for younger patients. Additionally, we found close to 60% of the physicians restarted OAC between 4 and 14 days in both scenarios.

Intracerebral haematoma and caged-ball valve

When participants were asked to contemplate whether they would consider correcting coagulopathy in patients who had a caged-ball MHV, most

participants acknowledged positively toward correcting the coagulopathy (Figure 39). Only 1.4% of the participants did not answer this question. We did not find any statistical significant difference between responses of the two physician specialities using Fisher`s Exact test (P value 0.82).

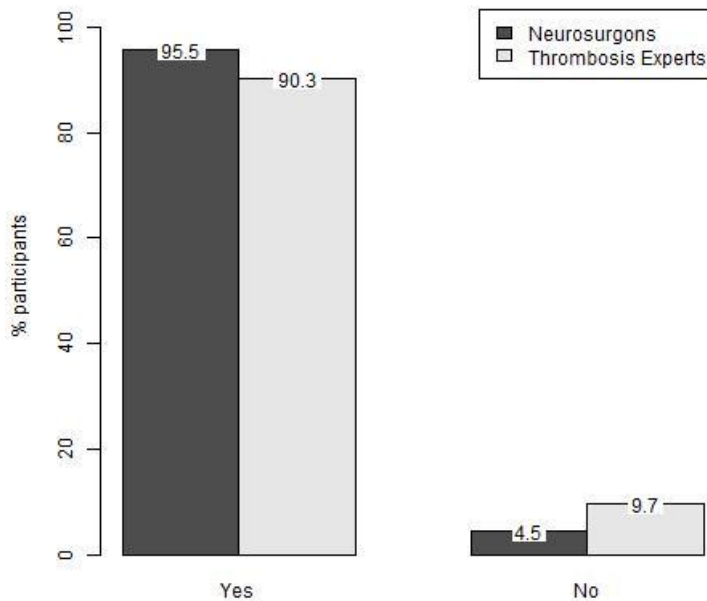


Figure 39: Physicians' decisions in correcting coagulopathy in patients with intracerebral haematoma and caged-ball valves.

While 3.8% of the respondents did not provide the timing that they would re-institute the OAC, many physicians wanted to restart OAC in patients with caged-ball valves within the first 5 days following an intracerebral haematoma (Figure 40). There was no statistical significant difference between the responses of the two physician specialities using Pearson Chi-Square (P value 0.3).

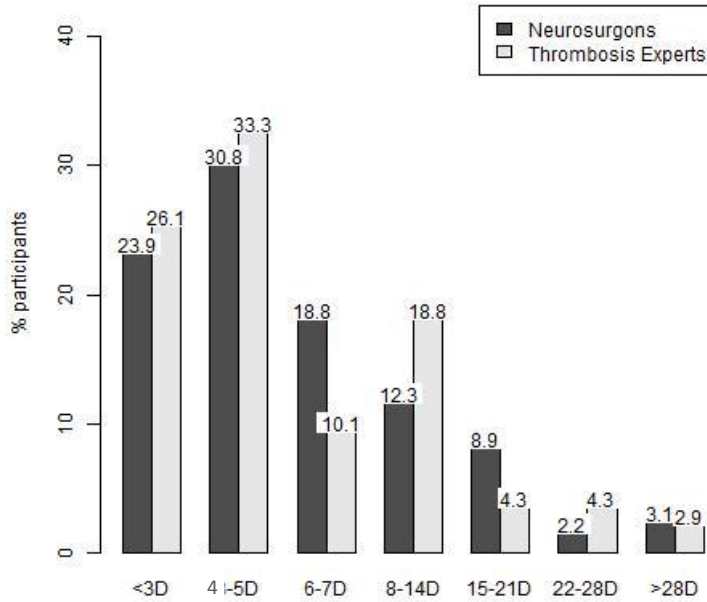


Figure 40: Timing for restarting OAC in patients with intracerebral haematoma and caged-ball valves.

In summary, the response of physicians when questioned when they would restart OAC in intracerebral haematoma patients with caged-ball valves, about 24% chose 3 days or less while 30% chose 4 to 5 days. Additionally, we found about 60% of physicians started OAC between 4 and 14 days. This response was similar for both physician specialities.

Intracerebral haematoma and valve location

When participants were asked to consider the location of the MHV (mitral or aortic), the majority of physicians corrected the coagulopathy in both mitral and aortic scenarios (Figures 41 & 42). We only had 1.6% or less of missing

data for each location of the MHV and we found that there were no statistical differences between the two physician specialities for the two valve location scenarios using Fisher`s Exact test (P value 0.47 & 0.13 respectively).

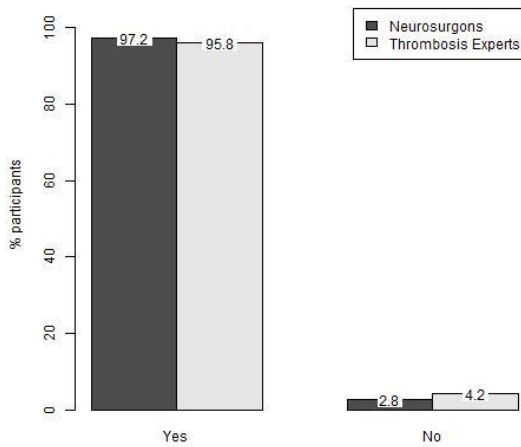


Figure 41: Physician decisions in correcting coagulopathy in patients with intracerebral haematoma and mitral valves.

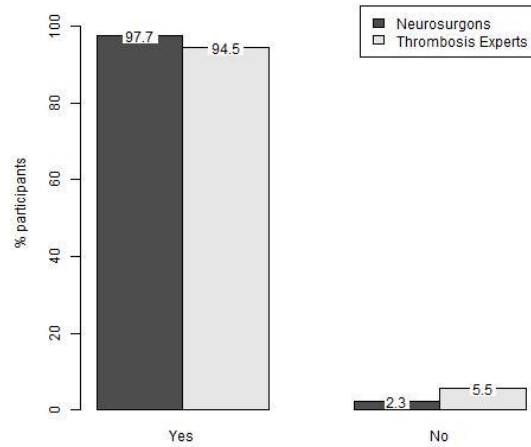


Figure 42: Physician decisions in correcting coagulopathy in patients with intracerebral haematoma and aortic valves.

Both neurosurgeons and thrombosis experts responded similarly when presented with the decision of when to restart OAC in patients with mitral or aortic MHV (Figures 43 and 44). A total of 2.8% of the participants did not provide timing for when they would reinstitute OAC therapy in patients with the mitral MHV, while 2.4% did not provide timing for patients with aortic MHV. We found that there were no statistical differences between the responses of the two physician specialities for the two valve location scenarios using Pearson Chi-Square test (P value 0.95 & 0.11 respectively).

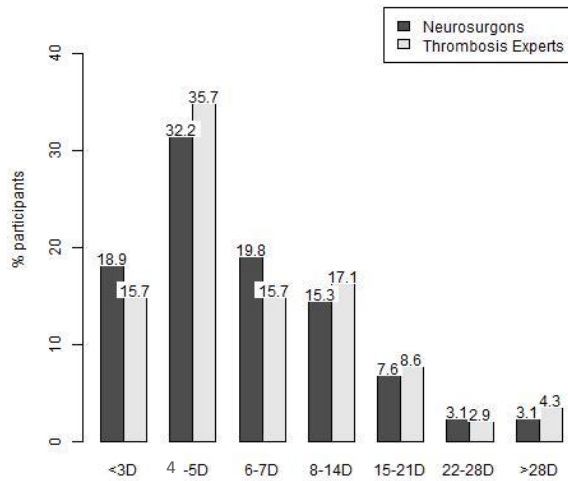


Figure 43: Timing of restarting OAC in patients with intracerebral haematoma and mitral MHVs.

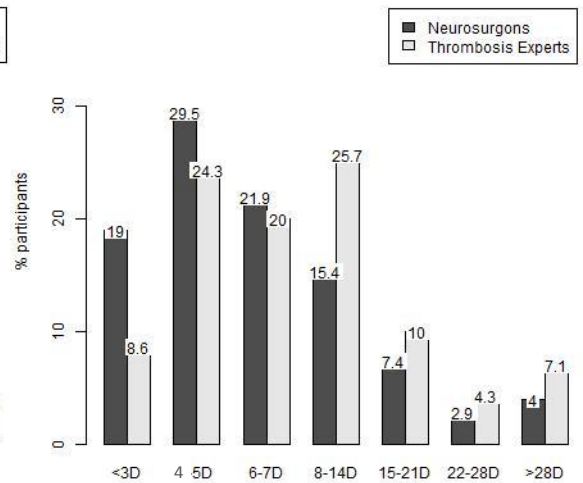


Figure 44: Timing of restarting OAC in patients with intracerebral haematoma and aortic MHVs.

We examined whether the number of respondents and their restart timing choices were different between the two valve location scenarios using goodness of fit test. We found that there was a statistical significant difference between the two scenarios (P value 0.001). Physicians restarted OAC therapy earlier when the MHV was in the mitral valve location compared to an aortic valve location.

Intracerebral haematoma and multiple MHVs

When patients had multiple MHVs, more thrombosis experts were reluctant to correct the coagulopathy in comparison to neurosurgeons (Figure 45). Only 1.8% of the participants did not answer this question. We did not find any statistical significant difference between the two physician specialities using Fisher's Exact test (P value 0.25).

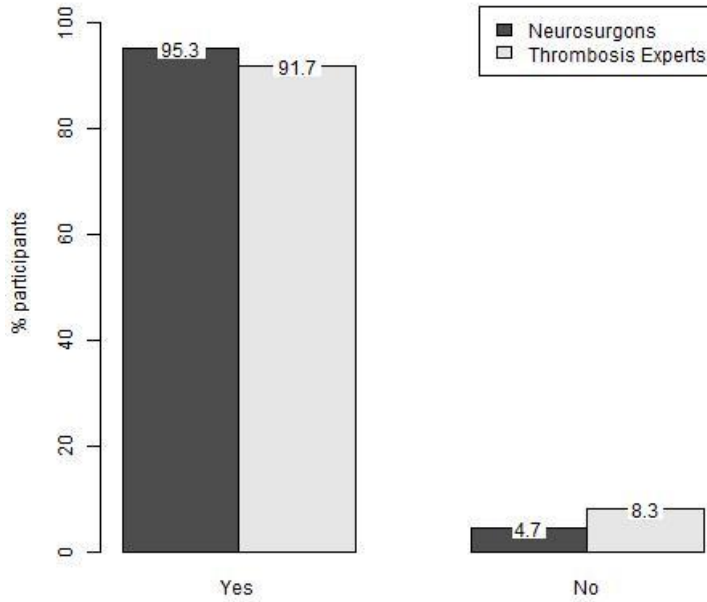


Figure 45: Physicians' decisions for correcting coagulopathy in patients with intracerebral haematoma and multiple MHVs.

A total of 3.4% of the respondents did not provide what timing they would re-institute the OAC. However, many physicians decided to re-institute OAC therapy within the first 5 days following an intracerebral haematoma (Figure 46). About 30% of the physicians started OAC on the 4th or 5th day while close to 25% restarted OAC within the first 3 days post haemorrhage.

There was no statistical significant difference between the responses of the two physician specialities using Pearson Chi-Square (P value 0.26).

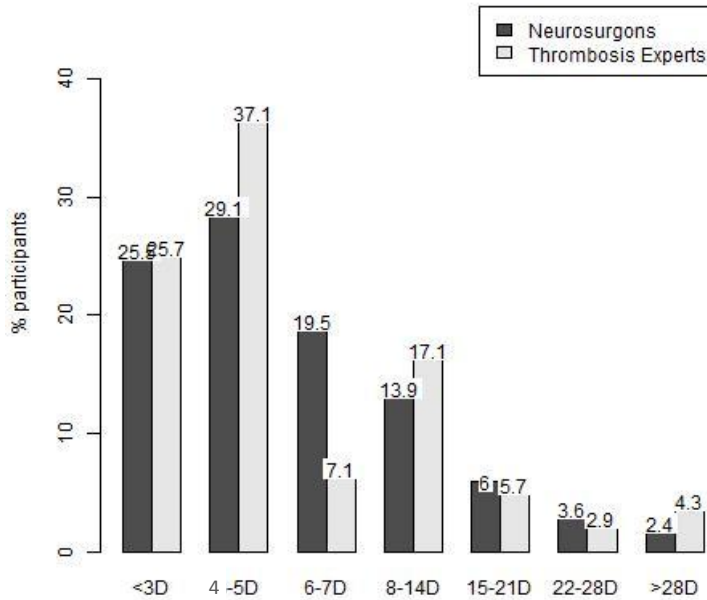


Figure 46: Timing of restarting OAC in patients with intracerebral haematoma and multiple MHVs.

In summary, when physicians were presented with the decision of when to restart OAC in patients with multiple MHVs, most replied that they would begin their patients on an OAC regimen within 5 days of ICH diagnosis. Both physician specialties responded similarly to this scenario.

Restarting oral anticoagulants in patients with subdural haemorrhage

Subdural haemorrhage in patients without risk factors

When participants were asked about 50-year-old patients with MHV taking OAC presenting with SDH, and who did not have any other risk factors,

the majority of physicians corrected the patient's coagulopathy (Figure 47).

There were 6.2% respondents who did not answer that question and there was no statistical significant difference between the responses of the two physician specialities using Fisher's Exact test (P value 0.26).

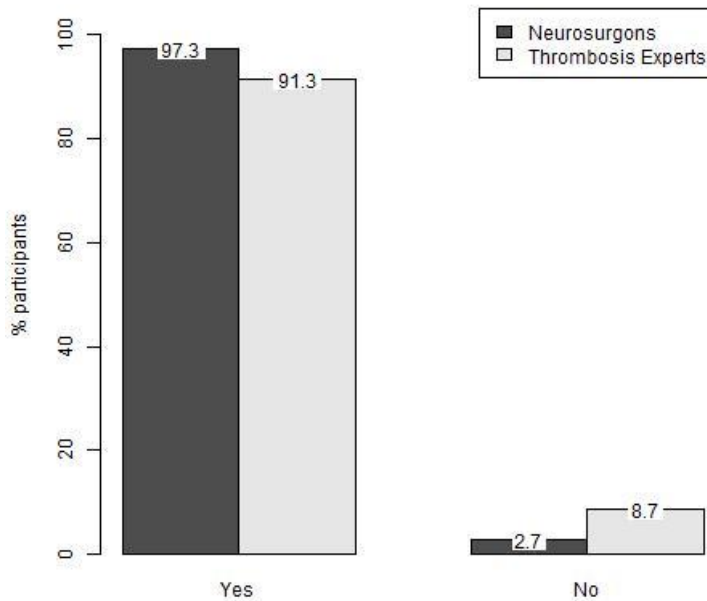


Figure 47: Physicians' decisions in correcting coagulopathy in patients with SDH and no risk factors.

A total of 7.3% of the respondents did not provide at what time point post haemorrhage they would re-institute the OAC. For physicians who responded, there was no apparent agreement about the timing for reinstating OAC (Figure 48). There was no statistical significant difference in the responses between the two physician specialities using Pearson Chi-Square test (P value 0.98).

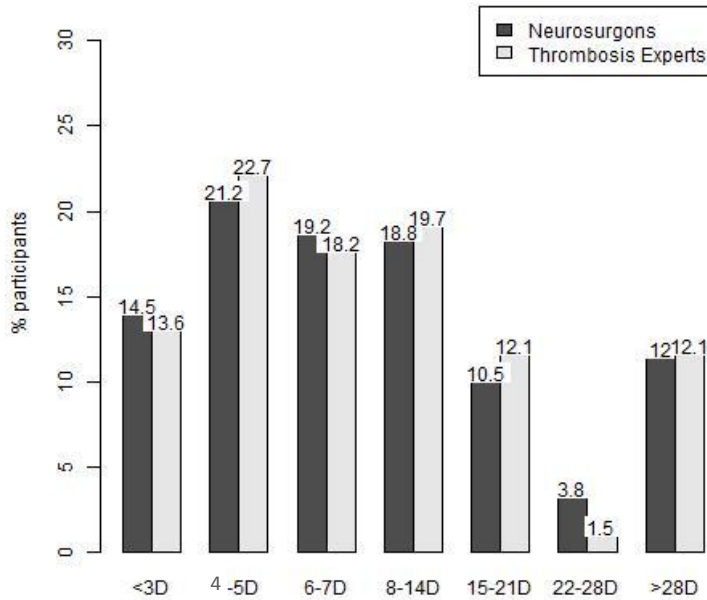


Figure 48: Timing of restarting OAC in patients with SDH and no risk factors.

However, it would appear that about 60% of physicians restarted OAC between days 4 and 14.

Subdural haematoma and surgical intervention

When participants were asked about their management of patients who underwent surgical treatment for their SHD, almost all participants agreed they would correct the coagulopathy in these patients (Figure 49). Only 2.6% did not answer this question. We did not find any statistical significant difference between the responses of the two physician specialities using Fisher's Exact test (P value 0.07).

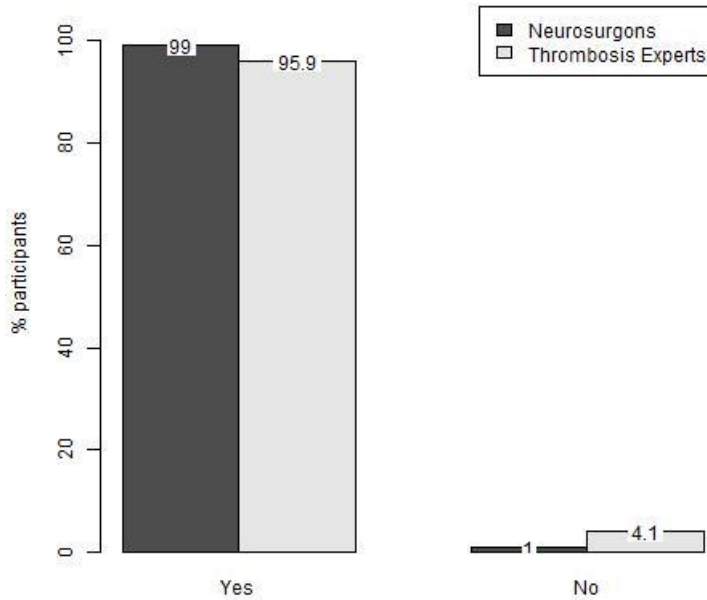


Figure 49: Physicians' decisions in correcting coagulopathy in patients with SDH who had surgical intervention.

Only 2.8% of the respondents did not provide what timing they would re-institute the OAC in patients after surgical intervention for subdural haematoma. Regardless of physician specialty, there was no clear agreement about the timing of OAC restart (Figure 50). There was no statistical significant difference between the responses of the two physician specialities using Pearson Chi-Square test (P value 0.85).

Similarly for patients with no risk factors, we found about 60% of physicians restarted OAC between day 4 and day 14 post SDH.

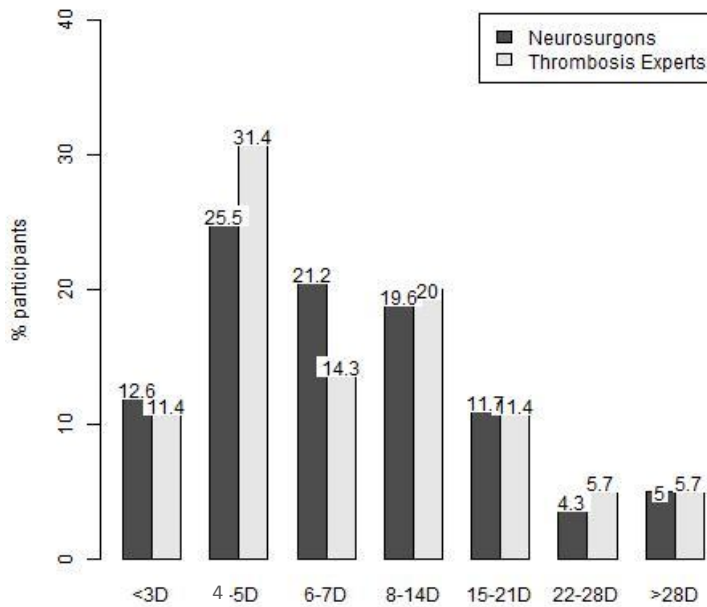


Figure 50: Timing of restarting OAC in patients with SDH who had surgical intervention.

Subdural haematoma and haematoma size

When participants were asked whether the size of the SDH would influence their decision to correct the coagulopathy, 27.4% of thrombosis experts and 12.4% of neurosurgeons said that they would not correct the coagulopathy if the haematoma was small (less than 30 cm³). This response was stronger among thrombosis experts (Figure 51). However, when the SDH was large in size (more than 30 cm³) almost all of the respondents replied that they would correct the coagulopathy (Figure 52). We had less than 3% missing data for each scenario of haematoma size and we found that there were statistical differences in the responses between the two physician specialities for

the two scenarios of haematoma size using Pearson Chi-Square and Fisher's Exact tests (P value 0.002 & 0.025 respectively).

