

Management of Therapeutic Anticoagulation in Perioperative Period and Post Cerebral Haemorrhage: Which the Best Strategies?

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Abstract

Case Report

Anticoagulation is essential for patients with mechanical heart valves; however, its management in peri operative period could be a dilemma. Frequently, bridging therapy is applied in this situation to prevent thromboembolic events. The risk and benefit of this strategy is not completely clarified. Furthermore, it become more complex if haemorrhagic complication was associated especially intracerebral localization. In lacking of data supporting a specific treatment strategy, The management of these patients often poses a significant challenge to balance between providing increasing bleeding events and providing ischemic complication. We report a case report of using bridging therapy in patient with mechanical valve in periprocedural cardiac resynchronization surgery complicated by hemorrhagic cerebral hematoma, through which we will discuss the therapeutic modalities of this patients in the light of studies and consensus of learned societies.

Keywords: Bridging therapy, oral anticoagulant, intracerebral haemorrhage, mechanical valve.

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INTRODUCTION

Periprocedural management of oral anticoagulant agents represents a common dilemma in daily medical practice and requires balancing of thromboembolic risk against bleeding risk. In interventional cardiology, the patients referred for cardiac implantable electrophysiological device (CIED) insertion and treated with oral anticoagulant agents poses a particular challenge because of their frequently overlapping elevated risks for bleeding and ischemic events. For patients at high risk for thromboembolic events, like mechanical valve; Low molecular weight heparin (LMWH) is frequently applied as bridging therapy during perioperative interruption of anticoagulation. There have been few results from clinical trials to support the safety and efficacy of this approach.

However, it becomes more complex when hemorrhagic events occur. Intracerebral Hemorrhage (ICH) following cardiac resynchronization therapy (CRT), as one type of these bleeding events. That poses a therapeutic dilemma on the appropriate use of anticoagulants to maintain mechanical valve free of

thrombosis meanwhile stabilizing hematoma volume to control bleeding events.

This report illustrates an example of all these difficult situations: intracerebral hematoma secondary bridging anticoagulation and highlights the difficult balance of providing periprocedural thrombosis protection in patients with valve prosthesis while avoiding bleeding events.

CASE PRESENTATION

A 57-year-old man, having diabetes as a cardiovascular risk factor. Her medical history indicated an aortic mechanical valve replacement and mitral valve plasty following severe aortic regurgitation associated with important left ventricular dilatation, His regular medication included Vitamin K antagonist (VKA) 4 mg once daily. presented to the emergency department with a subacute history of dyspnea grade III NYHA and episode syncope without trauma; On physical examination, the patient was alert with a Glasgow Coma Scale of 15/15; Cardiovascular and chest examinations were unremarkable; a brain CT scan is performed without abnormalities: Laboratory investigations revealed normal full blood count and

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biochemistry, the international normalized ratio (INR) was 3. After cardiac investigations; a CRT was indicated in front of the presence on the Electrocardiogram a BBG with in transthoracic echocardiography dilated cardiomyopathy in severe dysfunction and who had already received 3 months of medical treatment maximum tolerated; Surgery for resynchronization was performed with interrupting anti VKA and bridging therapy with heparin 3days preprocedural. The patient was started on, anti VKA in addition to the therapeutic low-molecular weight heparin started postoperatively, until the INR returned to therapeutic range. Five days after, the patient presented generalized headache; the INR was 2,6. An urgent Head Computed Tomography (CT) was organized which revealed an acute fronto parieto temporal right subdural hematoma (SDH) measuring 12mm exerting a mass effect on the lateral ventricle

with discrete subfalcine herniation (5.5mm). Based upon these findings, the case was discussed with neurosurgical team who advised to stop anti VKA and control in 48 hours. The patient was subsequently started on therapeutic low-molecular weight heparin (1.5 mg/kg divided over two-doses/24 h). A repeat head CT was done after two days, which revealed worsening of the SDH becoming 16X12mm and worsening of Subfalcine Herniation (10mm) and appearance of a left fronto parieto temporal SDH of 4mm. A surgical evacuation of hematoma using craniotomy with bone flap was performed. The heparin therapy was continued throughout the perioperative period. In post operatively, the patient present a neurological and respiratory deteriorations requiring mechanical ventilation with positive inotropic supports without improvement leading to death after 3 days post-op.