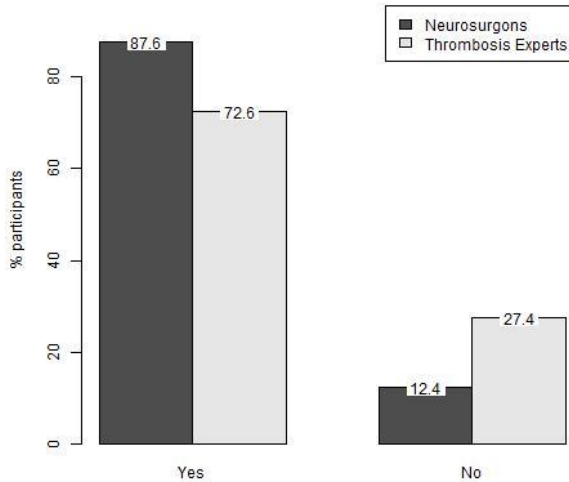


Figure 51: Physician decisions in correcting coagulopathy in patients with small SDHs.

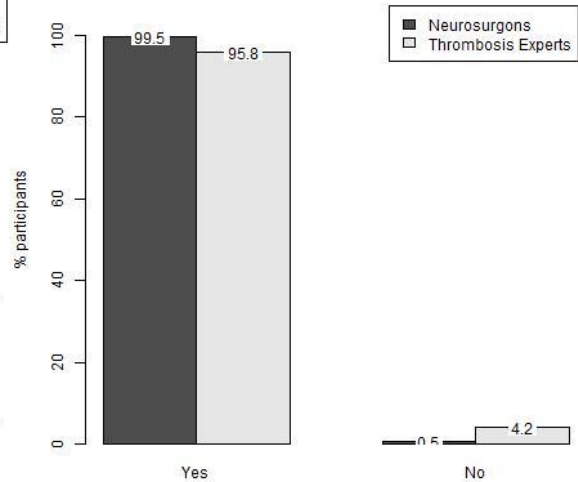


Figure 52: Physician decisions in correcting coagulopathy in patients with large SDHs.

Regarding the time at which OAC would be restarted, physicians were more reluctant to restart OAC very early (3 days or less) when the haematoma was large (Figures 53 & 54). However, 8.5% of the participants did not provide timing in the case of small haematomas, while 2.8% did not provide timing in the case of large haematomas. We found that there were no statistical differences between the responses of the two physician specialities for the two haematoma size scenarios using Pearson Chi-Square test (P value 0.12 & 0.72 respectively).

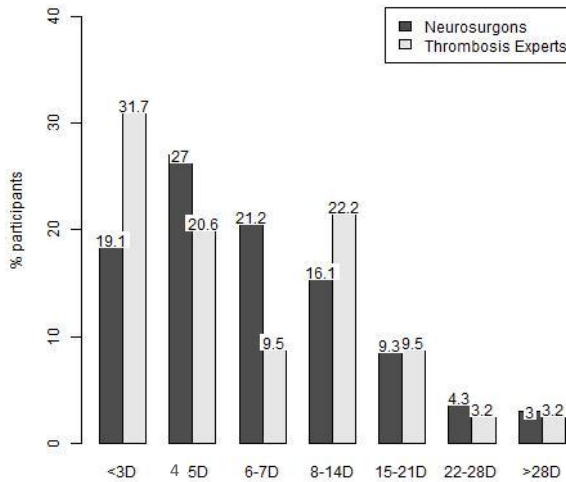


Figure 53: Timing of restarting OAC in patients with small SDHs.

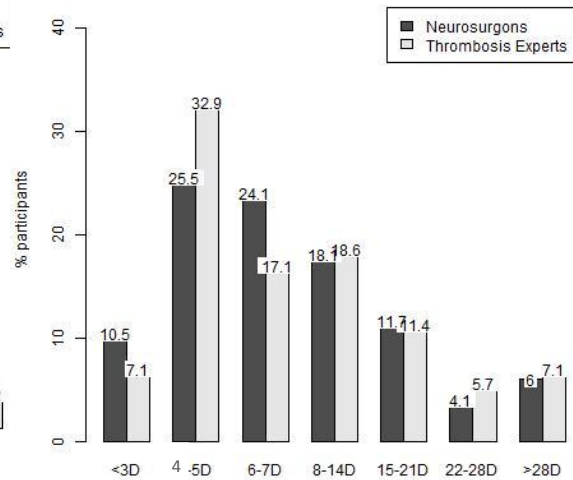


Figure 54: Timing of restarting OAC in patients with large SDHs.

We examined whether the number of respondents and their choices were different between the two scenarios of small and large haematomas using goodness of fit test. We found that there was a statistical significant difference between the two scenarios (P value 0.001) with an earlier OAC restart time for smaller haematomas versus larger haematomas.

Subdural haematoma and atrial fibrillation

When participants were asked to consider patients' stage of atrial fibrillation, there were slightly more participants who would not correct a patient's coagulopathy if the patient scored 2 or more in CHADS2. This was more obvious within the thrombosis experts compared to the neurosurgeon group (Figures 55 & 56). We had 3% or less missing data for CHADS2 0-1 and

CHADS2 2 or more scenarios. We found statistical differences between the responses of the two physician specialties for the two CHADS2 scenarios using Fisher`s Exact test (P value 0.001 & 0.003 respectively).

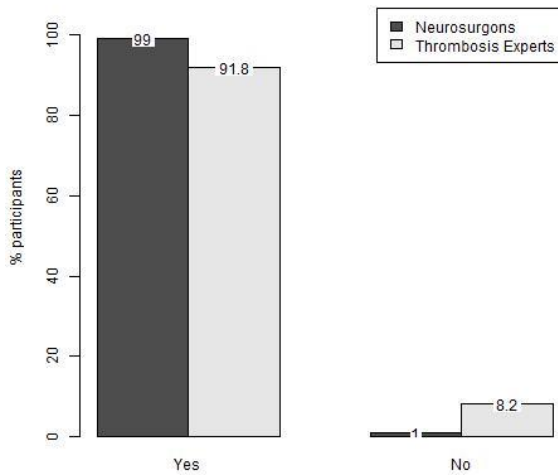


Figure 55: Physician decisions in correcting coagulopathy in patients with SDH and CHADS2 0-1.

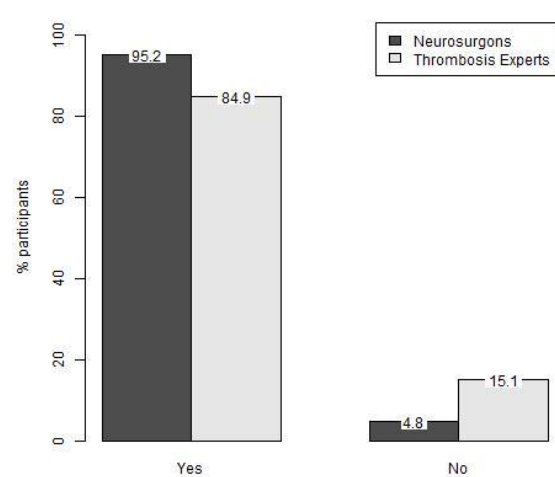


Figure 56: Physician decisions in correcting coagulopathy in patients with SDH and CHADS2 2 or more.

There were more respondents who were willing to restart OAC earlier (3 days or less) in patients who scored 2 or more on the CHADS2 scoring; this being more obvious among the thrombosis experts (Figures 57 & 58). A total of 4.8% of the participants did not provide timing in the case of CHADS2 2 or more, while 3% did not provide timing in the case of CHADS2 0-1. We found that there were no statistical differences between the responses of the two physician specialties for the two CHADS2 scenarios using Pearson Chi-Square test (P value 0.48 & 0.88 respectively).

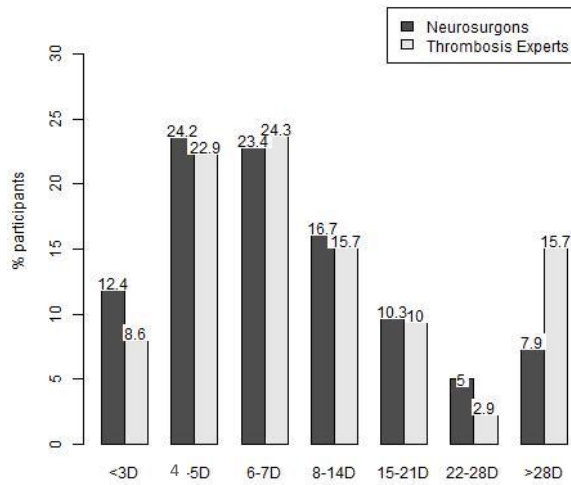


Figure 57: Timing of restarting OAC in patients with SDH and CHADS2 0-1.

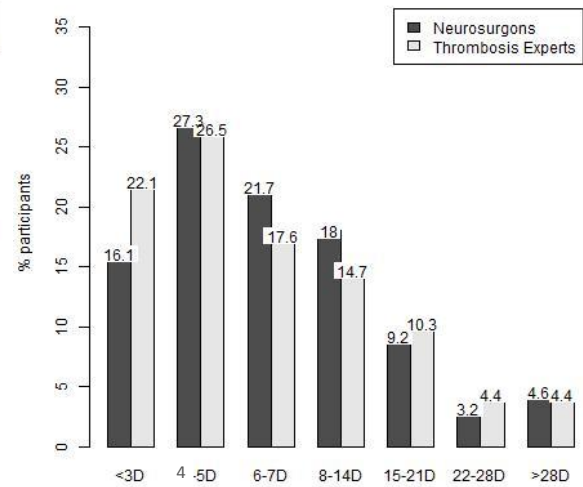


Figure 58: Timing of restarting OAC in patients with SDH and CHADS2 2 or more.

We examined whether the number of respondents and their choices were different between the two CHADS2 scenarios using goodness of fit test. We found that there was a statistical significant difference between the two scenarios (P value 0.001) with patients scoring 2 or more being restarted on OAC earlier than patients who scored 0 or 1, especially when being treated by a thrombosis expert.

Subdural haematoma and deep venous thrombosis

When participants were asked about their management of patients who had a DVT in the last month before the SDH, 11% of the thrombosis experts did not correct the coagulopathy while only 2.4% of the neurosurgeons did not correct the coagulopathy (Figure 59). Only 2.6% of respondents did not answer

this question. We found these responses between the two physician specialities to show statistical significant difference as determined using Fisher's Exact test (P value 0.002).

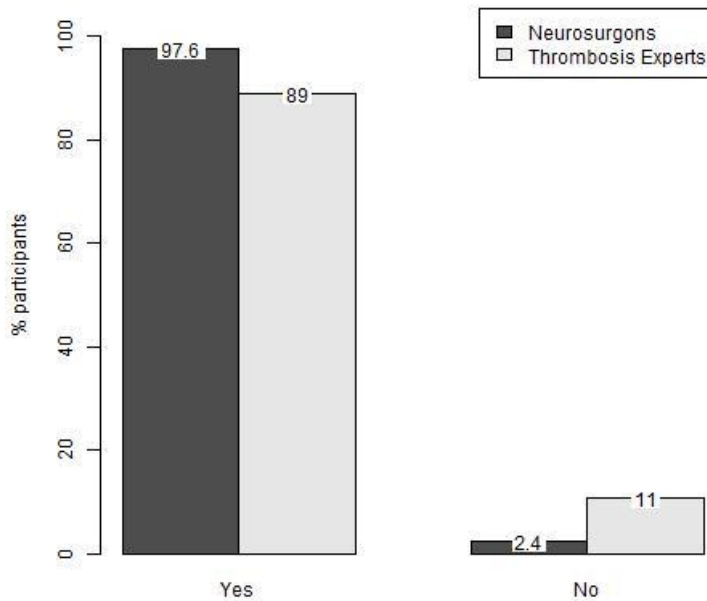


Figure 59: Physician decisions in correcting coagulopathy in patients with SDH and DVT.

A total of 2.3% of the respondents did not provide what timing they would re-institute the OAC. There was no clear agreement between physicians about the timing they would restart the OAC therapy (Figure 60). There was no statistical significant difference between the responses of the two physician specialities using Pearson Chi-Square (P value 0.43).

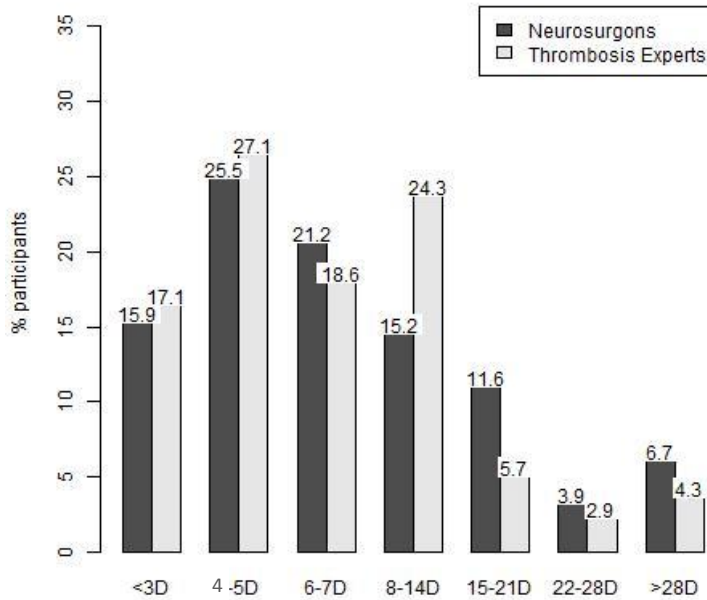


Figure 60: Timing of restarting OAC in patients with SDH and DVT.

In summary, when physicians were challenged with a patient who presented with SDH and suffered a DVT in the month preceding the bleed, more thrombosis experts were eager on not correcting a patient's coagulopathy. Additionally, about 60% of physicians restarted OAC between day 4 and day 14 post haemorrhage.

Subdural haematoma and pulmonary embolism

When patients had a pulmonary embolism (PE) in the last month before they suffered a SDH, more thrombosis experts chose not to correct the coagulopathy compared to neurosurgeons (Figure 61). However, there was still a large majority of physicians who would correct coagulopathy in patients who experienced PE in the month preceding the ICH and there was no statistical

significant difference between the responses of the two physician specialities using Pearson Chi-Square (P value 0.32). Only 2.8% of the participants did not answer this question.

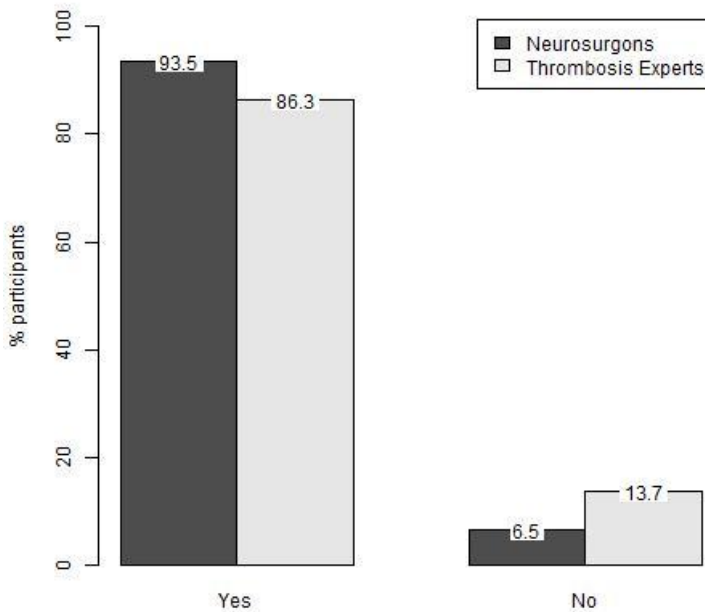


Figure 61: Physicians' decisions in correcting coagulopathy in patients with SDH and PE.

A total of 5% of the respondents did not provide a time for re-instituting the OAC. There was no clear agreement between physicians about the timing of OAC resumption (Figure 62). There was no statistical significant difference between the responses of the two physician specialities using Pearson Chi-Square (P value 0.77).

Similar to patients with DVT, close to 60% of physicians restarted OAC between day 4 and day 14.

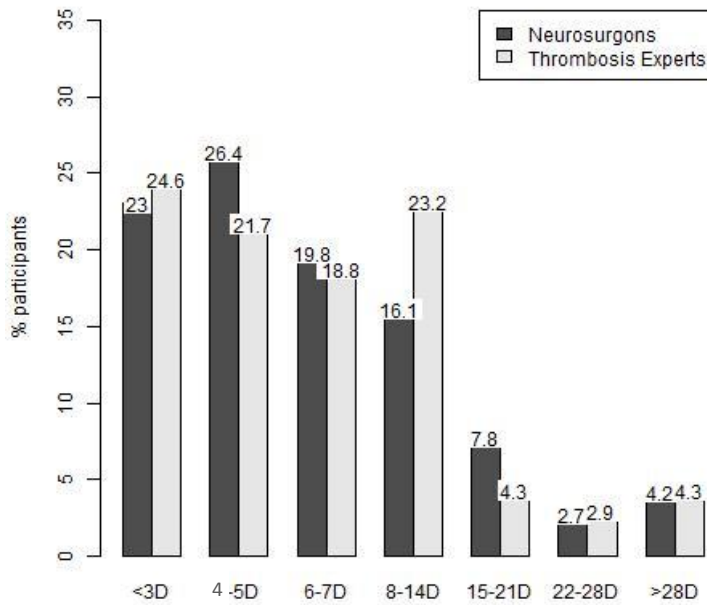


Figure 62: Timing of restarting OAC in patients with SDH and PE.

In summary, physicians chose to correct the patient’s coagulopathy even if patients experienced a recent PE. While statistically not significant, more thrombosis experts decided against correcting the patient’s coagulopathy than neurosurgeons. Again, the time at which physicians choose to reinstitute OAC treatment remains undecided for patients with ICH who had a recent PE.

Subdural haematoma and patient age

When participants were asked about correcting coagulopathy when patients were young (less than 30 years), there were more thrombosis experts who did not correct the coagulopathy (Figure 63). However, when the patient was older (more than 75 years), the majority of physicians chose to correct the

coagulopathy. There was no clear difference in the neurosurgeon and thrombosis experts' responses for treating older patients with subdural haematomas (Figure 64). We only had 3.2% or less missing data for each scenario of age.

We found that there was a statistical difference between the responses between the two physician specialties when the patients were young. This difference in the treatment chosen was not evident when the patient was older. Analysis was calculated using Fisher's Exact test (P value 0.001 & 0.15 respectively).

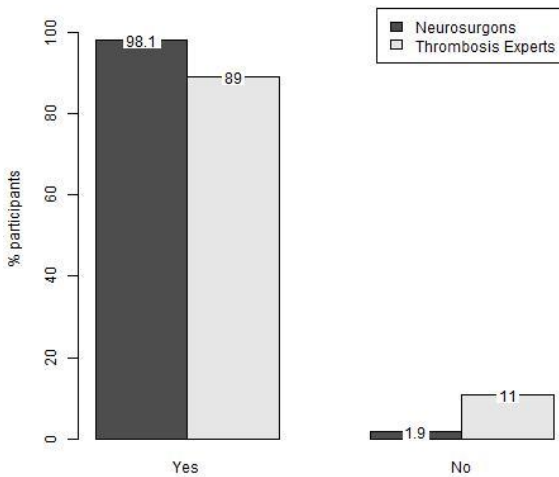


Figure 63: Physicians' decisions in correcting coagulopathy in young-age patients with SDH.

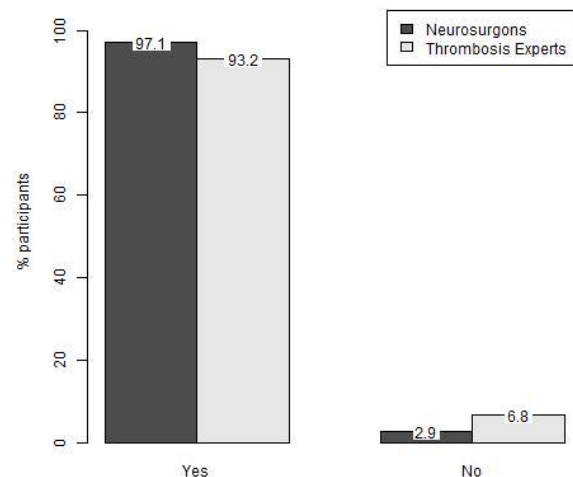


Figure 64: Physicians' decisions in correcting coagulopathy in old-age patients with SDH.

Physician specialties presented very similar responses concerning restarting OAC when both age scenarios were considered (Figures 65 & 66). A total of 3.6% of the participants did not provide the timing in the young age scenario, while 4.6% did not provide the timing in the old age scenario. We found that there were no statistical differences between the responses of the two physician specialties for the two age scenarios using Pearson Chi-Square test (P value 0.59 & 0.11 respectively).

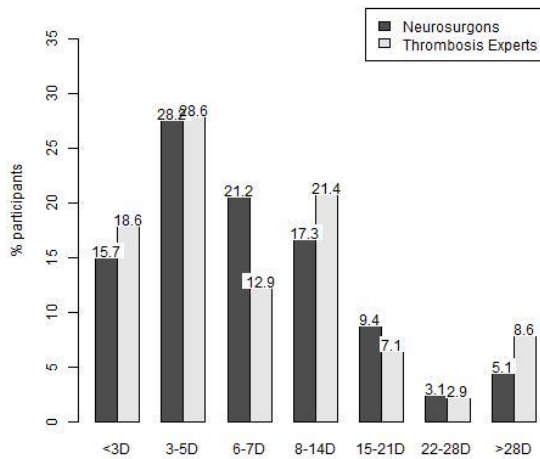


Figure 65: Timing of restarting OAC in young-age patients with SDH.

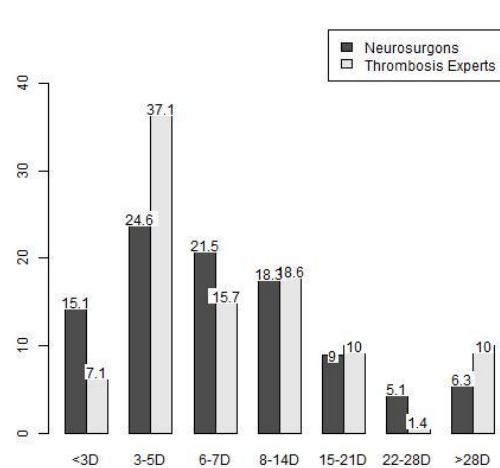


Figure 66: Timing of restarting OAC in old-age patients with SDH.

We examined whether the number of respondents and their choices differed between the two age scenarios using goodness of fit test. We found that there was a statistical significant difference between the two age scenarios (P value 0.001) with thrombosis experts being more inclined to restart OAC in the older patients between days 4 and 5 than the neurosurgeons who treated older

patients more readily at less than 3 days. By comparison, younger patients were treated similarly by neurosurgeons and thrombosis experts.

Subdural haematoma and caged-ball valve

When participants were asked to consider patients who had a caged-ball MHV, there were more thrombosis experts who did correct the coagulopathy (Figure 67). A total of 3% of the participants did not answer this question. We found that there was a statistical significant difference between the responses of the two physician specialities using Fisher's Exact test (P value 0.001) with more thrombosis experts not correcting patients' coagulopathy.

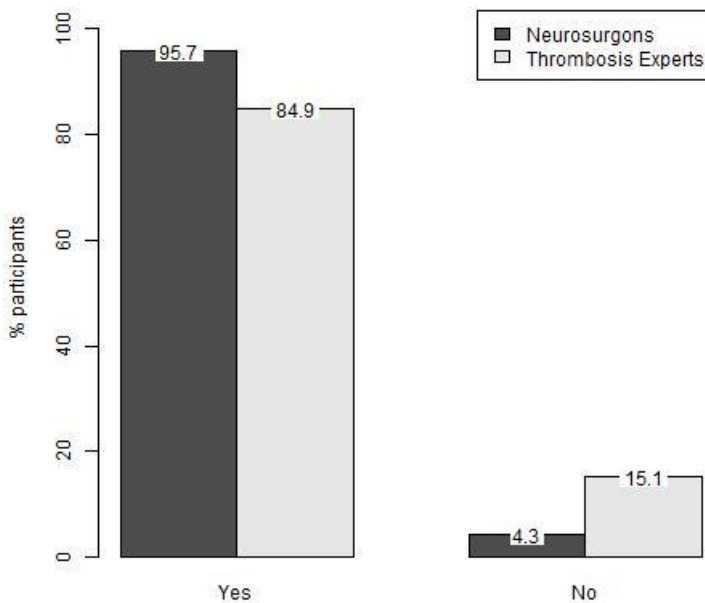


Figure 67: Physicians' decisions in correcting coagulopathy in patients with SDH and caged-ball valves.

A total of 4.6% of the respondents did not provide what timing they would re-institute the OAC. Many physicians wanted to restart OAC within the first 5 days (Figure 68). There was no statistical significant difference between the

responses of the two physician specialities using Pearson Chi-Square (P value 0.35).

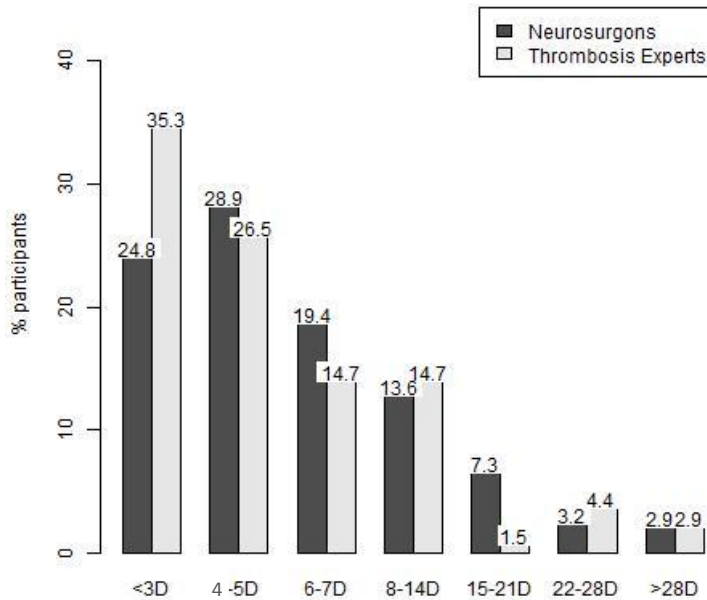


Figure 68: Timing of restarting OAC in patients with SDH and caged-ball valves.

In summary, this question regarding preference of time for restarting OAC in patients with caged-ball valve implants indicated that more thrombosis experts did not correct the coagulopathy and close to 60% of the physicians restarted OAC between days 4 and 14.

Subdural haematoma and valve location

When participants were asked to consider the location of the MHV, either mitral or aortic, more thrombosis experts did not correct the coagulopathy in both valve location scenarios (Figures 69 & 70). We only had 2.8% missing data for each scenario. We found a statistical difference between the responses of the two physician specialities for the two valve location scenarios using Fisher's

Exact test (P value 0.001 and 0.02 respectively) with more thrombosis experts not correcting the coagulopathy for both mitral and aortic MHV compared to neurosurgeons.

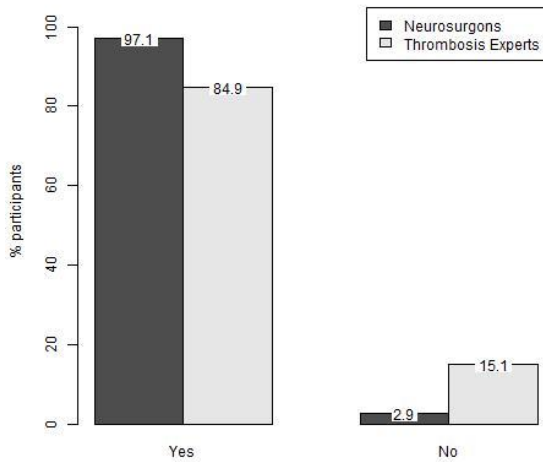


Figure 69: Physicians' decisions in correcting coagulopathy in patients with SDH and mitral MHVs.

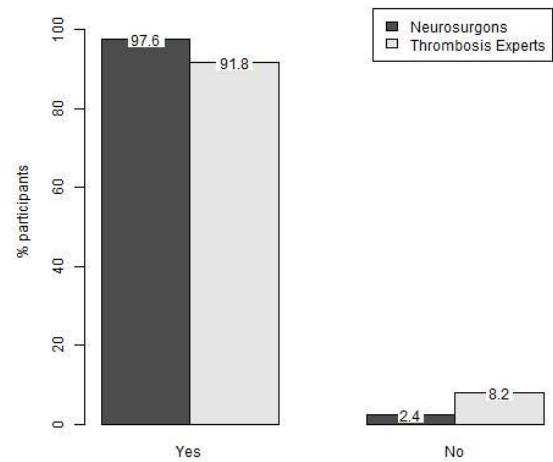


Figure 70: Physician's decisions in correcting coagulopathy in patients with SDH and aortic MHVs.

Physicians responded similarly concerning restarting time of OAC in both mitral and aortic MHV scenarios (Figures 71 & 72). A total of 4% of the participants did not provide timing of OAC restart in the mitral valve scenario, while 3.2% did not provide timing in the aortic valve scenario. We found that there were no statistical differences between the responses of the two physician specialties for the two valve location scenarios using Pearson Chi-Square test (P value 0.74 & 0.60 respectively).

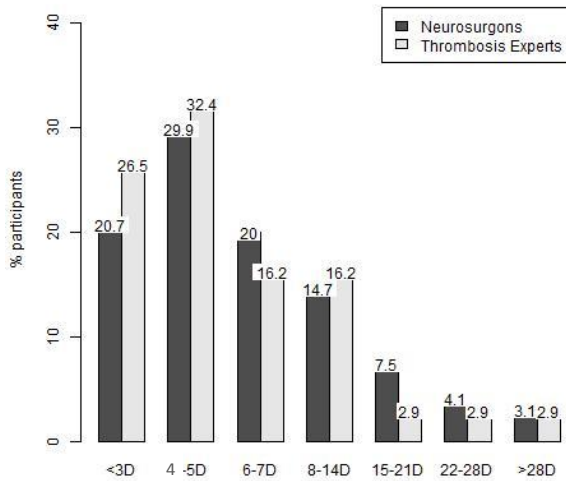


Figure 71: Timing of restarting OAC in patients with SDH and mitral MHVs.

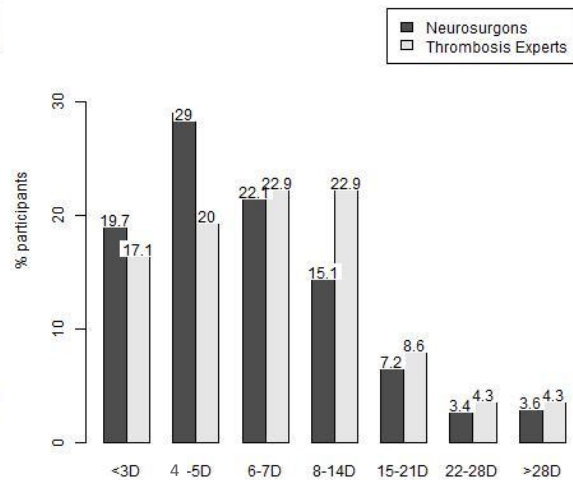


Figure 72: Timing of restarting OAC in patients with SDH and aortic MHVs.

We examined whether the number of respondents and their choices were different between the two valve location scenarios using goodness of fit test. We found that there was a statistical significant difference between the two scenarios of valve location (P value 0.001) with more physicians restarting OAC therapy earlier (less than 5 days) when the MHV was in the mitral valve position compared to an aortic valve position.

Subdural haematoma and multiple MHVs

When patients had multiple MHVs, thrombosis experts were more reluctant to correct the coagulopathy (Figure 73) than neurosurgeons. A total of 3.2% of the participants did not answer this question. There was a statistical significant difference between the responses for the two physician specialities using Fisher's Exact test (P value 0.001).

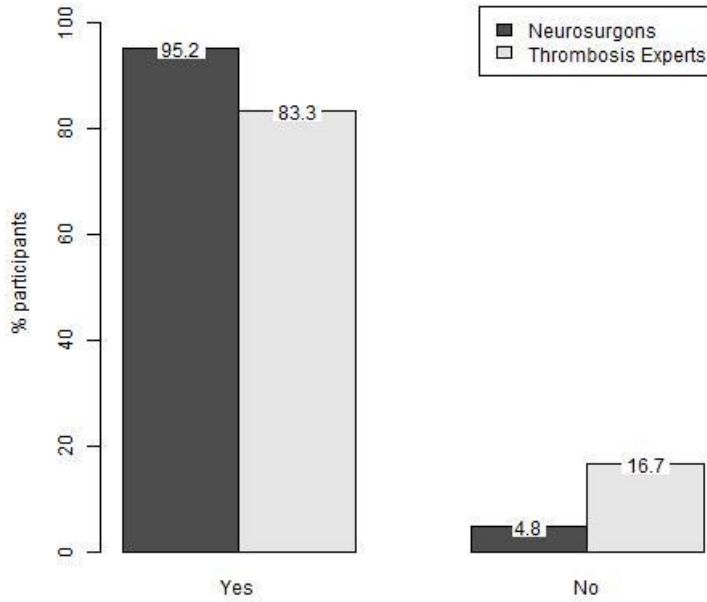


Figure 73: Physicians' decisions about correcting coagulopathy in patients with SDH and multiple MHVs.

A total of 4.8% of the respondents did not provide the timing that they would re-institute the OAC. Many physicians decided to reinstitute the OAC within the first 5 days post SDH (Figure 74). There was no statistical significant difference between the responses from the two physician specialties using Pearson Chi-Square (P value 0.54). Additionally, we found about 60% of physicians restarted OAC between day 4 and day 14.

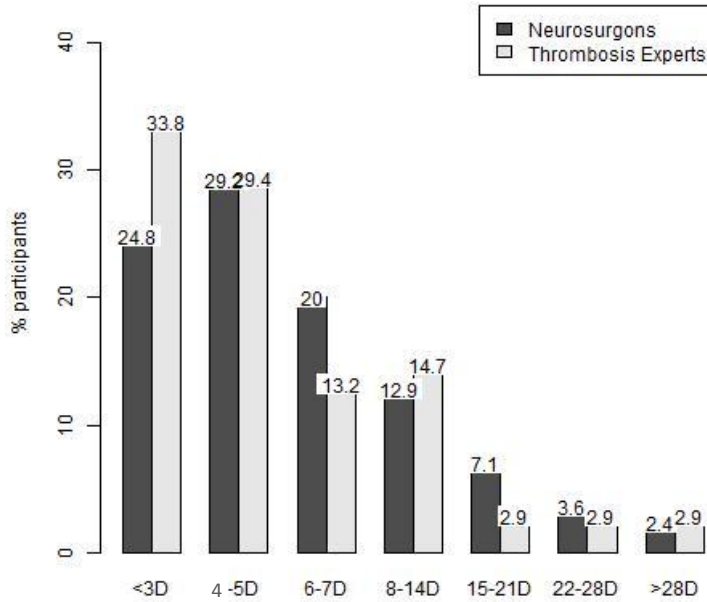


Figure 74: Timing of restarting OAC in patients with SDH and multiple MHVs.

In summary, more thrombosis experts did not correct the coagulopathy in comparison to neurosurgeons. However, the majority of neurosurgeons (95.2%) and thrombosis experts (83.3%) indicated that they would correct the coagulopathy in patients with multiple MHVs. However, no clear time for restarting OAC in patients with SDH and multiple MHVs was elicited.

Clinical risk factors and timing of restarting oral anticoagulant

We conducted a goodness of fit test to examine whether there were differences between the number of participants and their choices among different clinical risk factors. For a reference we used the clinical scenario where patients did not have any risk factors. We performed our analyses comparing different patient risk factors to patients with no risk. We completed our analyses for both intracerebral and subdural haematomas.

We found that there were statistically significant differences in the responses to timing of restarting OAC if patients had clinical risk factors compared to patients with no risk factors. These significant findings were consistent for both intracerebral and subdural haematoma questionnaires (Tables 19 & 20). In addition, this analysis held true for neurosurgeons and the thrombosis physicians.

Table 19: Restarting time of OAC in patients with clinical risk factors versus patients with no risk factors in the setting of intracerebral haematoma.

Clinical situation	Chi-squared value	P value
Recent cranial surgery	791.77	0.001
Small haematoma (less than 30 cm ³)	754.20	0.001
Large haematoma (more than 30 cm ³)	897.61	0.001
Patient with CHADS2 0-1	722.50	0.001
Patient with CHADS2 ≥2	883.70	0.001
Recent history of DVT	894.68	0.001
Recent history of PE	638.11	0.001
Young age (less than 30 years)	1.2e+03	0.001
Old age (more than 75 years)	1.1e+03	0.001
Patient with caged-ball valve	727.15	0.001
Patient with mitral valve	825.80	0.001
Patient with aortic valve	914.48	0.001
Patient with multiple valves	793.55	0.001

Table 20: Rrestarting time of OAC in patients with clinical risk factors versus patients with no risk factors in the setting of subdural haematoma.

Clinical situation	Chi-squared value	P value
Recent cranial surgery	827.64	0.001
Small hematoma (less than 30 cm ³)	738.23	0.001
Large hematoma (more than 30 cm ³)	1.0e+03	0.001
Patient with CHADS2 0-1	872.40	0.001
Patient with CHADS2 ≥2	938.72	0.001
Recent history of DVT	1.0e+03	0.001
Recent history of PE	839.51	0.001
Young age (less than 30 years)	1.2e+03	0.001
Old age (more than 75 years)	1.1e+03	0.001
Patient with caged-ball valve	914.05	0.001
Patient with mitral valve	882.77	0.001
Patient with aortic valve	1.0e+03	0.001
Patient with multiple valves	850.37	0.001

Types of intracranial haematoma and timing of restarting oral anticoagulant

When we compared the participants' timing for restarting OAC in the setting of intracerebral haematoma and subdural haematoma for the same clinical situations (Figure 75), we found in the majority of clinical situations there were slightly more participants who would restart OAC in the first 3 days in the setting of subdural haematoma. When we examined this statistically comparing

the median of timing categories together (Table 21) we could not find any statistical significant differences among all clinical situations.

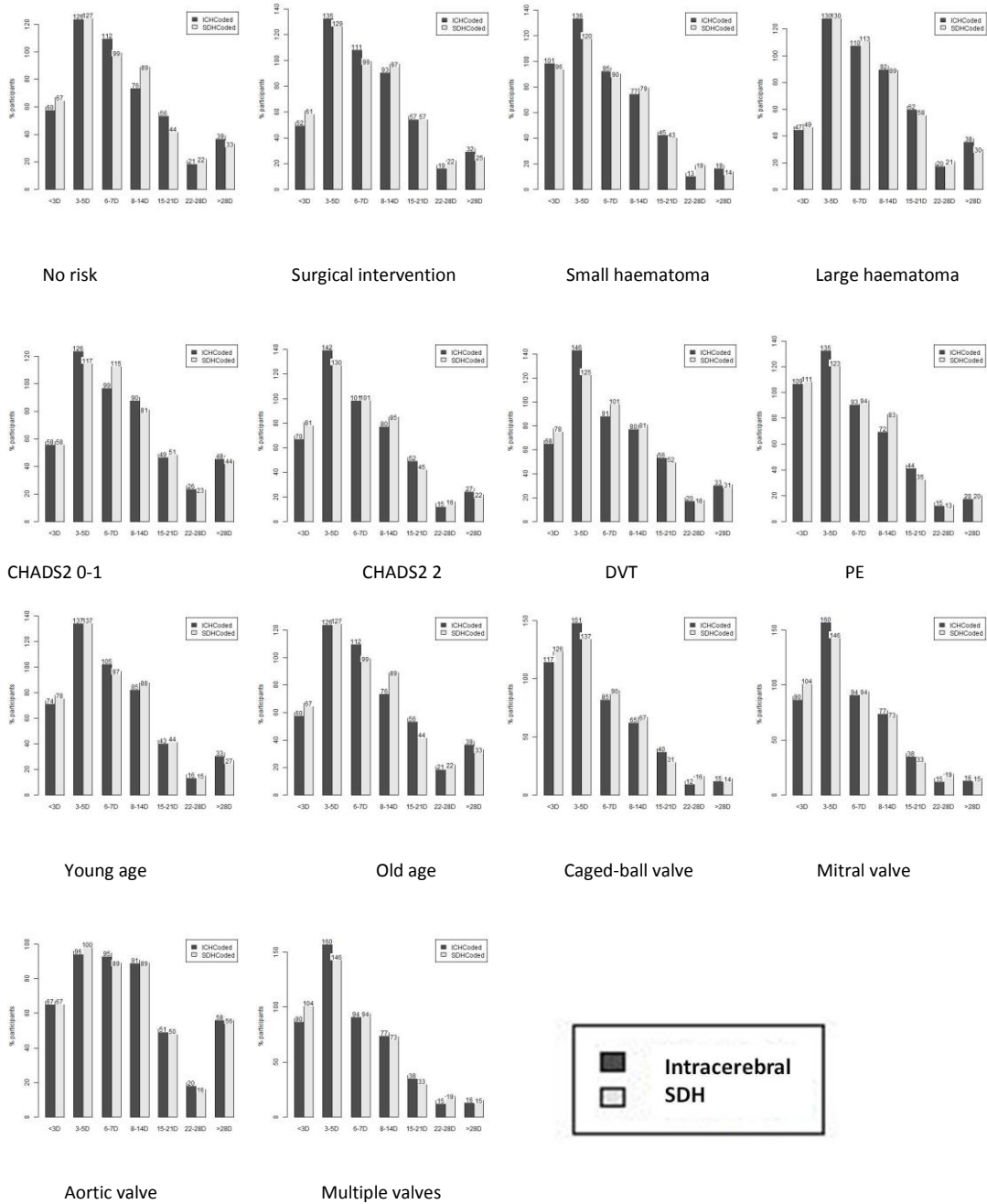


Figure 75: OAC restarting time for intracerebral haematoma versus subdural haematoma.