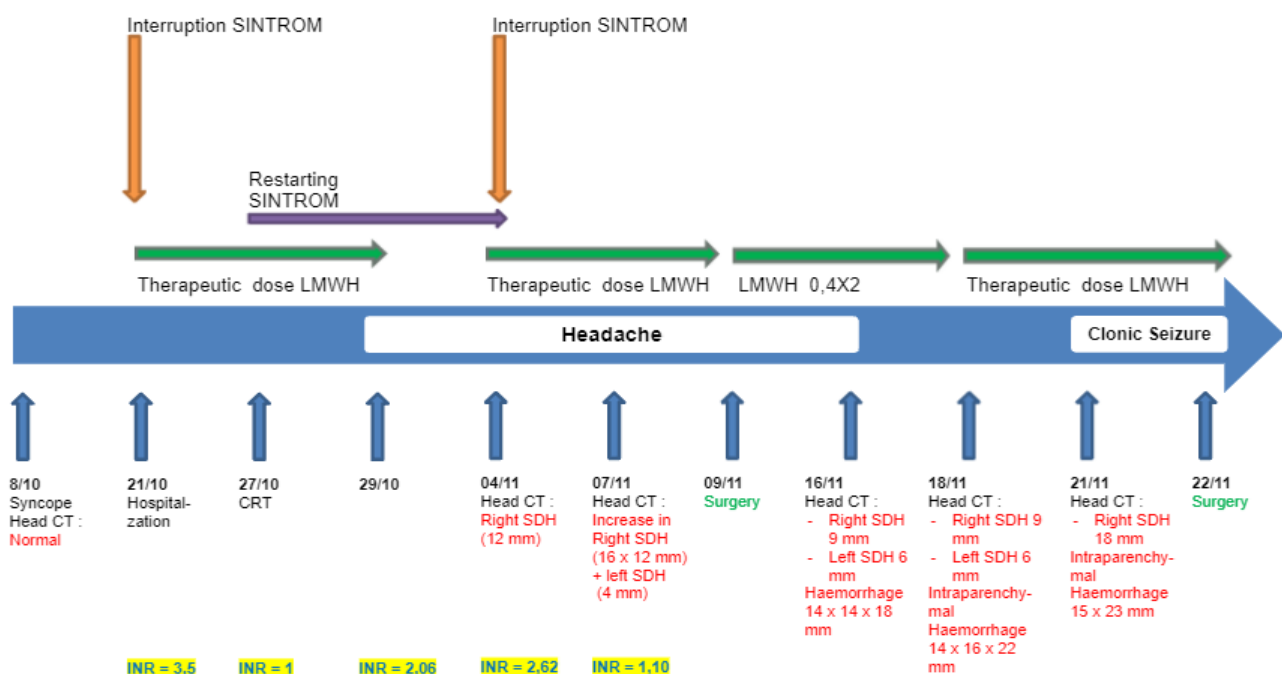


Figure 1: Time course of VKA treatment, Heparin bridging, radiology, coagulation/fibrinolysis tests, and head CT's finding in our patient; INR, international normalized ratio; CT: computer tomography; CRT: cardiac resynchronization therapy; SDH: sundural hematoma

SCOPE OF THE PROBLEM

The problems that arise in our patient is:

Initially, was it necessary to use bridging therapy in this patient?

The management of the VKA and intracranial hemorrhage: Should we stop oral anticoagulants treatment when the risk of thromboembolism is there and when should we restart oral anticoagulation therapy?

DISCUSSION

Bridging therapy or not in perioperative procedures: Old Dilemma

An Increasing number of patients use oral anticoagulants for the prevention of arterial thromboembolic events, and one tenth of them require temporary interruption in preparation for an elective procedure or surgery. To reduce the bleeding risk for patients undergoing invasive procedures, oral anticoagulant is typically interrupted prior to the procedure, and then continued when hemostasis is achieved postprocedurally. Because the interruption of anticoagulation may expose patients to the risk of thromboembolism, heparin bridging (unfractionated

heparin [UFH] or low-molecular-weight heparin [LMWH]) is administered to minimize the period of inadequate level of anticoagulation [1, 2]. This bridging therapy is widely used in perioperative period. However, this safety and efficacy is not completely clarified for patients who need an anticoagulation interruption before invasive procedures. Two main concerns remain unsolved, the risk of thromboembolism, and the risk of bleeding [3].