Table 21: OAC restarting time in patients with intracerebral and subdural haematomas.

Clinical situation	Intracerebral (median timing category)	Subdural (median timing category)	t-statistic	<i>P</i> value
No risk patient	6-7 days	6-7 days	0.39	0.69
Surgical intervention	6-7 days	6-7 days	0.48	0.63
Small haematoma	6-7 days	6-7 days	0.40	0.69
Large haematoma	6-7 days	6-7 days	0.79	0.43
CHADS2 0-1	6-7 days	6-7 days	0.33	0.74
CHADS2 ≥2	6-7 days	6-7 days	0.71	0.48
DVT	6-7 days	6-7 days	0.35	0.73
PE	6-7 days	6-7 days	0.13	0.90
Young age	6-7 days	6-7 days	0.57	0.57
Old age	6-7 days	6-7 days	0.84	0.40
Caged-ball valve	4-5 days	4-5 days	0.28	0.78
Mitral valve	4-5 days	4-5 days	0.44	0.66
Aortic valve	6-7 days	6-7 days	0.58	0.56
Multiple valves	4-5 days	4-5 days	0.092	0.93

Participants' characteristics and demographics in relation to OAC restarting time

Evaluating participants' characteristics (number of years in practice, country of practice, type of practice and average annual number of ICH cases in patients with MHV the participant managed) (Figures 76 -79), we found that the average number of cases managed by participants each year was the only statistically significant factor (Table 22).

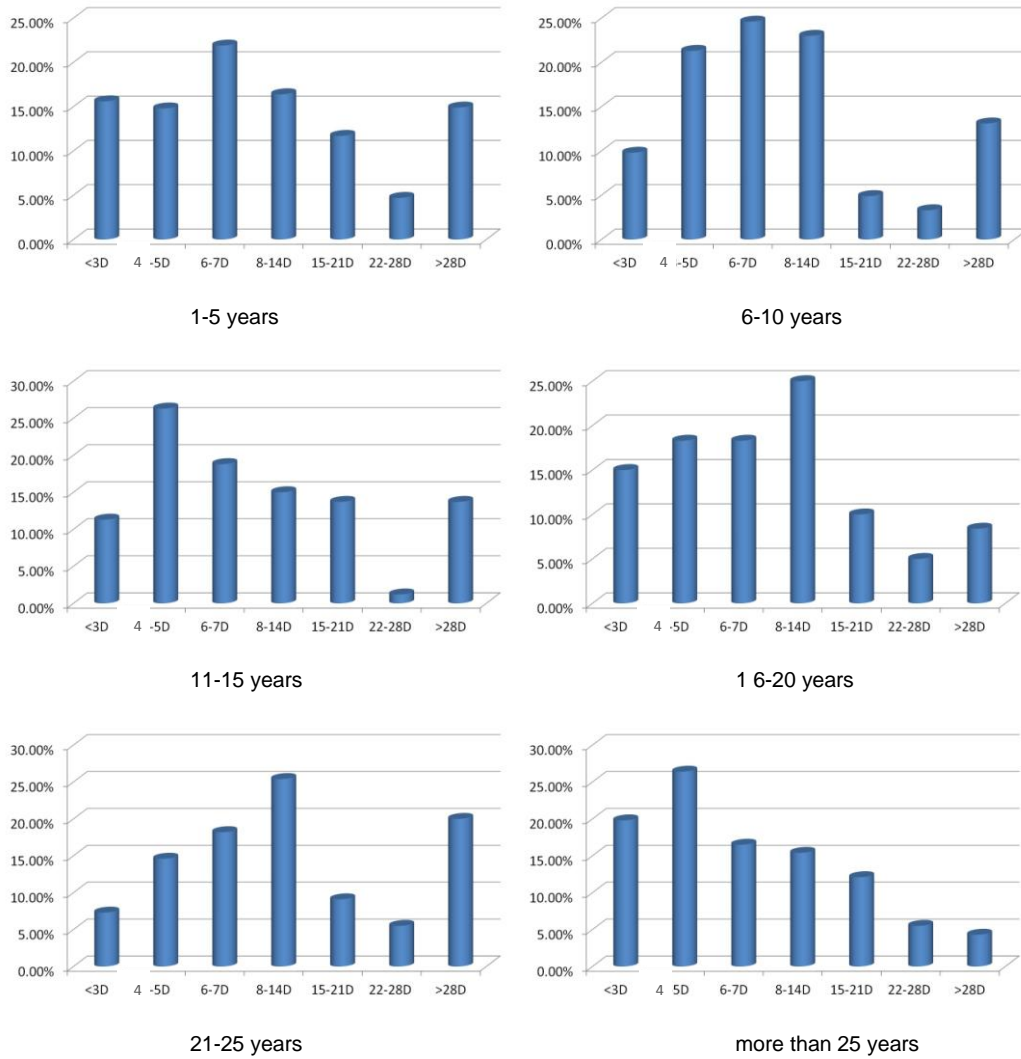


Figure 76: Physician's years in practice in relation to timing of restarting OAC.

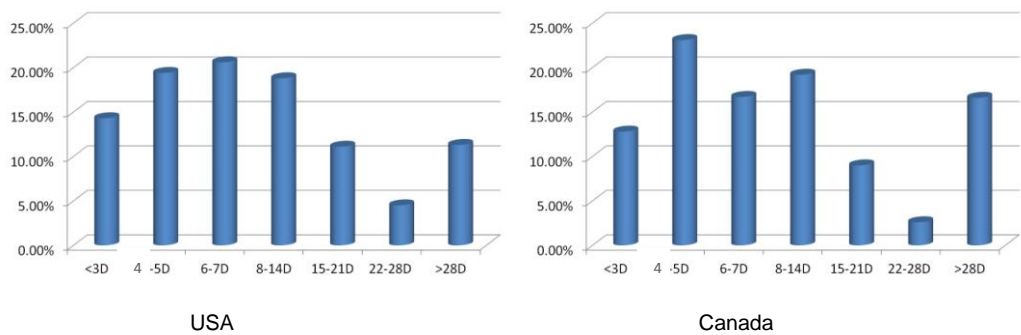


Figure 77: Physician's county of practice in relation to timing of restarting OAC.

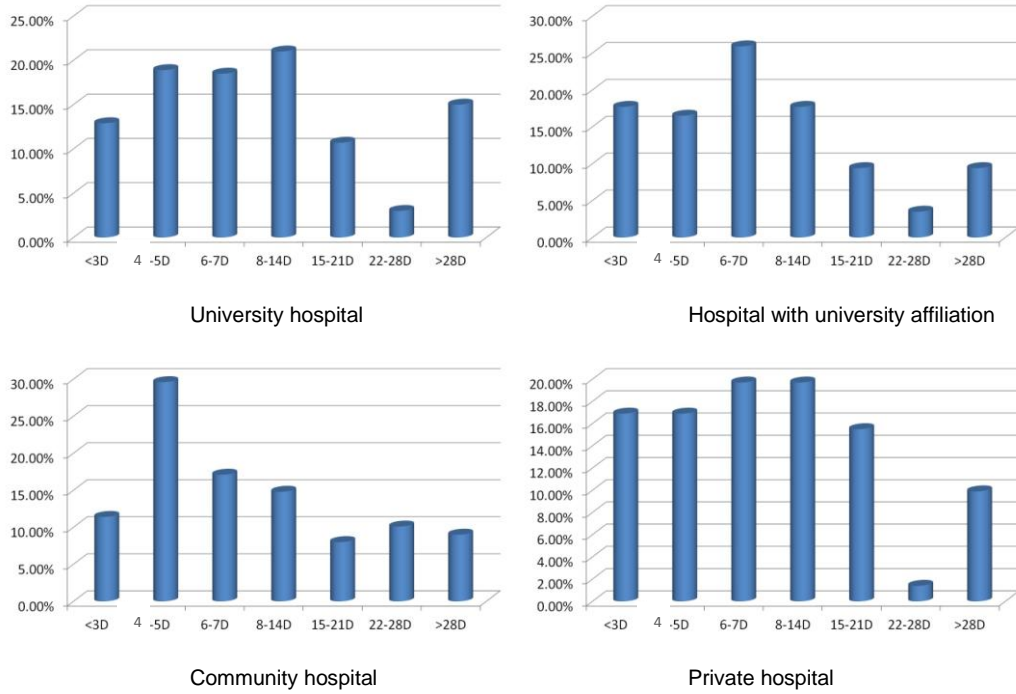


Figure 78: Physician`s type of practice in relation to timing of restarting OAC.

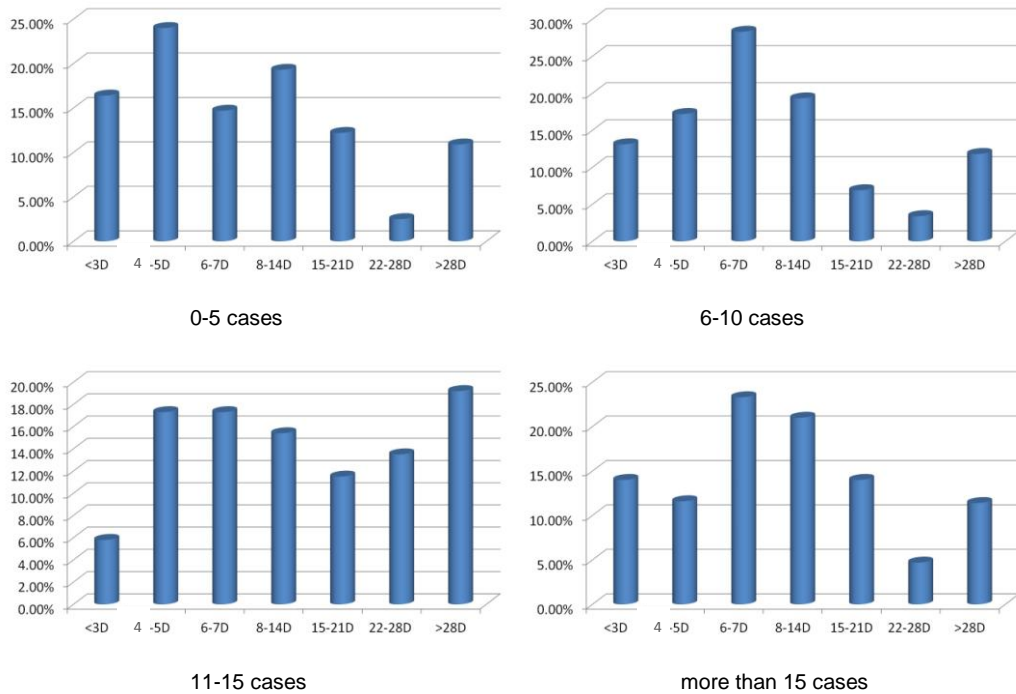


Figure 79: The average number of cases treated by the physician in relation to timing of restarting OAC.

Table 22: Statistical evaluation of participants' characteristics in relation to OAC restarting time.

Characteristics	X2 value	P value
Practice years	32.22	0.36
Country of practice	3.47	0.75
Type of practice	25.63	0.11
Average number of cases annually	34.75	0.01

We then used Poisson regression model to evaluate the relation of the participants' choices of timing of restarting OAC as a function of the participants' characteristics and demographics for the two clinical scenarios. We did not find any of these to be consistently statistically significant.

Participants' willingness to participate in further studies

Participants were asked if they were interested in having their patients participate in future RCT or prospective cohort studies. There were 479 respondents who answered the question about RCT and 478 answered the question about the cohort study.

For the RCT study, 62.4% of the respondents indicated that they were not interested in participation in such a study (Figure 80). For respondents indicating a willingness to participate in a RCT, there was a higher percentage of thrombosis experts than neurosurgeons who revealed a willingness to participate. However, this difference in response between physician specialities was not statistically significant (X^2 0.68, P value 0.41).

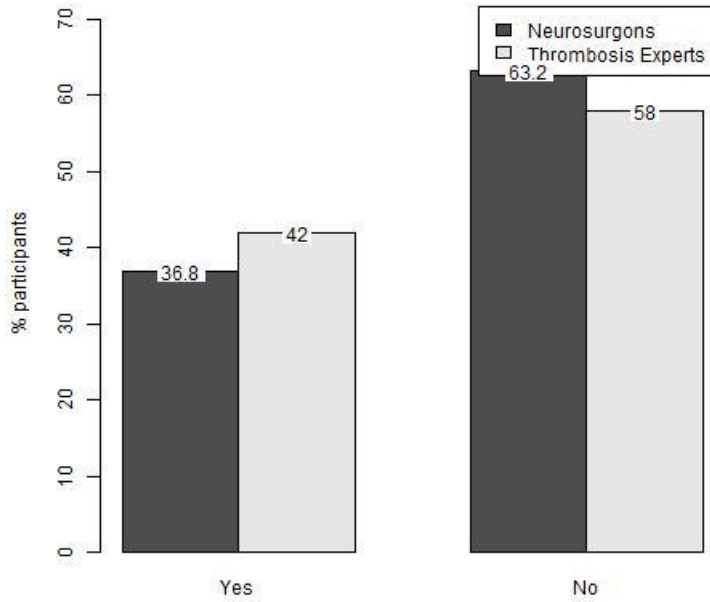


Figure 80: Physicians' willingness in having their patients participate in a RCT study.

We found respondents had slightly more interest in participating in a cohort study (Figure 81). Again we did not find any statistical difference in responses between the two physician specialities ($\chi^2 3.67$, P value 0.06).

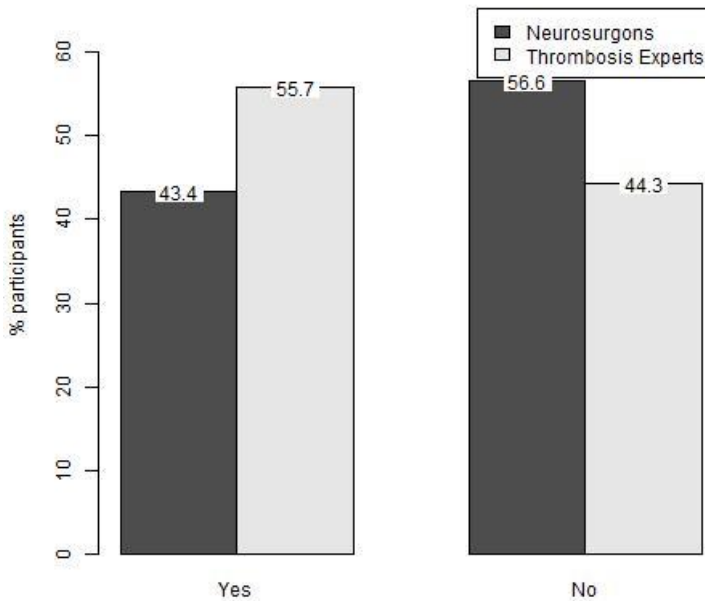


Figure 81: Physicians willingness in having their patients participate in a cohort study.

When we considered respondent's type of practice (academic, which include physicians at a university hospital or hospitals with a university affiliation, versus non-academic, which include physicians at community hospitals or private hospitals), academic physicians were more interested in participating in a RCT study (Figure 82) or cohort study (Figure 83) than physicians at non-academic centres. We found this difference to be statistically significant for both RCT and cohort studies (χ^2 14.77, P value 0.001 & χ^2 12.76, P value 0.001, respectively).

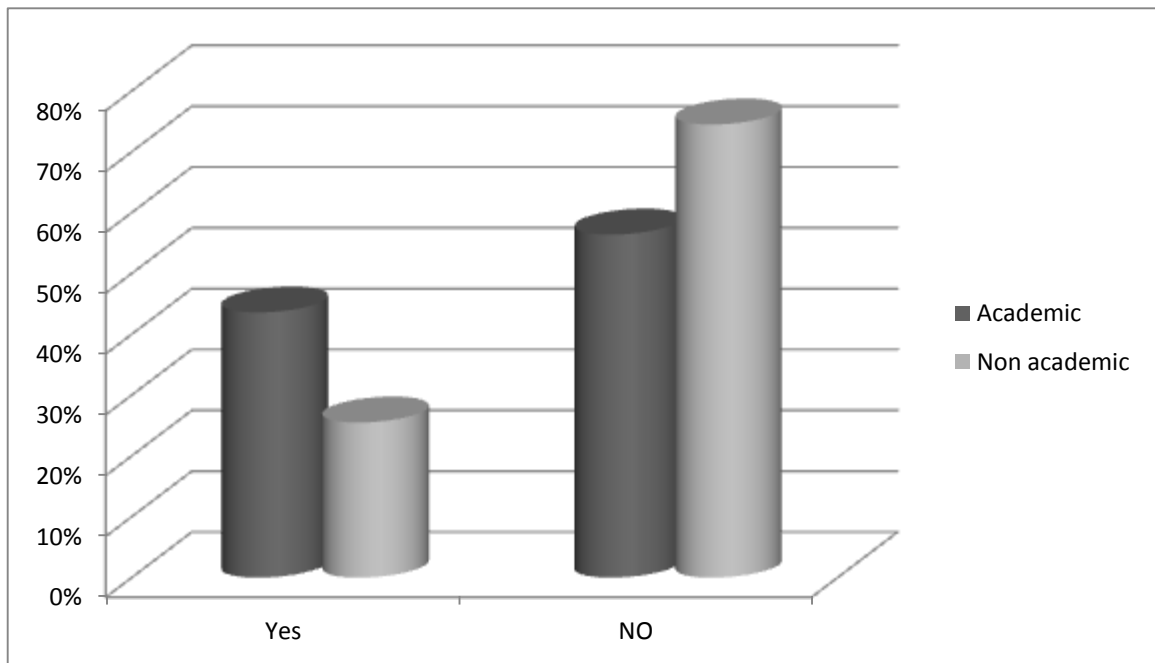


Figure 82: Physicians' willingness to participate in RCT study based on their type of practice.

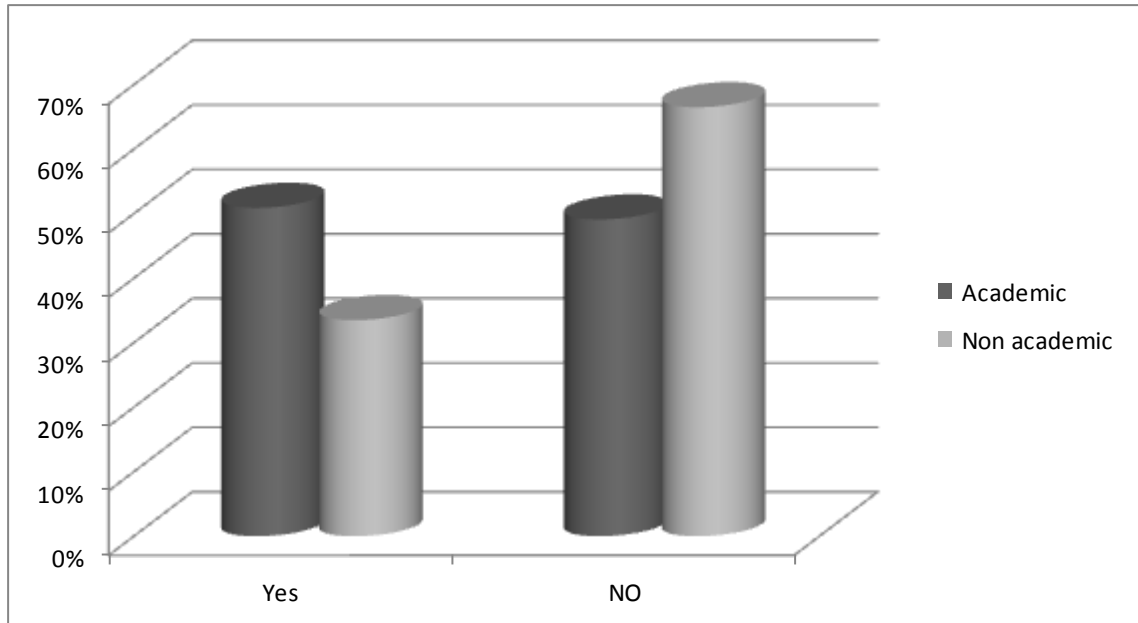


Figure 83: Physicians' willingness to participate in a cohort study based on their type of practice.

In summary, it would appear that physicians' practice setting contributes to their willingness to participate in future studies, either RCT or cohort studies. The participants' responses indicated that they are more willing to participate in a cohort study than a RCT study.

Discussion

Patients with MHV are always placed on lifelong treatment with OAC to minimize the risk of stroke, valve thromboses, and peripheral emboli. However, OAC therapy predisposes patients to ICH. Following diagnosis of an ICH, OAC therapy is usually withheld for a period of time, but then resumed to mitigate the risk of thromboembolic complications. From our systematic review we were unable to discern the best time to resume OAC in patients with MHV following

an ICH. For this reason we undertook a survey to better understand physician practices when treating patients with MHV who present with an ICH.

Population and sampling

We targeted neurosurgeons and thrombosis experts for our survey participants because most cases of ICH in patients with MHV are managed by these two medical specialities. To minimize practice variations we focused on thrombosis experts and neurosurgeons in USA and Canada. We included these two countries because the medical and residency training share a lot of similarities. Also speciality certificates from either country are recognized by the other country.

AANS has the largest number of members in North America²⁰¹. Many members of the AANS have interest in one of the subspecialties of neurosurgery and not all of those members would manage patients with ICH and MHV. Because of this we excluded members with clearly identifiable subspecialties in spine, paediatric, functional neurosurgery, epilepsy, and peripheral nerves. We were able to identify members' subspecialty either through their address in the membership directory or through the website of the hospital where they work. In cases where we were not able to identify the neurosurgeon's subspecialty, we included them in our target population.

The ISTH is one of the largest specialised societies focusing on thrombosis²⁰². We were able to identify members' country of practice through their address in the membership directory. We used a similar mechanism to the

one we used with the neurosurgeons to identify ISTH members with a paediatric subspecialty or who were scientists.

We may have sent our survey to members of AANS and ISTH who did not manage ICH in patients with MHV and this may have negatively affected our response rate, which was 34.31%.

Survey variables, design, validity, conduction, and monitoring

In our survey we included all variables we identified from our systematic review that may affect a physician's decision regarding timing of restarting OAC. Some participants in their comments added that they consider CT scan findings (mainly whether or not the haematoma changed in size) as a factor that may cause them to consider restarting OAC earlier. Some physicians considered initially managing patients with heparin before restarting OAC therapy. We did not include heparin in our questionnaire because our main goal focussed on the restarting time of OAC.

The main part of our questionnaire was concerned with the optimal time when OAC should be restarted. No similar surveys could be identified in the literature and as such we were not able to compare our questionnaire to any other questionnaires. Our systematic literature review identified the first week after diagnosis of the ICH as very critical regarding timing of reinstating OAC. For this reason we divided the first week into three different time categories (≤ 3 days, 4-5 days, and 6-7 days).

Our first draft of the questionnaire included four clinical scenarios (intracerebral haematoma, subdural haematoma, cerebellar haematoma and other types of ICH). Face/content validity was evaluated by consulting experts at our local institute. Two major feedback comments were provided regarding our initial questionnaire. The first comment was that the questionnaire was too long. We therefore modified our initial questionnaire to only include intracerebral haematomas and subdural haematomas since these form the majority of ICH types. The second feedback was concerned with the size of the initial haematoma. Many of our experts recommended including the size as one of the clinical risk factors, which we did in our final survey.

Our questionnaire test-retest correlation coefficient was 0.91 and when we measured that for questions only concerned with timing of restarting OAC it was 0.85. These results were above 0.7, which is recommended by many literatures^{222, 223}, especially in surveys that focus on group-level differences.

We utilized an internet-based survey because it was very convenient to our target population, less expensive, and was helpful in ensuring accuracy of data editing. One of the downsides of using an internet-based survey is that participants may open the link but fail to answer the survey. SurveyMonkey does not recognize this as a non-respondent. To minimize non-respondents we manually deleted them and included them as non-respondent and they received reminder e-mails. Another limitation of internet-based surveys is that our e-mails may have been sorted as junk mail by some of the participants' e-mail services. To avoid our survey being directed to the recipients' junk folder, all our

e-mails were sent as if they were from the main investigator and did not have SurveyMonkey in the subject. Despite this we recognize that it was possible that some e-mails may have been delivered to the recipients' junk folder.

We tried to apply most of Dillman's recommendations^{219, 224, 244, 245} in conducting our survey using the internet. However, we were not able to send a personalised e-mail to each prospective participant with their name because the SurveyMonkey website does not provide such a feature. To overcome this problem we could have sent e-mails with just the link, but this would have caused us to lose the advantage of tracing non-respondents.

We did not provide any monetary incentive to our participants, but a nonmonetary incentive was given to participants in the form of an option to receive the survey results. Such consideration has been shown to improve the response rate^{225, 248} in internet-based surveys.

Response rate

Our survey response rate was 34.3%. This rate is higher than previously published results given our target population. O'Neill et al.²²⁶ did a survey of ventriculostomy and intracranial pressure monitor placement. Their survey was also internet based and was sent to 3100 neurosurgeons. O'Neill et al. reported a response rate of 30%. Other surveys of neurosurgeons reported response rates of 23.9% to 31%^{227,228}. Nahed et al.²²⁷ sent a survey to AANS members and reported a 31% response rate. Our neurosurgeons' response rate was 33.9%, while thrombosis experts showed a 37.1% response rate. We believe by

considering Dillman's recommendations in our design and conduction of the survey, in addition to focusing our survey sample on physicians who usually manage patients with MHV and ICH, we improved our response rate compared to the previously mentioned published surveys.

Respondent characteristics

Close to half of our thrombosis expert respondents were from Canada. This is most likely related to the fact that Dr. Wells is a well known senior thrombosis expert in Canada, a fact that may have improved our response rate from Canadian thrombosis experts. Our univariate analysis showed that the country of participant's practice was not statistically related to participants' choice of OAC restarting time.

We noticed that about one third of thrombosis experts had been practicing for more than 25 years. About one third of neurosurgeons had only been practicing for 5 years or less and only 17.4% for more than 25 years. This might be explained by our small sample of thrombosis experts in comparison to our neurosurgery participant group. A further explanation as to the differences in the participant groups is that the thrombosis experts' population is more senior than the neurosurgeons. However, neither years of practice nor speciality was significant in our analyses.

We found the majority of thrombosis experts worked within an academic setting, with very few in the community setting and none in the private setting. This is most likely related to the fact that thrombosis experts work in more

tertiary centres compared to neurosurgeons, at least mainly in the USA. While many neurosurgeons work in an academic setting, physicians of this specialty are represented more than thrombosis experts in community and private settings.

Another interesting finding was that neurosurgeons manage on average more cases of ICH in patients with MHV than thrombosis experts. This might be related to that many cases might have been managed by neurosurgeons only without involving thrombosis experts.

Missing data

Variables with missing data did not exceed 10%. The highest missing variable was only 7.3% so we did not need to impute the data. We noticed that the percentage of missing data increased for variables located at the end of the survey. For example, the subdural haematoma scenario had more missing data than the intracerebral haematoma scenario. This may either be related to the length of the survey or that some participants would manage both scenarios the same way. We did notice that some participants answered identically for both scenarios. In our analysis we did not find any statistical significant differences in timing of restarting OAC for intracerebral versus subdural scenarios.

Correction of coagulopathy

We found that more than 95% of the participants in most clinical situations would correct the coagulopathy. This finding was similar among

thrombosis experts and neurosurgeons. Such a decision was consistent with most recommendations in management of ICH associated with OAC. Also our systematic review identified the same recommendation. In all of our identified case series studies, patients' coagulopathies were corrected.

However, with certain clinical risk factors more participants were willing not to correct the coagulopathy. These clinical factors were patient related (patients who scored 2 or more in CHADS2-atrial fibrillation scoring system, recent DVT, recent PE, small size haematoma, caged-ball valve and multiple valves). Despite knowledge that some of these factors may increase the risk of thromboembolic complications, most literature, as we mentioned previously, recommend correcting coagulopathy in the acute phase. Interestingly, despite all recommendations there are still physicians who would not correct the coagulopathy.

Another interesting but not statistically significant finding we identified from our respondents was that more thrombosis experts were reluctant to correct patients' coagulopathy in the setting of SDH compared to intracerebral haematomas. There is no literature to support this and actually most available literature, as discussed previously, recommends correcting a patient's coagulopathy.

Restarting time of oral anticoagulant

We found very wide variations in responses among our participants regarding the best time to restart OAC following an ICH. There was no

agreement on the timing of restarting OAC in any clinical situation for both intracerebral and subdural haematomas; however, the majority of participants would restart OAC at a time ranging from day 4 to day 14 post ICH diagnosis. The variations in practice were not related to participants' speciality, country of practice, years of practice, or type of practice. This finding was very similar to findings from our systematic review. Clearly there is no agreement among thrombosis experts or neurosurgeons regarding time of restarting OAC in patients with MHV following an ICH. This is most likely a reflection of the lack of data. In our systematic review some studies recommended restarting OAC as early as 3 days post ICH, while others recommended waiting for 3 to 4 weeks.

We found for certain clinical risk factors, mainly patients who scored 2 or more of CHADS₂, recent DVT, recent PE, caged-ball valve, mitral valve location, and multiple valves, that more participants were willing to restart their patients on OAC within the first 3 days post ICH, but there was still wide variation among participant responses. This data makes sense given that with these risk factors some participants were reluctant to correct the coagulopathy. Our results suggest that physicians manage each clinical situation differently and without clear agreement on when is the ideal OAC restarting time. However, more than two thirds of the physicians restarted OAC between day 4 and day 14 in the majority of clinical scenarios.

When we analysed our two clinical scenarios according to the presence of clinical risk factors, we found that there was a statistically significant difference in restart time between the clinical risk factors.

We found the number of years the physician had been in practice to be the only statistically significant participant characteristic in relation to OAC restarting time. Our result suggests that physicians who manage less than 5 cases per year are more likely to restart OAC earlier than those who manage 6-15 cases per year. However, when we performed multinomial logistic regression analysis we did not find this relation to be constantly statistically significant when we considered each time category. We therefore did not include this analysis given its limited clinical meaning.

Participants' willingness to participate in future studies

It is surprising that more than half of our participants were not willing to participate in RCT or cohort studies. There was slightly more interest in the cohort study and this might be because physicians felt cohort studies are safer for their patients. In the comments section on the survey some respondents added that they were not willing to risk their patients in a RCT. This finding supports that the natural history of restarting OAC in patients with MHV and ICH is not clear for the majority of physicians, yet they fear to evaluate it.

External validity and potential bias

One caveat of this survey was that respondents were answering questions of theoretical clinical scenarios, so participants may have answered differently than what their actual practice would have been. To minimize this we

included many clinical risk factors within two different scenarios. We believe this helped resemble the clinical variations physicians face in their practice.

This survey may have been affected by self selection bias; our response rate was higher than many published rates within our target population. We applied most of Dillman's guidelines to improve our response rate. Despite all of our effort, self selection bias cannot be completely eliminated from our results.

Another possible bias in our survey was variable error caused by the order of the questions. We did not examine the effect of changing the order of questions in our questionnaire. Dillman described five types of order effects that can influence responses to questions, with one of them being an anchoring effect. We acknowledge that our survey may have been affected by this bias.

Lastly, we cannot eliminate from our results the bias arising from non-respondents. We tried to minimize this affect, as we discussed previously, but it is impossible to completely eliminate such bias.

Regardless of these limitations, our cross-sectional survey included members from the AANS and ISTH within Canada and USA. The response rate was close to one third, which is more than most published surveys of these groups. The majority of neurosurgeons and thrombosis experts in both countries are members of these two organisations. We believe the survey is representative of the practice of neurosurgeons and thrombosis experts in Canada and USA when they face ICH in patients with MHV with consideration of possible biases that are mentioned above.

Conclusion

Our survey showed that there is wide variation in the current practice of neurosurgeons and thrombosis specialists when they face the dilemma of managing patients with ICH and MHV. The variation was minimal regarding deciding to correct patients' coagulopathy, but was very wide when it came to deciding the ideal time to restart patients on an OAC regimen.

A physician's decision was influenced by factors related to both the patient and the valve itself. Surprisingly, the type of intracranial haematoma did not have any influence on their decision.

The variation observed in physician decisions regarding when they restart their patients on OAC most likely reflects the huge gap in the literature pertaining to the natural history of this clinical dilemma. Physicians continually attempt to make the best decision in their opinion that would benefit the patient and minimize risks for the patient. This concern was also voiced in the reluctance of some physicians to involve their patients in clinical studies.

CHAPTER 4

Proposed future study

Evaluating the risks and benefits of restarting oral anticoagulant in 5 to 9 days after intracranial haemorrhage in patients with mechanical heart valve(s); a multi centre cohort study

Background, literature update, and rationale

Patients with mechanical heart valves (MHV) require lifelong anticoagulation with oral anticoagulants (OAC). This lifelong need for OAC is agreed upon by almost all cardiac guidelines¹²⁻¹⁵. MHV are thrombogenic because they expose the blood to an artificial surface²²⁹. Our systematic review and many literature have highlighted the strong evidence that OAC reduces the risk of thromboembolic complications associated with OAC by approximately 75%^{6, 8,9,22,230}.

One of the major complications related to OAC is development of an intracranial haemorrhage (ICH). Recent studies demonstrate that the reported incidence of ICH in patients taking OAC has increased compared to the 1990s^{231,233}, exhibiting an approximate 4-fold increase. The rate of ICH in patients with MHV who take OAC is close to 1% per patient-year^{10, 15, 24-26, 232}. ICHs that are associated with OAC correlate with high mortality and morbidity^{34, 35, 234}. A recent study from the Registry of the Canadian Stroke Network found the in-hospital

mortality rate to be 45.1% in patients with ICH secondary to OAC ²³¹. These results are similar to those we discussed earlier in the systematic review.

The current management of patients with ICH secondary to OAC includes correcting the patient's coagulopathy. Recent literature agrees that immediate reversal of coagulopathy is indicated ²³⁵. The main management of reversing the coagulopathy includes administration of vitamin K and fresh frozen plasma, in addition to factor VIIa and prothrombin complex concentrate on some occasions ^{236, 237}. Once patients have their INR corrected they are at an increased risk for thromboembolic complications including valve thrombosis, embolic stroke, deep venous thrombosis (DVT), and pulmonary embolus (PE). However, restarting patients on OAC puts them at risk of rebleeding. It is therefore important to find the right time to restart OAC and to balance the risks of thromboembolic complications with the risk of recurrent ICH. The ideal time of restarting patients on their OAC after being diagnosed with an ICH has not yet been established, as we demonstrated in the systematic review and the survey.

In our systematic review we examined the literature between January 1950 and April 2012, but we were unable to draw conclusions on the ideal time to restart OAC therapy after patients with MHV experienced an ICH. Our systematic review suggested that resuming OAC therapy after 3 to 7 days might present the time with lowest risk of rebleeding or developing thromboembolic complications. However, our systematic review was limited by poor quality

studies (Table 10), and a small number of patients included in these studies. We found significant heterogeneity among the studies preventing a meaningful analysis. Our systematic review has therefore identified a gap in the literature regarding the ideal time to reinstitute OAC therapy in patients with MHV and presenting with an ICH.

Since the systematic review we performed a literature update and we did not find any published RCT or large cohort study answering this question. Robinson et al.²³⁸ published a case series about safety of recombinant activated factor VIIa in patients with warfarin-associated haemorrhages of the central nervous system. Their series included 6 patients with MHV and ICH; all patients had their INR corrected in addition to administration of factor VIIa. Two of these patients developed thromboembolic complications; one patient developed a stroke 5 days after their ICH, while the other developed a DVT 21 days after their initial presentation. Robinson et al. did not report timing of restarting OAC or the rate of recurrent ICH.

Krittalak et al.²³⁹ published a retrospective study comprising 26 patients with MHV and ICH. Five of their patients died from complications of ICH. No data was found for 3 of the patients from Krittalak's study. OAC was withheld for 1 to 26 days. Three patients developed thromboembolic complications. This study did not include data about risks of recurrent ICH. A more recent study by Yeon et al.⁵² presented a prospective study that included 20 patients with warfarin-associated subdural haematoma (SDH). Twelve of their patients had

MHV, all patients had their INR corrected, and all of them underwent surgical intervention. OAC for these patients was restarted on day 3, their new targeted INR was 1.7 – 2.5, and followup was at 6 months after surgery. One patient developed a recurrent SDH 21 days after his initial surgery. Yeon et al. did not observe any thromboembolic complications in their patients. This recurrent rate of 8.3% is promising, but this was a very small study, probably with patient selection bias.

None of the studies included in our systematic review or those identified during our updated search were designed to answer the question of when the ideal time is to restart OAC in patients with MHV and ICH. The majority of studies were retrospective studies and included patients who were taking OAC for a variety of reasons including MHV, atrial fibrillation, DVT, and stroke. The need to restart OAC in patients with these conditions is different. For example, patients with MHV should have their OAC restarted again, while patients with the other scenarios may not require restarting their OAC. Furthermore, the majority of the studies included a small number of patients with the largest study in our systematic review including only 26 patients. Another major concern about the available literature is that many studies focused on one aspect of the two concerns about restarting OAC (i.e. either the risk of recurrent ICH or thromboembolic complications), but not both. In many cases the type of ICH was not specified. There are many types of ICH with intracerebral and SDH being the most common. Each type of ICH has a different pathophysiology and the rate of recurrence might be different. Additionally, almost all of the available

literature are low quality studies as determined by Oxford Level of Evidence and NOS scoring, and the majority had a short followup of approximately 3 months.

The literature included in our systematic review report where OAC was withheld from 1 to 42 days showed the following results: 1) Recurrence of ICH ranged from zero to 50%, with the overall recurrence of ICH in our systematic review being 14%. 2) The development of valve thrombosis ranged from zero to 17% with the overall occurrence of valve thrombosis in our systematic review being 7%. 3) The development of CVA ranged from zero to 25%. However, there was significant heterogeneity among the studies. It is thus obvious that the available literature does not yield insight about the ideal time of restarting OAC in patients with MHV.

This gap in literature creates a clear dilemma for physicians managing patients with MHV and ICH. Most physicians manage these patients based on their experience. Our survey included 1267 neurosurgeons and 202 thrombosis experts; the overall response rate to our survey was 34.3%. Our survey results showed clear variation in the practice of physicians when they are faced with treating patients with MHV presenting with ICH. The variation observed in practise was not related to physician speciality, years of practice, country, or type of practice. Our survey also showed that physicians consider many factors when they are deciding on a time to restart OAC in patients with MHV presenting with an ICH. The survey did not show a difference in practice between intracerebral haematomas and SDHs. One of the major findings in our

survey was that the majority of physicians were willing to restart OAC in the range of 4 to 14 days.

A recent study by Hawryluk et al²⁴⁰ showed similar variations when neurosurgeons were faced with a patient presenting with a spinal haematoma who was also on OAC therapy. At the 78th annual AANS meeting in 2010 Hawryluk et al. presented the case where a patient who was receiving OAC secondary to atrial fibrillation presented with a spontaneous spinal haematoma within a spinal cord tumour. At this meeting the audience was asked when they would restart OAC. Although there are differences between the case presented by Hawryluk et al. and the focus of our study, a noteworthy finding was that the majority of respondents in their audience, as well as our survey, indicated that they have difficulty managing patients who need to be restarted on OAC. Also, the majority of the audience respondents indicated that they depended on their clinical judgment and their experience when they managed such patients.

Given the variation between treating physicians managing restarting OAC in patients with MHV and ICH, a study is needed to address this issue. Two study options are available for addressing the research questions, one being a RCT and the other a cohort study. However, owing to the variation in the current practices identified in our survey, as well as the concern expressed by physicians of exposing their patients to risks by being involved in a research study, a RCT is likely not viable. Furthermore, in a RCT it is difficult to randomise

patients to certain OAC restarting times without strong evidence to support the chosen times.

It is therefore deemed at this point in time that a prospective multicentric cohort study would be the most appropriate study. Such a study would identify the risk of having recurrent ICH, valve thrombosis and thromboembolic complications in relation to the restart time of OAC. This study will also provide more understanding of other factors that affect outcomes. Given that the majority of physician participants in our survey were comfortable restarting OAC close to one week after ICH diagnosis, we proposed the starting time to be between 5 and 9 days from the initial diagnosis of ICH. Further, we propose that this study will be more acceptable than a RCT. In our survey a greater percentage of respondents were willing to enrol their patients in a cohort study.

The proposed cohort study will include all oral anticoagulants, but we anticipate that warfarin will be the most common drug since warfarin is currently the most widely used oral anticoagulant and new OACs have not been used in patients with MHV.

Objectives

Primary objective

The primary objective of this study is to accurately determine the rate of ICH recurrence and the rate of development of thromboembolic complications (valve thrombosis, PE, DVT and embolic stroke) if OAC is restarted between day

5 and 9 from the initial ICH diagnosis. The study population are adult patients (≥ 18 years) with MHV who present with ICH while on an OAC regimen.

Secondary objectives

The secondary objectives of our cohort study include the following:

- To see if the restart day is better earlier or later in the 5-9 day time period.
- To see if the rates of events are different between patients presenting with intracerebral haemorrhage versus SDH.
- To see if risk factors (including patient's age, recent cranial surgical intervention, haematoma size, patient's CHADS2 scoring, recent history of DVT, recent history of PE, valve type, valve multiplicity, and valve location) influence the recurrent ICH or thromboembolic complication rates.

Study outcomes, definitions, and measurement

Primary outcomes

The primary safety outcome is recurrent ICH. The primary efficacy outcome is thromboembolic events. Most of the studies included in our systematic review reported outcomes within a short followup from the initial ICH. We expect most outcomes, if they occur, will happen within the first 3 to 6 months from the initial ICH.

Recurrent ICH is one of the main feared and lethal complications associated with restarting OAC. In our proposed cohort study a recurrent ICH is defined as any new intracranial bleeding diagnosed clinically by a physician and confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) and occurring after the patient's OAC has been resumed.

Valve thrombosis, in our study, is defined as clinical diagnosis of thrombosis of the prosthetic valve confirmed by diagnostic tests (transthoracic (TTE) or transoesophageal (TEE) Doppler echocardiography) and which developed after the patient's initial ICH.

Developments of PE or DVT are complications that could happen in patients with MHV from withholding their OAC in the high risk period after the initial ICH. Both complications are usually first clinically suspected and then radiologically confirmed^{5, 229}. In our cohort study PE will be considered if it is clinically diagnosed and radiologically confirmed. The same guidelines will be applied for DVT.

A serious complication that could happen in patients with MHV when they are not taking their OAC is embolic stroke²³⁰. A daily risk of 0.016% has been estimated^{185, 239}. Thrombus formation on the surface of the MHV is usually the main source for the embolic stroke^{208, 229}. For our study, a stroke needs to be clinically diagnosed and confirmed radiologically with either a CT or MRI.

In our proposed cohort study timing of restarting OAC will be calculated in hours from the time of initial diagnosis of intracranial haemorrhage to the time the patient is restarted on their OAC. If timing in hours cannot be recorded, then it should be recorded in days, considering the time of initial diagnosis as the zero time.

Secondary outcomes

The majority of ICH are either intracerebral or subdural ^{19, 28}, with the latter being less common. In our study an intracerebral haemorrhage will include all parenchymal intracranial haematomas that have been confirmed by CT or MRI. Subdural haematomas will be considered if the haematoma is in the subdural space and has been confirmed by CT or MRI. In the case that SDH is also associated with an intracerebral haematoma, or any other type of ICH, we will count this haemorrhage as a SDH in our analysis.

Patient-related risk factors that may affect a physician's decision to restart OAC will also be recorded. Most of these factors have been discussed earlier in our survey section. Our survey analysis showed that the physician's choice of restarting OAC was significantly different according to certain patient-related factors such as age and haematoma size. In our proposed study haematoma will be reported as small ($\leq 30 \text{ cm}^3$) or large ($> 30 \text{ cm}^3$). All cranial surgical procedures will be considered as surgical interventions (this may include craniotomy, craniectomy, burr hole, insertion of external ventricular drain, or

insertion of an intracranial pressure monitor) as these may also influence OAC restart decisions.

CHADS2 scores (a risk factor for stroke) will be recorded. The CHADS2 scoring system (one point each for congestive heart failure, hypertension, age of 75 or more, diabetes mellitus; two points for prior stroke) is usually used to predicate the risk of a stroke ^{207,208}. Many guidelines recommend OAC in patients with 2 or more points ^{208, 230}. Physicians may consider restarting OAC in patients with MHV and CHADS2 of 2 points or more sooner than those with CHADS2 of zero or one point. Our previous survey result had confirmed this difference in practice.

Other factors to record in our study will include a previous history of DVT or PE, initial INR and the targeted INR after resumption of OAC. Some studies have shown that higher intensities of anticoagulation further increase the risk of ICH ^{19, 24}. The targeted INR in patients with MHV is recommended to be between 2.5 and 3.5 by most guidelines and literature ¹²⁻¹⁵. We will record the actual INR numbers and for our analysis will divide INR into three ranges, namely therapeutic (2-4), sub-therapeutic (<2) and supra-therapeutic (>4).

Another factor that may contribute to the timing of restarting OAC is whether the patient undergoes bridging therapy with unfractionated heparin (UFH) or low molecular weight heparin (LMWH). Some physicians may manage patients initially with heparin prior to restarting the patient on OAC. We will record heparin use, the timing of starting heparin from the initial ICH, and the

duration of therapy. Specific antiplatelet therapy such as aspirin, Plavix, and Aggrenox will be noted, as well as timing of therapy if pre ICH, post ICH and duration of use.

Outcomes assessment

Outcomes of interest are observed daily as standard of care in patients with MHV and ICH. To ensure that all enrolled patients undergo the same standard for reporting outcomes the following guidelines must be considered for outcomes to be reported in our study.

Patients should have a CT or MRI prior to restarting OAC; this will be used as a baseline when recurrent ICH is suspected.

For recurrence of an ICH, this should be clinically suspected (decreased level of consciousness, new cranial nerve findings, changes in speech, new or worsening weakness, etc) and radiologically confirmed by CT or MRI. Valve thrombosis should be clinically suspected (dyspnea, orthopnea, recent congestive heart failure, TIA etc), and confirmed radiologically by TTE or TEE. PE should be clinically suspected (tachypnea, chest pain on inspiration, tachycardia, low oxygen saturation, etc) and confirmed by thoracic CT or VQ scan. DVT should be clinically suspected (unilateral leg pain or swelling, calf tenderness, etc), and Doppler ultrasound is required to confirm DVT diagnosis. Embolic stroke should be clinically suspected (sudden new or worsening weakness, sudden cranial nerve deficit, sudden change in speech, etc) and

confirmed by CT or MRI. All diagnostic imaging will require reports from the radiologist at the patient's institute. Given that diagnostic criteria are well defined we will not require central adjudication of outcome events.

Study design

Our proposed study will be a prospective multicenter single arm observational cohort study of patients with MHV and ICH who have their OAC resumed in 5 to 9 days from their initial ICH. The study will be hospital based and potential patient participants will be identified by the treating neurosurgeon while the patients are in the hospital. Patients will be asked to participate in the study by the treating physician or co-investigator if the patient meets the inclusion criteria. Patients' baseline characteristics will be recorded in the case report form.

The intervention for this study will be the time of OAC therapy resumption. The time of diagnosis of the initial ICH will be considered as zero time. All timing related to variables will be recorded in reference to the zero time.

Patient outcomes will be identified while the patient is in the hospital or during the patient's scheduled followup. Patients will be assessed for potential outcomes on a daily basis by the treating neurosurgeon or his/her team. Data will be recorded on a daily basis by the treating physician and the research nurse.

After patients have been discharged from hospital scheduled followups will be in the following sequence; 1 month \pm one week, 3 months \pm two weeks and 6 months \pm 3 weeks. Timing of the followups will be based on the zero time for each patient. On the followup visits patients will be evaluated by the neurosurgeon or his/her team for potential outcomes and data will be recorded by the treating team and the research nurse.

All patient data, clinical variables and outcomes will be recorded in the case report form (Appendix E). Copies will be sent to the coordinating centre in Ottawa for entry into a computer-based password protected central database. A centres-cordinator will be responsible in communicating with all centres. Data from each centre will be provided to the study's principle investigator (PI) at 2 months (to ensure protocol compliance) and then every 6 months until the end of the study (5 years).

It is hard to identify the ideal followup duration. Most of the studies in our systematic review had a short followup of approximately 2-3 months. However, from previous studies in the literature and from our survey, as well as the expected pathophysiology of such situations, we expect most outcomes to occur within the first 3 to 6 months following the initial ICH, and such events are biologically plausible to be related to the initial event. For our proposed cohort study we will follow patients for 6 months.

An interim analysis will be conducted every 6 months from starting the cohort study to ensure we are within the right recruitment plan.

Study intervention

In our cohort study the intervention in patient care will be the timing of restarting patients on their OAC following diagnosis of an ICH. Although all OAC will be included in this study, we expect that the majority of patients will receive warfarin as their OAC. The anticoagulant drugs will be administered orally and the dose will be considered as irrelevant for our study. If outcomes occur, the INR will be reported.

The time for restarting patients on their OAC will be in the range of 5 to 9 days. The choice between those days will be left to the discrepancy of the treating team (which may include a thrombosis expert). However, the exact day when the patient's OAC is restarted will be recorded in the case report form. As previously mentioned, this timing will be in reference to the time of initial ICH diagnosis.

Potential risks and benefits

As our proposed study is an observational cohort study, it will not interfere with the original management of the patient by his/her physician. While the patient is in the hospital and during the followup we will simply record outcomes without intervening with the patient's management. Also, our followups will be scheduled within the same timeframe the patient is normally scheduled for his/her followup with the treating neurosurgeon. For the purpose of this study we will request confirmatory tests if outcomes are clinically suspected. Again this request would not be exceptional in that most of the time these tests are

routinely requested by the treating physician. There are therefore no potential risks for the patient by enrolling in our observational cohort study.

Participating patients may gain direct and indirect benefit from being enrolled in the study. By enrolling patients in our observational study the awareness of the treating physician may be raised and this may be reflected in potentially better patient care. Additionally, the study protocol provides some standardization in the management of patients with MHV and ICH. It is also hoped that participants may feel satisfied by knowing that they are contributing to research that may help improve care for patients such as themselves in the future.

Study enrollment and withdrawal

Study population and eligibility criteria

Participants in our proposed study must be adult patients (over 18 years of age) who had MHV implanted and who present to a hospital with ICH while they are receiving OAC. Their OAC should be restarted between 5 and 9 days from their initial ICH. The study population will be drawn from many centres and will be recruited while they are inpatients.

Since many OACs are associated with possible congenital fetal risk during pregnancy, pregnant women on OAC are considered as a special group and usually managed differently during pregnancy. For this reason pregnant women are excluded from our proposed study.

Inclusion criteria

In order for patients to be eligible to participate in this study they must meet all of the following criteria:

- Adult age group (>18 years).
- MHV patient receiving OAC who present with ICH.
- The ICH is clinically diagnosed and confirmed radiologically (by CT or MRI) within the four days prior to enrolling in the study.
- Agreement from the treating neurosurgeon or his/her team to restart OAC 5 to 9 days from the initial ICH.
- The patient or patient`s proxy (power of attorney) is able to provide signed and dated informed consent.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in our proposed study:

- Pregnancy.
- Patients who are not permanently living within the province or state of the centre where they are receiving treatment.

Recruitment and retention

A total of 218 patients are needed for this study. The target recruitment is 55 patient participants every year. We anticipate that each centre will recruit 8 to 10 patients per year. A total of seven centres are required for the study. Each centre will be monitored for their patient recruitment at 2 months from their start and then every 6 months. The principle investigator will then review patient recruitment with the participating centres at 2 months from their start and then every 6 months.

By the end of the first year the target number of recruited patients is 55. If this is not achieved after one year, each centre's performance will be reviewed by the principle investigator. The two investigators (PI and the centre co-investigator) will ensure that all recruitment strategies are applied within that centre. In the event a centre has low patient recruitment, new specific strategies may be added depending on the reasons for low performance of the centre. Additionally, if we have not reached the target number of patients within the first 2 years, we may try to recruit an additional two centres to compensate for low patient recruitment.

Centre recruitment

Prior to starting the process of patient recruitment, the principle investigator will contact potential co-investigators at various centres. Potential co-investigators will be identified from our survey respondents where 43% of our neurosurgery respondents were willing to participate in a cohort study and the

majority of them provided their e-mail addresses. The study protocol will be forwarded to each potential co-investigator to ensure that this study is viable within their centre and also to ensure that their centre is able to provide the targeted patient recruitment.

Eligibility for each centre will be evaluated by the PI. Each centre should have at least two neurosurgeons who manage such cases. Each centre should manage on average at least 10 patients with MHV and ICH every year. Each centre should be able to provide a research nurse and be willing to follow the study protocol. Also, each centre should have the ability to perform the required laboratory and radiologic tests for reporting the outcomes as described previously.

We aim to enroll a total of seven centres from Canada and the USA for a five-year period. Ideally three within Canada and four within the USA, but this is not mandatory for the study since our survey showed that the country of practice was not a statistically significant variable affecting physicians' choice of restarting time.

Once centres are identified meetings will be organised between the principle investigator and co-investigators. These meetings will be web-based conferences to outline the study design and discuss study conduct. Approval from the ethics board within each centre is required prior to starting patient recruitment. All centres should use the same patients' recruitment strategies, which is described below.

Patient recruitment

To improve patient recruitment within each centre the co-investigator at each centre will present and introduce the study protocol to the division or department of neurosurgery. We will therefore provide each co-investigator with a copy of our systematic review and results from our survey so that they may include it in their presentation to their departments.

Eligible patients will be identified and recruited by the treating neurosurgeon or local co-investigator. To improve patient recruitment at each centre the research nurse will contact the on-call neurosurgery team on a daily basis to review whether any potential patients were admitted to the hospital. If a potential patient is identified, the research nurse will contact the treating neurosurgeon or local co-investigator prior to attempts to recruit the patient. Written informed consent will be obtained from all patients prior to enrolling them in the study. Recruited patients will be followed by the research nurse on a daily basis until the patient is discharged from the neurosurgery unit. The scheduled followup for patients will be arranged by the research nurse to ensure that the patients follow the guidelines.

Strategies to improve centre and patient recruitment

The following strategies will be considered to improve the success of both centre and patient recruitment:

- Prior to contacting potential centres we plan on presenting our systematic review and survey results at one of the major annual North American neurosurgery meetings, for example the AANS annual meeting. Following presentation of our results at this meeting we will announce that a cohort study will be conducted to address the risks and benefits of restarting OAC in 5-9 days after ICH. By making our study known we hope to elicit a positive involvement from many medical centres.

- Another strategy to improve centre recruitment is to approach centres that we have already identified through our survey where neurosurgeons have been identified as being interested in participating in our study.

- To improve patient recruitment the research nurse or co-investigator within each centre will send weekly e-mails to the neurosurgeons as a reminder about the study. If physician assistants or nurse practitioners are involved in neurosurgery patient management, they will also be included in e-mail correspondence.

- A study poster will be posted at the neurosurgery nursing station to remind treating physicians and medical personnel about the study. The co-investigator and research nurse contact information will also be included in this poster.

- To ensure that all eligible patients are identified the research nurse will contact the neurosurgery on-call team on a daily basis as described previously.

- The PI will ensure that patient recruitment is achieving the recruitment goals. The principle investigator will discuss with co-investigators alternative strategies to improve patient recruitment if centres fall behind the targeted patient recruitment goals.
- The PI will review patient recruitment achievements at 2 months and then every 6 months following the commencement of patient recruitment. If patient recruitment is lower than expected, the abovementioned strategies will be reviewed with each co-investigator. If patient recruitment is low, actions may be taken that could include dropping centres that have not recruited any patients and adding new centres.

Strategies to maintain patient retention

In an attempt to maintain patients for the duration of the study the following strategies will be considered:

- Each patient's address and contact information will be recorded in the patient's case report form to ensure a means of contacting them to remind them of scheduled followup appointments.
- Each patient will be asked to provide a second person to contact in the event the patient cannot be reached by the research group.
- Patient followup will be coordinated by the treating neurosurgeon to ensure that scheduled followup of the study meets the treating physician's followup schedule.

- Patients will be contacted by the research nurse to remind them of their followup prior to the date on which the followup is scheduled. At that time the research nurse will reinforce with the patient the value of their participation in the study.
- The research nurse will also contact patients should any patient miss their followup and another followup will be arranged.

Participant withdrawal and dropout

Given that this is an observational study we do not expect patients to withdraw themselves from the study. However, participation is voluntary and patients have the right to withdraw themselves from the study at any time.

Patients who decide to withdraw will be removed from our database and will not be included in the analysis.

Study termination

The study will be terminated if the number of patients needed for the study is reached before completing five years. Furthermore, if the recruitment strategies fail to achieve the required number of patient participants by five years, the study might be terminated after consideration of other options. In the case that the study is terminated without completing adequate recruitment of patients, the analyses will still be completed as planned.

Study schedule and data collection

Baseline assessment

Once the patient agrees to be enrolled in the study the clinical assessment will be done by the treating neurosurgeon or the physician team as described in this protocol. The research nurse will review the patient's medical history and diagnostic and laboratory tests with the physician to ensure that the patient meets the inclusion criteria.

The following data will be collected and recorded by the treating team and research nurse in the following sequence (Appendix E):

Visit 1, Day 0

- Patient's demographic data including date of birth, address, and contact information.
- Patient's baseline medical history and diagnostic test results; this includes patient- and valve-related factors. Patient-related factors include age, sex, CHADS2 scoring, history of PE within the month prior to the ICH, history of DVT within the month prior to the ICH, and use of antiplatelets. Valve-related factors include MHV location (aortic, mitral or tricuspid), MHV type (caged-ball, tilting-disk, or bileaflet) and valve number (single or multiple).
- Time of the initial ICH (i.e. the time of diagnosis).
- INR level at the time of ICH diagnosis.
- The type and size of the initial ICH as reported by the radiologist.

- If the patient's coagulopathy was corrected and medication used to correct the patient's coagulopathy.
- Type of OAC the patient was receiving before presenting with the ICH.
- Use of heparin therapy.

Data will be obtained from the patient, the patient's family, or the patient's medical records.

Followup visits (daily and outpatient visits)

Followup visits will be done on a daily basis while the patient is in the hospital and during the 1-month, 3-month, and 6-month followup. During the followup visits the following data will be obtained from the patient, the patient's physician, the patient's medical record, and the patient's laboratory and radiologic testing:

- Timing of cranial intervention if any surgical intervention had been done.
- Day of restarting OAC, if the patient has been started on OAC therapy.
- The targeted INR if OAC has been restarted.
- Type of OAC if it has been restarted.
- Day of starting, dose, type, and indication of heparin therapy if the patient has been started on heparin therapy.

- Day of starting antiplatelet therapy if patients have been started on antiplatelet therapy.
- If a patient has a clinically suspected recurrence of ICH (decreased level of consciousness, new cranial nerve findings, changes in speech, new or worsening weakness, etc) and confirmatory CT or MRI.
- Timing of recurrence of ICH if it happens.
- Type of recurrent ICH if it happens.
- INR level at the recurrence of ICH if it happens.
- If patients have a clinically suspected valve thrombosis (dyspnea, orthopnea, recent congestive heart failure, TIA etc) and confirmatory TTE or TEE.
- Timing of valve thrombosis if it happens.
- If the patient has a clinically suspected PE (tachypnea, chest pain on inspiration, tachycardia, low oxygen saturation etc) and a confirmatory thoracic CT or VQ scan.
- Timing of PE if it happens.
- If the patient has a clinically suspected DVT (unilateral leg pain or swelling, calf tenderness, etc) and a confirmatory Doppler ultrasound.
- Timing of DVT if it happens.

- If a patient has a clinically suspected ischemic stroke (sudden, new, or worsening weakness, sudden cranial nerve deficit, sudden change in speech etc) and confirmatory tests by CT or MRI.
- Timing of ischemic stroke if it happens.

Study evaluations

Clinical evaluation

Clinical evaluations will be performed by the neurosurgery team who will obtain the medical history from the patient through direct interview. Included in the clinical evaluation is the physical assessment, which will be performed daily by the neurosurgery team while the patient is in hospital. The physical assessment will include vital sign, neurologic exam, cardiac exam, respiratory exam, and examination of lower extremities.

The research nurse will ensure that all needed history and physical exams in the case report form are completed.

Laboratory evaluation

INRs will be done and recorded at the time of initial diagnosis of ICH and also during followup.

Radiologic evaluation

The radiological evaluations have been outlined in the outcome assessment section.

Statistical consideration

Sample size consideration

It is hard to estimate the actual proportion of patient participants who will develop outcome events. Previous studies that were included in our systematic review had a recurrence ICH rate from 4% to 50%. Our systematic review analysis showed an overall recurrence rate of 16%. For the purpose of sample calculation, we used 15% as the recurrence rate.

Using a confidence level of 95% for the interval and 0.1 precision of the confidence interval, we calculated that the sample size should be 196 patients. However, we expect approximately 10% or less of the patients will drop out or will be lost for followup. To accommodate for this anticipated loss of patient numbers the needed number of participants was multiplied by $(1 / (1 - 0.1))$. With the number calculated to accommodate patient loss, a value of 218 was achieved and therefore a total of 218 patients will be needed to complete our study.

Planned interim analyses

Interim analyses will be conducted by the principle investigator every 6 months; the main goal of these analyses is to ensure adequate recruitment of patient numbers. While these analyses will ensure the recruitment of a sufficient number of patients, it will also help to identify missing data.

Final analysis plan

Outcome variables are rate of recurrent ICH and rate of thromboembolic complications. The following variables will be considered as covariates: Age, sex, haematoma size, CHADS2 scoring, history of PE, history of DVT, valve numbers, antiplatelet use, surgical intervention, bridging heparin use, INR levels, valve type, valve location and patient's study centre.

The following variables will be analysed as dichotomous variables: Sex, type of ICH, haematoma size (large or small), CHADS2 scoring (CHADS2 of 0-1, CHADS2 ≥ 2), history of PE, history of DVT, valve number (single, multiple), antiplatelet use at the time of ICH, surgical intervention after initial haematoma, bridging heparin use after initial ICH, antiplatelet use after ICH. While patient age will be analysed as a continuous variable, the following variables will be analysed as categorical data: INR at diagnosis (sub-therapeutic, therapeutic, and supra-therapeutic), valve type (caged-ball, tilting-disk, and bileaflet), valve location (mitral, aortic, or tricuspid), target INR after restarting OAC (sub-therapeutic, therapeutic, and supra-therapeutic), INR at recurrence of ICH (sub-therapeutic, therapeutic, and supra-therapeutic) and patient's study centre.

Descriptive analysis will be presented for patients' demographic, risk factors, types of initial ICH, and development of valve thrombosis, PE, DVT or embolic stroke. Data will be presented as the mean \pm standard deviation for continuous variable. Proportions will be presented for dichotomous and categorical data. Comparison for continuous data will be performed using the

student t-test and Chi square statistics or Fisher's Exact test for categorical and binary variables.

For our primary outcomes, univariate analysis will be used to calculate outcome frequencies and percentages. A 95% confidence interval will be calculated as well. Analysis will be done at the conventional alpha value of 0.05. To examine the difference between types of ICH results will be stratified by the type of initial ICH (intracerebral or SDH). Comparison will be done using Chi square statistics or Fisher's Exact test and the one sample Z-test or Mann-Whitney rank test. All tests will be done at the conventional alpha value of 0.05.

To examine if the risk factors influence the ICH recurrent and thromboembolic complication rates, a multivariate logistic regression analysis will be done for each outcome including all significant covariates. Results will be presented in odds ratio.

To identify the ideal day within the 5 to 9 day period to restart OAC, timing of restarting OAC post ICH will be divided into five categories (day 5, day 6, day 7, day 8, and day 9). A dummy variable will also be created to group some of these categories into one category. A logistic regression model will be used with considering day 5 as the reference day. Analysis will be done for each outcome, as well as combining the two outcomes as one outcome (given that both outcomes have a poor prognosis).

All tests of significance will be 2-tailed and a significance level of 5% will be considered statistically significant. All data analysis will be performed using SAS version 9.2 and/or SPSS software. Also a statistician will be all statistical analyses to ensure analysis accuracy and adequacy.

Missing data

For possible missing data the following strategy is proposed: If missing data for a variable is less than 10%, no action will be taken and analysis will be performed as planned. A variable with 35% or more missing data will be excluded from the analysis. If missing data is between 11% and 34%, we will consider multiple imputations for the missing data. If this is needed, it will be done with the assistance of a statistician

Data handling and record keeping

Co-investigators' responsibilities

Each patient and centre will be given identification numbers. All patients' demographic data, clinical data, outcome reports, diagnostic and laboratory results will be recorded in the respective case report form initially. Records will be kept in a secure place within the local investigator's institute. Only the co-investigator and the research team will have access to these records.

All copies of case report forms will be sent to the PI and the centres-coordinator. Copies will include all data except the patient's demographic data to

protect their privacy. Data will be checked for accuracy and completeness by the PI and his research team. Data will then be entered into a computer-based password protected central database. The co-investigator at each centre will be responsible for ensuring completeness, accuracy, legibility and reporting data within the timelines. All documents should be completed in a neat and legible manner to ensure accurate interpretation of the data.

Principle investigator responsibility

The study's PI will ensure review of all data from co-investigators within the timelines. PI will ensure that all data are entered into the master database. The master database will be stored at the Ottawa Hospital servers and only accessed within the institute. Only the research team will have access to it.

The PI will be the main communicator between co-investigators. The PI will ensure there is no missing data. Every patient will have an identification number in addition to the centre number. Final analysis will be done utilizing the master database.

The PI will retain the master database for a minimum of 15 years from the completion of the study.

Quality control and quality assurance

At each centre the research nurse will ensure that patient eligibility, baseline clinical data, and daily assessments are completed as per the study protocol. If any data is missing the research nurse will contact the neurosurgery

team to ensure compliance and accuracy of the missing data. This ideally should be done within 48 hours from the time the missing data is identified. The research nurse will follow this protocol on a daily basis for every patient recruited while the patient is in the hospital.

For followup visits the research nurse will arrange the dates in coordination with the neurosurgery team as per the study protocol. Dates will be recorded and provided to the patient. The research nurse will contact the patient prior to the patient's followup date to remind the patient. During followup visits the research nurse will ensure that all required data is completed by the neurosurgery team. If any data is missing the research nurse will ask the neurosurgery team to complete the missing data while the patient is still in the clinic area. If missing data is identified after the patient has left the hospital, the research nurse will try to arrange another followup visit within five days. This will be coordinated with the patient and the neurosurgery team.

Prior to submission of case report forms to the PI the co-investigator will review the case report forms. If missing data is identified, the research nurse will review the patient's data sheet. If the data is still missing the patient's medical record will be reviewed and if data still is missing the patient and neurosurgeon will be contacted to fill the missing data.

The PI will review the master database every 6 months as described previously. If missing data is identified by the PI, the co-investigator will be

contacted. The co-investigator will follow the same protocol as described in the previous paragraph.

Ethical Issues

Ethical standard

The PI will ensure that this study is conducted in full conformity with the Tri-Council Policy Statement and the International Ethical Guidelines for Biomedical Research Involving Human Subjects²⁴³. The study protocol and the associated informed consent form will be submitted for approval by the research ethics board at the PI's institute. Also, each participating centre must provide approval for the study protocol and the associated informed consent by their local ethics board. Any future amendments to the protocol or the consent must also be approved before they are placed into use.

Informed consent process

An informed written consent (Appendix F) must be obtained before the patient may be enrolled in this study. The informed consent is a process that will be initiated prior to the patient agreeing to participate in this study and continues throughout the patient's participation in the study. Extensive discussion about the possible risks and the benefits of participating in this study will be provided to the patients, patients' proxy and/or their families. A consent form describing the study, study intervention, and possible risks and benefits will be given to the patients.

The consent form will be approved by the institutional research ethics board prior to using it. Patients or patients' proxies will be asked to read and review the consent form. Upon reviewing the consent, the neurosurgeon or co-investigator will explain the research study to the patient and answer any questions that the patient may have. The patient must sign the informed consent prior to being enrolled in the study.

Potential patient participants will have the opportunity to discuss the study with their family members and will be given the chance to think about it prior to agreeing to participate. Patients may withdraw their consent at any time during the course of the study. A copy of the informed consent will be given to the patient for their records. The rights and welfare of the patients will be protected and the quality of their medical care will not be adversely affected should they decline to participate in the study.

Each co-investigator participating in the study will receive a model informed consent form for participation. Each co-investigator will place the information from the model informed consent into their institution template.

Participants' confidentiality

Patient confidentiality is strictly held in trust by the PI, co-investigators, and the research teams. This confidentiality is extended to cover laboratory tests and radiologic results, in addition to the clinical information relating to participants.

The study protocol, documentation, data and all other information generated through this study will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the principle investigator.

The research ethics board at each participating centre may review their centre study record for quality assessment any time they indicate. Patients will not be identified in any publication or presentation generated from this proposed study.

Appendix A: Electronic Databases Search Strategies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>

Search Strategy:

-
- 1 exp anticoagulants/ (159197)
 - 2 (anticoagulant\$ or anticoagulat\$.tw. (49485)
 - 3 4-hydroxycoumarins/ or 4-hydroxycoumarin\$.tw. (856)
 - 4 acenocoumarol/ or (acenocoumarol or sintrom or sinthrome).tw. (1172)
 - 5 dicumarol/ or (dicoumarin or dicoumarol or dicumarol).tw. (2318)
 - 6 phenprocoumon/ or (phenprocoumon or marcumar or marcoumar or falithrom).tw. (988)
 - 7 Warfarin/ or (warfarin or coumadin).tw. (16410)
 - 8 or/1-7 (182054)
 - 9 Heart Valve Prosthesis/ or Heart Valve Prosthesis Implantation/ (30717)
 - 10 (valve\$ adj3 (prothes\$ or prosthetic or replacement\$ or mechanical or artificial)).tw. (25821)
 - 11 (mechanical heart adj2 (prothes\$ or prosthetic or replacement\$)).tw. (290)
 - 12 9 or 10 or 11 (38718)
 - 13 intracranial hemorrhages/ or cerebral hemorrhage/ or basal ganglia hemorrhage/ or putaminal hemorrhage/ or cerebral hemorrhage, traumatic/ (26396)
 - 14 intracranial hemorrhage, traumatic/ or brain hemorrhage, traumatic/ or brain stem hemorrhage, traumatic/ or cerebral hemorrhage, traumatic/ or hematoma, epidural, cranial/ or hematoma, subdural/ or hematoma, subdural, intracranial/ or subarachnoid hemorrhage, traumatic/ (8352)
 - 15 Subarachnoid Hemorrhage/ (13669)
 - 16 ((brain or intracranial or cerebral or cerebrum or cerebellum or intracerebral or subdural or subarachnoid or basal ganglia or putaminal) adj2 (hemorrhage\$ or haemorrhage\$ or hematoma\$ or haematoma\$ or bleed\$)).tw. (36338)
 - 17 or/13-16 (58633)
 - 18 8 and 12 and 17 (169)
 - 19 (201007\$ or 201008\$).ed. (154985) – limit to April 30, 2012
 - 20 18 not 19 (167)
 - 21 animals/ not humans/ (3432541)
 - 22 20 not 21 (167)

Database: EMBASE Classic+EMBASE <1947 to 2012 Week 20>

Search Strategy:

-
- 1 exp anticoagulant agent/ (396696)
 - 2 (anticoagulant\$ or anticoagulat\$.tw. (66887)
 - 3 4 hydroxycoumarin derivative/ or 4-hydroxycoumarin\$.tw. (729)
 - 4 acenocoumarol/ or (acenocoumarol or sintrom or sinthrome).tw. (3998)
 - 5 dicoumarol/ or (dicoumarin or dicoumarol or dicumarol).tw. (5183)
 - 6 phenprocoumon/ or (phenprocoumon or marcumar or marcoumar or falithrom).tw. (3891)
 - 7 warfarin/ or (warfarin or coumadin).tw. (46979)
 - 8 or/1-7 (415242)
 - 9 exp heart valve prosthesis/ or heart valve replacement/ or aorta valve replacement/ or mitral valve replacement/ (40374)
 - 10 (valve\$ adj3 (prothes\$ or prosthetic or replacement\$ or mechanical or artificial)).tw. (31598)
 - 11 (mechanical heart adj2 (prothes\$ or prosthetic or replacement\$)).tw. (324)
 - 12 9 or 10 or 11 (48024)

- 13 brain hemorrhage/ or basal ganglion hemorrhage/ or cerebellum hemorrhage/ or subarachnoid hemorrhage/ (62891)
- 14 subdural hematoma/ or epidural hematoma/ or cranial hematoma/ (13657)
- 15 ((brain or intracranial or cerebral or cerebrum or cerebellum or intracerebral or subdural or subarachnoid or basal ganglia or putaminal) adj2 (hemorrhage\$ or haemorrhage\$ or hematoma\$ or haematoma\$ or bleed\$)).tw. (48690)
- 16 or/13-15 (85036)
- 17 8 and 12 and 16 (355)
- 18 limit 17 to yr="1950 -Current" (355)
- 19 animals/ not humans/ (1237513)
- 20 18 not 19 (355)
- 21 ("201028" or "201029" or "201030").em. (92590) – limit to April 30, 2012
- 22 20 not 21 (350)

Database: Scopus

Search Strategy:

(TITLE-ABS-KEY(anticoagulant* OR anticoagulat* OR 4-hydroxycoumarin* OR acenocoumarol OR sintrom OR sinthrome OR dicumarol OR dicoumarin OR dicoumarol OR phenprocoumon OR marcumar OR marcumar OR falithrom OR warfarin OR coumadin))
 AND (TITLE-ABS-KEY(valve* prosthes* OR valve prosthetic OR valve* replacement* OR valve* mechanical OR valve* artificial OR mechanical heart OR heart valve*))
 AND (TITLE-ABS-KEY((hemorrhage* OR haemorrhage* OR hematoma* OR haematoma* OR bleed*)
 AND (intracranial OR cerebral OR basal ganglia OR putaminal OR brain OR cerebrum OR cerebellum OR intracerebral OR subdural OR subarachnoid)))

Database: CCTR, CDSR, DARE

EBM Reviews - Cochrane Central Register of Controlled Trials	2nd Quarter 2012
EBM Reviews - Cochrane Database of Systematic Reviews	2005 to April 2012
EBM Reviews - Database of Abstracts of Reviews of Effects	2nd Quarter 2012

Search Strategy:

- 1 exp anticoagulants/ (6316)
- 2 (anticoagulant\$ or anticoagulat\$).tw. (3275)
- 3 4-hydroxycoumarins/ or 4-hydroxycoumarin\$.tw. (20)
- 4 acenocoumarol/ or (acenocoumarol or sintrom or sinthrome).tw. (154)
- 5 dicumarol/ or (dicoumarin or dicoumarol or dicumarol).tw. (57)
- 6 phenprocoumon/ or (phenprocoumon or marcumar or marcumar or falithrom).tw. (151)
- 7 Warfarin/ or (warfarin or coumadin).tw. (1575)
- 8 or/1-7 (8563)
- 9 Heart Valve Prosthesis/ or Heart Valve Prosthesis Implantation/ (565)
- 10 (valve\$ adj3 (prosthes\$ or prosthetic or replacement\$ or mechanical or artificial)).tw. (817)
- 11 (mechanical heart adj2 (prosthes\$ or prosthetic or replacement\$)).tw. (35)
- 12 9 or 10 or 11 (987)
- 13 intracranial hemorrhages/ or cerebral hemorrhage/ or basal ganglia hemorrhage/ or putaminal hemorrhage/ or cerebral hemorrhage, traumatic/ (547)
- 14 intracranial hemorrhage, traumatic/ or brain hemorrhage, traumatic/ or brain stem hemorrhage, traumatic/ or cerebral hemorrhage, traumatic/ or hematoma, epidural, cranial/ or hematoma, subdural/ or hematoma, subdural, intracranial/ or subarachnoid hemorrhage, traumatic/ (34)

- 15 Subarachnoid Hemorrhage/ (280)
 16 ((brain or intracranial or cerebral or cerebrum or cerebellum or intracerebral or subdural or subarachnoid or basal ganglia or putaminal) adj2 (hemorrhage\$ or haemorrhage\$ or hematoma\$ or haematoma\$ or bleed\$)).tw. (2139)
 17 or/13-16 (2469)
 18 8 and 12 and 17 (13)

Database: Web of Science

Time span=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.

Search Strategy:

#21	#20 AND #10 AND #7
#20	#19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11
#19	TS=(putaminal hemorrhage* OR putaminal haemorrhage* OR putaminal hematoma* OR putaminal haematoma* OR putaminal bleed*)
#18	TS=(basal ganglia hemorrhage* OR basal ganglia haemorrhage* OR basal ganglia hematoma* OR basal ganglia haematoma* OR basal ganglia bleed*)
#17	TS=(subarachnoid hemorrhage* OR subarachnoid haemorrhage* OR subarachnoid hematoma* OR subarachnoid haematoma* OR subarachnoid bleed*)
#16	TS=(subdural hemorrhage* OR subdural haemorrhage* OR subudral hematoma* OR subdural haematoma* OR subdural bleed*)
#15	TS=(intracerebral hemorrhage* OR intracerebral haemorrhage* OR intracerebral hematoma* OR intracerebral haematoma* OR intracerebral bleed*)
#14	TS=(cerebrum hemorrhage* OR cerebrum haemorrhage* OR cerebrum hematoma* OR cerebum haematoma* OR cerebrum bleed*)
#13	TS=(cerebral hemorrhage* OR cerebral haemorrhage* OR cerebral hematoma* OR cerebral haematoma* OR cerebral bleed*)
#12	TS=(intracranial hemorrhage* OR intracranial haemorrhage* OR intracranial hematoma* OR intracranial haematoma* OR intracranial bleed*)
#11	TS=(brain hemorrhage* OR brain haemorrhage* OR brain hematoma* OR brain haematoma* OR brain bleed*)
#10	#9 OR #8
#9	TS=(mechanical heart prosthes* OR mechnical heart prosthetic OR mechanical heart replacement*)

#8	TS=(valve* prothes* OR prosthetic valve* OR valve replacement* OR replacement valve* OR mechanical valve* OR artificial valve*)
#7	#6 OR #5 OR #4 OR #3 OR #2 OR #1
#6	TS=(warfarin OR coumadin)
#5	TS=(phenprocoumon OR marcumar OR marcoumar OR falithrom)
#4	TS=(dicoumarin OR dicoumarol OR dicumarol)
#3	TS=(acenocoumarol OR sintrom OR sinthrome)
#2	TS=4-hydroxycoumarin*
#1	TS= (anticoagulant* OR anticoagulat*)

Database: Global Health

Search Strategy:

#	Query
S74	S12 and S20 and S73
S73	(S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72)
S72	(putaminal N2 bleed*)
S71	(basal ganglia N2 bleed*)
S70	(subarachnoid N2 bleed*)
S69	(subdural N2 bleed*)
S68	(intracerebral N2 bleed*)
S67	(cerebellum N2 bleed*)
S66	(cerebrum N2 bleed*)
S65	(cerebral N2 bleed*)

S64	(intracranial N2 bleed*)
S63	(brain N2 bleed*)
S62	(putaminal N2 haematoma*)
S61	(basal ganglia N2 haematoma*)
S60	(subarachnoid N2 haematoma*)
S59	(subdural N2 haematoma*)
S58	(intracerebral N2 haematoma*)
S57	(cerebellum N2 haematoma*)
S56	(cerebrum N2 haematoma*)
S55	(cerebral N2 haematoma*)
S54	(intracranial N2 haematoma*)
S53	(brain N2 haematoma*)
S52	(putaminal N2 hematoma*)
S51	(basal ganglia N2 hematoma*)
S50	(subarachnoid N2 hematoma*)
S49	(subdural N2 hematoma*)
S48	(intracerebral N2 hematoma*)
S47	(cerebellum N2 hematoma*)
S46	(cerebrum N2 hematoma*)
S45	(cerebral N2 hematoma*)
S44	(intracranial N2 hematoma*)
S43	(brain N2 hematoma*)
S42	(putaminal N2 hemorrhage*)
S41	(basal ganglia N2 hemorrhage*)
S40	(subarachnoid N2 hemorrhage*)
S39	(subdural N2 hemorrhage*)
S38	(intracerebral N2 hemorrhage*)

S37	(cerebellum N2 hemorrhage*)
S36	(cerebrum N2 hemorrhage*)
S35	(cerebral N2 hemorrhage*)
S34	(intracranial N2 hemorrhage*)
S33	(brain N2 hemorrhage*)
S32	(putaminal N2 haemorrhage*)
S31	(basal ganglia N2 haemorrhage*)
S30	(subarachnoid N2 haemorrhage*)
S29	(subdural N2 haemorrhage*)
S28	(intracerebral N2 haemorrhage*)
S27	(cerebellum N2 haemorrhage*)
S26	(cerebrum N2 haemorrhage*)
S25	(cerebral N2 haemorrhage*)
S24	(intracranial N2 haemorrhage*)
S23	(brain N2 haemorrhage*)
S22	haematoma
S21	haemorrhage
S20	(S13 or S14 or S15 or S16 or S17 or S18 or S19)
S19	mechanical heart
S18	(valve* N3 artificial)
S17	(valve* N3 mechanical)
S16	(valve* N3 replacement*)
S15	(valve* N3 prosthetic*)
S14	(valve* N3 prosthes*)
S13	heart valves and prostheses
S12	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
S11	coumadin

S10	warfarin
S9	(marcumar or marcoumar or falithrom)
S8	phenprocoumon
S7	(dicoumarin or dicoumarol or dicumarol)
S6	dicumarol
S5	(sintrom or sinthrome)
S4	acenocoumarol
S3	4-hydroxycoumarin*
S2	(anticoagulant* or anticoagulat*)
S1	anticoagulants

Database : LILACS

Search Strategy:

anticoagulant\$ or anticoagulat\$ or 4-hydroxycoumarin\$ or
acenocoumarol or sintrom or sinthrome or dicumarol or dicoumarin or
dicoumarol or dicumarol or phenprocoumon or marcumar or marcoumar or falithrom or warfarin or
coumadin [Words] and hemorrhage\$ or haemorrhage\$ or hematoma\$ or haematoma\$ or bleed\$
[Words] and valve\$ or prothes\$ or mechanical or artificial [Words]

Appendix B: Methodological Quality Rating Scale (MQRS)

	Points
Randomization to condition	4
Quality control of treatments	1
Outcome data from > 70% of participants at follow-up	2
Follow-up for at least 12 months after intake	2
Outcome data collected by in-person or telephone interview	1
Collaterals interviewed in >50% of cases	1
Self-report checked against objective information source	1
Treatment dropouts included in some outcome analysis	1
Case lost to follow-up reported and considered in outcome	1
Outcome data collected by personnel blind to treatment condition	1
Acceptable statistical analysis of group differences	1
Study findings replicated at multiple sites	1
Total	17

Appendix C: The Survey Questionnaire

Please check the box next to the most appropriate response

1- What is your specialty? Neurosurgery Haematology Other (specify)

2- What position do you currently hold?

3- How many years have you been in practice? 0-5 6-10 11-15 16-20 21-25 >25

4- What is your country of practice? USA Canada Other (Specify)

5- What type of practice do you have?

University hospital Hospital with university affiliation Community hospital Private

6- On average, how many cases of intracranial haemorrhage in patients with mechanical heart valve (MHV) do you see every year?

0-5 6-10 11-15 more than 15

7- Consider the following clinical scenarios:

A 50-year-old patient with mechanical heart valve (MHV) and taking an oral anticoagulant presented with **intracerebral haemorrhage**

	Would you correct his/her coagulopathy?	When would you restart his oral anticoagulant from the time of diagnosis?
1) If this patient requires a craniotomy (or surgical evacuation of the haematoma)	Yes/No	1) First 72 hours 2) 73 hours-120 hours (4-5 days) 3) 121 hours-168 hours (6-7 days) 4) 8 days -14 days 5) 15 days-21 days 6) 22-28 days 7) More than 28 days
2) If this patient has a small haematoma (less than 30 cm ³)	Yes/No	Time menu
3) If this patient has a large haematoma (more than 30 cm ³)	Yes/No	Time menu

4) If this patient has a history of atrial fibrillation with more than 2 risk factors (CHADS 2)	Yes/No	Time menu
5) If this patient has a history of atrial fibrillation with less than 2 risk factors (CHADS 0-1)	Yes/No	Time menu
6) If this patient has a history of deep vein thrombosis in the past month	Yes/No	Time menu
7) If this patient has a history of pulmonary embolism in the past month	Yes/No	Time menu
8) If this patient's age is less than 30 years	Yes/No	Time menu
9) If this patient's age is greater than 75 years	Yes/No	Time menu
10) If this patient has a caged ball valve	Yes/No	Time menu
11) If the MHV is a mitral valve	Yes/No	Time menu
12) If the MHV is an aortic valve	Yes/No	Time menu
13) If this patient has multiple heart valves	Yes/No	Time menu
14) If the patient has none of the above factors, how would you manage the patient?	Yes/No	Time menu

B: A 50-year-old patient with MHV and taking an oral anticoagulant presented with **subdural haemorrhage**?

	Would you correct his/her coagulopathy?	When would you restart his oral anticoagulant from the time of diagnosis?
1) If this patient requires a craniotomy (or surgical evacuation of the haematoma)	Yes/No	1) First 72 hours 2) 73 hours-120 hours (4-5 days) 3) 121 hours -168 hours (6-7 days) 4) 8 days -14 days 5) 15 days -21 days 6) 22 – 28 days 7) More than 28 days

2) If this patient has a small haematoma (less than 30 cm ³)	Yes/No	Time menu
3) If the patient has a large hematoma (more than 30 cm ³)	Yes/No	Time menu
4) If this patient has a history of atrial fibrillation with more than 2 risk factors (CHADS 2)	Yes/No	Time menu
5) If this patient has a history of atrial fibrillation with less than 2 risk factors (CHADS 0-1)	Yes/No	Time menu
6) If this patient has a history of deep vein thrombosis in the past month	Yes/No	Time menu
7) If this patient has a history of pulmonary embolism in the past month	Yes/No	Time menu
8) If this patient's age is less than 30 years	Yes/No	Time menu
9) If this patient's age is greater than 75 years	Yes/No	Time menu
10) If this patient has a caged ball valve	Yes/No	Time menu
11) If the MHV is a mitral valve	Yes/No	Time menu
12) If the MHV is an aortic valve	Yes/No	Time menu
13) If this patient has multiple heart valves	Yes/No	Time menu
14) If the patient has none of the above factors, how would you manage the patient?	Yes/No	Time menu

8 – Would you be interested in having your patients participate in a randomized control trial aiming to address these clinical questions?

Yes/No Email

9 – Would you be interested in having your patients participate in a cohort study aiming to address these clinical questions?

Yes/No Email

10 – Would you like to be notified by email of the results of this study?

Yes/No Email

Appendix D: Invitation e-mail

E-mail subject: Dr. Phil Wells & Dr. Fahad Alkherayf ask your help with a short survey.

Dear Colleague:

We are a research group of neurosurgeons and thrombosis haematologists at the University of Ottawa, Ottawa Hospital. Dr Phil Wells is the thrombosis lead and I, Dr. Alkherayf (neurosurgery research fellow), the neurosurgery lead. The study has been approved by the Ottawa Hospital Research Ethics Board. As a neurosurgeon or thrombosis expert we value your opinion and ask that you please complete our short survey (takes less than 10 minutes) evaluating management of anticoagulation and associated intracerebral haemorrhage & acute subdural haematoma. We ask that, if you are not a clinician please open the survey and as such on the first question, then the survey will be done for you.

Managing patients with mechanical heart valves (MHV) who present with intracranial haemorrhage is challenging, especially the decision on when to restart oral anticoagulation and whether anticoagulation should be reversed at the time of the haemorrhagic presentation. Current literature and guidelines are limited in this regard. The aim of this survey is to identify the current practice of neurosurgeons and thrombosis experts with respect to these issues of reversal and restarting anticoagulation.

Your participation is very important as it will be helpful in filling a gap in the current literature. Because we know that your time is valuable, the survey has been designed to be simple and short with close-ended questions. Clinical scenarios contribute to the interest of the survey experience.

Participation is voluntary. Study information will be kept in a secure location at the University of Ottawa. The results of the study may be published or presented at professional meetings, but your identity will remain confidential. All research related study records will be kept for 15 years after termination of the study.

In the next three days you will receive a personalized e-mail containing a link to our survey.

With kind regards,

Appendix E: Case Report Form

Centre ID	Patient ID	Patient initials

Patient Eligibility Assessment

Inclusion criteria

	YES	NO
➤ Adult age group (>18 years)	<input type="radio"/>	<input type="radio"/>
➤ MHV patient receiving oral anticoagulant who present with intracranial haemorrhage.	<input type="radio"/>	<input type="radio"/>
➤ Intracranial haemorrhage is clinically diagnosed and confirmed radiologically (by CT or MRI) within the last four days .	<input type="radio"/>	<input type="radio"/>
➤ Patient`s OAC will be started in 5 to 9 days from the initial ICH.	<input type="radio"/>	<input type="radio"/>
➤ The patient or the proxy is able to provide signed and dated informed consent form.	<input type="radio"/>	<input type="radio"/>
➤ The patient or caregiver is willing and able to comply with all study procedures and be available for the duration of the study.	<input type="radio"/>	<input type="radio"/>

If yes to **all** of the inclusion criteria, the patient is eligible to participate in the study

Exclusion criteria

➤ Pregnancy.	<input type="radio"/>	<input type="radio"/>
➤ Patient who is not permanently living within the province or the state.	<input type="radio"/>	<input type="radio"/>

If yes to **any** of the exclusion criteria, the patient is ineligible for participation in this study.

Centre ID	Patient ID	Patient initials

Participant`s demographic data

Hospital medical record number

--	--	--	--	--	--	--	--	--	--

Date of birth and age

DOB	Age

Gender

Male (1)	
Female (2)	

Centre ID	Patient ID	Patient initials

Contact information

Address

Street:

House/ apartment number:

House number suffix:

Postal code:

City:

Province:

Phone number:

Email:

Second person contact information

Address

Street:

House/ apartment number:

House number suffix:

Postal code:

City:

Province:

Phone number:

Email

Centre ID	Patient ID	Patient initials

Baseline medical assessment

CHADS2 scoring

Condition	points
Congestive heart failure	1
Hypertension	1
Age >= 75 years	1
Diabetes mellitus	1
Prior stroke or TIA	2

Patients CHADS2 scoring

0-1 (1)	
≥2 (2)	

History of PE in the last month

Yes (1)	
No(2)	

History of DVT in the last month

Yes (1)	
No(2)	

Centre ID	Patient ID	Patient initials

Patient currently taking an antiplatelet agent

Yes (1)	
No(2)	

MHV location

Aortic (1)	
Mitral (2)	
Tricuspid (3)	

MHV type

Caged-ball (1)	
Tilting-disk (2)	
Bileaflet (3)	

MHV number

Single (1)	
Multiple (2)	

Centre ID	Patient ID	Patient initials

Date of diagnosis of the initial ICH

/ /

INR level at diagnosis

--

Type of ICH

Intracerebral (1)	
SDH (2)	
Others (3)	

Haematoma size

$\leq 30 \text{ cm}^3$ (1)	
$> 30 \text{ cm}^3$ (2)	

Centre ID	Patient ID	Patient initials

Was patient's coagulopathy corrected? Medication

Yes (1)	
No (2)	

If yes what medications were used to correct the coagulopathy

--

Type of OAC

--

Centre ID	Patient ID	Patient initials

Follow up visits reporting

(Daily visit and follow up sheet)

DAY:

Did patient have cranial surgical intervention?

Yes (1)	
No (2)	

If yes, when

/ /

Was the patient restarted on his/her OAC? When target INR type of

Yes (1)	
No (2)	

If yes,
When?

/ /

Number of days from the initial ICH

--

Target INR

--

Type of OAC

--

Centre ID	Patient ID	Patient initials

Any current heparin therapy?

Therapeutic IV UFH		If yes, start date & dose / /
Yes (1)		
No (2)		
Prophylactic UFH		If yes, start date & dose / /
Yes (1)		
No (2)		
Therapeutic LMWH		If yes, start date & dose / /
Yes (1)		
No (2)		
Prophylactic LMWH		If yes, start date & dose / /
Yes (1)		
No (2)		

Any current antiplatelet therapy?

Yes (1)	
No (2)	

If yes, date of antiplatelet therapy

/ /

Centre ID	Patient ID	Patient initials

Recurrence of ICH

Does patient have clinical suspicion of ICH recurrence?

Clinical suspicion

- Raised ICP (Sever headache, nausea, vomiting, .. etc)
- New confusion or worsening of patient confusion
- Decrease level of consciousness
- New cranial nerve finding
- Speech change
- Visual changes (decrease vision, double vision, nystagmus, ..etc)
- New or worsening weakness
- New or worsening of seizure
- Other clinical features make the treating physician suspicious of recurrent ICH

Yes (1)	<u>If yes please go to outcome event form</u>
No (2)	

Valve(s) thrombosis

Does patient have clinical suspicion of valve thrombosis

Clinical suspicion

- New or worsening dyspnea
- New or worsening orthopnea
- New or worsening congestive heart failure
- Symptoms of TIA
- Chest pain
- Loss of MHV sound
- Other clinical features make the treating physician suspicious of valve thrombosis

Yes (1)	<u>If yes please go to outcome event form</u>
No (2)	

Centre ID	Patient ID	Patient initials

Pulmonary embolism (PE)

Does patient have clinical suspicion of PE

Clinical suspension

- Tachypnea
- Tachycardia
- haemoptysis
- Chest pain on inspiration
- Low O2 saturation
- Pleural effusion
- Other clinical features make the treating physician suspicious of PE

Yes (1)	<u>If yes please go to outcome event form</u>
No (2)	

Deep venous thrombosis (DVT)

Does patient have clinical suspicion of DVT

Clinical suspension

- Unilateral limb pain
- Unilateral leg swelling
- Calf tenderness
- Limb discoloration, redness or heat
- Other clinical features make the treating physician suspicious of DVT

Yes (1)	<u>If yes please go to outcome event form</u>
No (2)	

Centre ID	Patient ID	Patient initials

Embolic stroke

Does patient have clinical suspicion of embolic stroke

Clinical suspension

- Sudden numbness, weakness of the face, arm or leg
- New confusion or worsening of patient confusion
- Acute new cranial nerve finding
- Sudden Speech change
- Sudden Visual changes (decrease vision, double vision, nystagmus, ..etc)
- Sudden trouble walking, dizziness or loss of balance
- New or worsening of seizure
- Other clinical features make the treating physician suspicious of ischemic stroke

Yes (1)	<u>If yes please go to outcome event form</u>
No (2)	

Centre ID	Patient ID	Patient initials

Outcome report form

Recurrent ICH

To report recurrence of ICH, CT or MRI must be done to confirm the diagnosis.

Please complete if CT/MRI is done and confirmed recurrence of ICH

CT or MRI date

/ /

Number of days from the initial ICH

--

INR level during recurrence of ICH

--

Type of recurrent ICH

Intracerebral (1)	
SDH (2)	
Others (3)	

Attach copy of the official radiologic report and clinical documentation report

Centre ID	Patient ID	Patient initials

Outcome report form

Valve(s) thrombosis

To report Valve thrombosis, TTE or TEE must be done to confirm the diagnosis.

Please complete if TTE/TEE is done and confirmed valve thrombosis

TTE or TEE date

Number of days from the initial ICH

Attach copy of the official radiologic report and clinical documentation report

Centre ID	Patient ID	Patient initials

Outcome report form

Pulmonary embolism (PE)

To report PE, thoracic CT or VQ scan must be done to confirm the diagnosis.

Please complete if thoracic CT or VQ scan is done and confirmed PE

Thoracic CT or VQ scan date

Number of days from the initial ICH

Attach copy of the official radiologic report and clinical documentation report

Centre ID	Patient ID	Patient initials

Outcome report form

Deep venous thrombosis (DVT)

To report DVT, Doppler ultrasound must be done to confirm the diagnosis.

Please complete if Doppler ultrasound is done and confirmed DVT

Doppler ultrasound date

Number of days from the initial ICH

Attach copy of the official radiologic report and clinical documentation report

Centre ID	Patient ID	Patient initials

Outcome report form

Embolic stroke

To report embolic stroke, CT/MRI must be done to confirm the diagnosis.

Please complete this if CT/MRI is done and confirmed ischemic stroke

CT or MRI date

Number of days from the initial ICH

Attach copy of the official radiologic report and clinical documentation report

Appendix F: Information sheet and consent form

Evaluating the risks and benefits of restarting oral anticoagulant in 5 to 9 days after intracranial haemorrhage in patients with mechanical heart valve(s); a multi centre cohort study

Introduction

You are being asked to participate in this study because your treating physician believes that it is required to restart your oral anticoagulant (blood thinners) between 5 and 9 days from the day of your intracranial bleed. Your doctor made this decision to restart your blood thinners at this time range based on his/her medical knowledge and because he/she believes this is the best time for your overall health.

Please read this information sheet and consent form carefully and ask as many questions as you like before deciding whether to participate in this research study. You can discuss this decision with your family, friends, and your health-care team.

Background of the study

There is evidence to suggest that patients with mechanical heart valve(s) and intracranial bleed, like yourself, should be restarted on your blood thinners once your blood clotting ability has been normalized. This is to minimize your risk of developing complications such as valve thrombosis (clots around your heart valve), development of lung clots, clots in deep veins, and stroke. However, there is risk of having another intracranial bleed if your blood thinners are started at an inappropriate time. The ideal time of restarting the blood thinners to balance the abovementioned risks is not well known.

Most of the time this decision is based on your doctor's experience and knowledge. Your doctor believes that your oral anticoagulants (blood thinners) should be restarted within 5 to 9 days from the diagnosis of your intracranial bleed.

The aim of this study is to monitor your risks of developing any of the following possible complications related to restarting your oral anticoagulant: Having another intracranial bleed, development of valve thrombosis (clot on your heart valve),

pulmonary embolism (blood clot in your lung), deep venous thrombosis (a blood clot in a deep vein), and stroke.

Purpose and design

If you agree to participate in this study you will receive your oral anticoagulant as recommended by your doctor. At the same time you will be monitored on a daily basis for the previously mentioned risks until you are discharged from the hospital. Also, additional followups will be scheduled at 1, 3 and 6 months from the day of your diagnosis.

Study procedures

During your hospital stay you will receive treatment as recommended by your doctor. In addition to that your treating team and a research nurse, who is dedicated for this study, will record your daily clinical evaluation, the exact day when your doctor restarts you on your oral anticoagulant, and any laboratory and radiologic reports that are related to the study. Development of any of the previously mentioned complications will also be reported and you will be treated by your doctor without any intervention from the research team.

Once you are discharged from the hospital, followups will be arranged in coordination with your doctor usually at one, three and six months from the initial bleed. During your followup visits your doctor will examine you for the same possible complications. This will be recorded in addition to any laboratory or diagnostic test results related to the study.

Length of the study

This study is expected to continue for approximately 5 years, but your participation will end after 6 months from your initial bleed.

Possible side effects and /or risks

Our study is observatory only; we record the course of your care without intervening with your doctor's treatment. For this study we request that your doctor perform some laboratory and radiologic tests to confirm possible complications if they are suspected. These tests are recommended and would usually be requested by your doctor regardless of the study. It is therefore extremely unlikely that you will experience any harm or side effect by participating in this study.

Benefits from the study

Although you may not receive any personal benefit from participation in this study, participation in this study may raise the awareness of your doctor and this may reflect in better care. Additionally, this study will provide some standardization on your treatment, which may also help to provide better health care for you. You may also feel satisfied by knowing that you are contributing to research that may help improve care for patients such as yourself in the future.

Withdrawal from the study

You have the right to withdraw from the study at any time without any impact to your current and future care at Hospital. However, if at any time you decide to withdraw, we request you discuss this with the study doctor or nurse before you stop the study. Please remember though that if you withdraw from the study you should still continue with your treatment and followups as recommended by your treating doctor. This is important for your safety and well-being.

In some cases your study participation could be discontinued by your study doctor without your consent, at any time for any of the following reasons:

- Your treating doctor feels it is in your best interest.
- The hospital authority such as the ethics board committee or cancels the study.

- You need additional medication that would interfere with the study.

You may cancel this consent at any time. If you withdraw your consent, the study doctor will no longer use and disclose your personal health information under the consent for this study, unless the study doctor needs to use and disclose some of your personal health information to preserve the scientific integrity.

Compensation

In the event of a research-related injury or illness, you will be provided with appropriate medical treatment/care. You are not waiving your legal right by agreeing to participate in this study. The study doctor and the hospital still have their legal and professional responsibilities.

Confidentiality

All personal health information will be kept confidential, unless release is required by law. Representatives of government regulators such as Health Canada, or....., representatives of the Hospital Research Ethics Board may review your original medical records under the supervision of Dr or his/her research staff for audit purposes.

You will not be identifiable in any publications or presentations resulting from this study. All the information which leaves the Hospital will be coded with an independent study number.

The link between your name and this independent study number will only be accessible by Dr..... and his/her research staff. The link and study files will be stored separately and securely. Both files will be kept for a period of ... years after the study has been completed. All paper records will be stored in a locked file and/or office. All electronic records will be stored on the hospital's server and protected by a user password, again only accessible by Dr and his/her research staff. At the end of the

retention period all paper records will be disposed of in confidential waste or shredded, and all electronic records will be deleted.

Voluntary participation

Your participation in this study is voluntary. If you choose not to participate or withdraw from the study in the future, your decision will not affect the care you receive at this institution at this time or in the future. You will not have any penalty or loss of benefits to which you are otherwise entitled.

New information about the study

You will be told of any new findings during the study that may affect your willingness to continue to participate in this study. You may be asked to sign a new consent form.

Questions about the study

If you have any questions about this study, you can contact Dr..... or

(contact information including address, phone number, email and website if available)

The Research Ethics Board has reviewed this study protocol. The considers the ethical aspects of all research involving human subjects at the ... Hospital. If you have any questions about your rights as a research subject, you may contact the chairperson of Research Ethic Board.

(contact information including address, phone number, email and website if available)

Consent Form

Timing of restarting oral anticoagulant in patients with mechanical heart valve and intracranial haemorrhage; a multi centre cohort study

I have read the 6 pages of the Patients Information Sheet and the Consent Form (or have had them read to me), and have had an opportunity to ask my doctor, the research doctor, or the research assistant/nurse any questions I had about this study.

My questions and/or concerns have been answered to my satisfaction and I agree to participate in this study. If I decide at a later stage in the study that I would like to withdraw my consent, I may do so at any time.

A copy of the Information Sheet and/or Consent Form will be provided to me should I want to review the information at a later date, if I need to contact someone about the study or my participation in the study, or simply for my records.

Signatures

Participant's name and signature

Date

Doctor's name and signature

Date

List of References

1. Butany J, Ahluwalia MS, Munroe C, et al. Mechanical heart valve prostheses: Identification and evaluation. *Cardiovascular Pathology*. 2003;12:1-22.
2. Schoen FJ. Future directions in tissue heart valves: Impact of recent insights from biology and pathology. *J Heart Valve Dis*. 1999;8:350-358.
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