There have been many published articles related to bridging anticoagulation, but the quality of evidence with best practices is uneven across studies [4, 5]. Current guidelines from the 2019 American College of Cardiology/American Heart Association suggest bridging anticoagulation used in patients with a high thrombosis risk, such as certain mechanical valve prostheses or recent pulmonary embolism during interruption of vitamin K antagonist (VKA) therapy [3]. However, these recommendations are primarily based on observational studies and experts' opinions. Indeed, In 2021 ESC/EACTS Guidelines for the management of valvular heart disease; Bridging of VKAs, when interruption is needed, is recommended in particular patients like mechanical valve. It is recommended that VKAs are timely discontinued prior to elective surgery to aim for an INR <1.5 [6]. However, the question of patients needing OAC interruption remained unresolved. This is why, a review of the various experiences and studies is necessary to specify these patients who need interruption and the safety of the therapy bridging.

A large trial of the BRUISE CONTROL, randomized 681 patients with an annual risk of thromboembolic events of 5% or more from 17 centers. 203 patients had a prosthetic valve. They evaluated the safety of performing pacemaker or ICD surgery without interruption of warfarin therapy in patients requiring oral anticoagulation therapy. They found that this strategy is associated with a significantly lower rate of device-pocket hematoma, as compared with bridging therapy with heparin (3.5% vs. 16.0%). They also found that continued warfarin therapy, with a median INR of 2.3 (interquartile range, 2.0 to 2.6), was not associated with any major perioperative bleeding events and was associated with greater patient satisfaction. These results suggest that continuation of warfarin during pacemaker or ICD surgery may be preferable to bridging therapy with heparin, at least for patients like those enrolled in this trial [7].

For the same reason; Siegal *et al* recently conducted a meta-analysis including more than 12,000 patients in 34 studies, with only one randomized trial. The types of invasive or surgical procedures varied among studies. Twelve studies included cardiac device implantation. Indications for anticoagulation of bridged patients were reported in 30 studies as mechanical heart valve (24%). The comparison groups in these studies

included mostly patients in whom oral anticoagulation therapy was discontinued without bridging, with smaller numbers of patients in whom oral anticoagulation therapy was continued during surgery. The authors concluded that bridging with heparin leads to a risk of overall bleeding that is 5 times as high, and a risk of major bleeding that is 3.6 times as high, as the respective risks associated with no bridging therapy. The risk of thromboembolic events did not differ significantly between the two treatment strategies [8]. Although Siegal and colleagues concluded that bridging anticoagulation increases bleeding risk and produces similar thromboembolic risk, their review included only one underpowered randomized trial together with some observational studies with no control arm to assess the safety and efficacy of bridging therapy

To better clarify the risk and benefit of bridging therapy, in 2020, KUO ET AL conducted a meta-analysis. Eighteen studies were included (N = 23 364). They comparing interrupted anticoagulation with or without bridging and continuous oral anticoagulation in patients at moderate-to-high thromboembolic risk before invasive procedures. Bridging anticoagulation was associated with increased bleeding risk compared to non-bridging [9]. Once again, these results do not support routine use of bridging during anticoagulation interruption.

In the same way, in 2021 the protocol of the WICH study is published to compare Continuous warfarin administration versus heparin bridging therapy in post colorectal polypectomy haemorrhage. The results of this randomised controlled trial will provide valuable information for the standardisation of management of anticoagulants in patients scheduled to undergo colorectal polypectomy [10].

Then, non-bridging management seems to have a favorable risk-benefit profile in terms of thromboembolic and bleeding complications. There are some explanations for the bleeding risk of bridging anticoagulation. First, heparin-induced thrombocytopenia may contribute to postoperative bleeding [11]. Second, due to the interindividual variability in the sensitivity of aPTT test (the most common laboratory measurement to monitor UFH), control of aPTT range may not correlate well with the activity of bridging anticoagulation [11]. another explanation, especially for resynchronization therapy like our patient ; that has been proposed for lower rate of device pocket hematoma in continued warfarin is the concept of an “anticoagulant stress test [12]. That is, if patients undergo surgery while receiving full-dose anticoagulation therapy, any excessive bleeding will be detectable and appropriately managed while the wound is still open. In contrast, if bridging therapy with heparin is used, such bleeding maybe apparent only when full-dose anticoagulation therapy is resumed postoperatively. With systematic reviews and meta-

analysis overall favoring a strategy of maintenance of VKA therapy for CIED insertion, uninterrupted VKA use became the standard approach [7, 13].

Therefore, Noah's team summarized from vertical studies, the standard approach to managing warfarin-treated patients in need of elective surgery, as

shown in the figure. The authors can establish an algorithm where they could define ICD insertion like a minor surgery (Figure) [14]. That's why, recently 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy conclude that Heparin bridging of anticoagulated patients is not recommended [15].

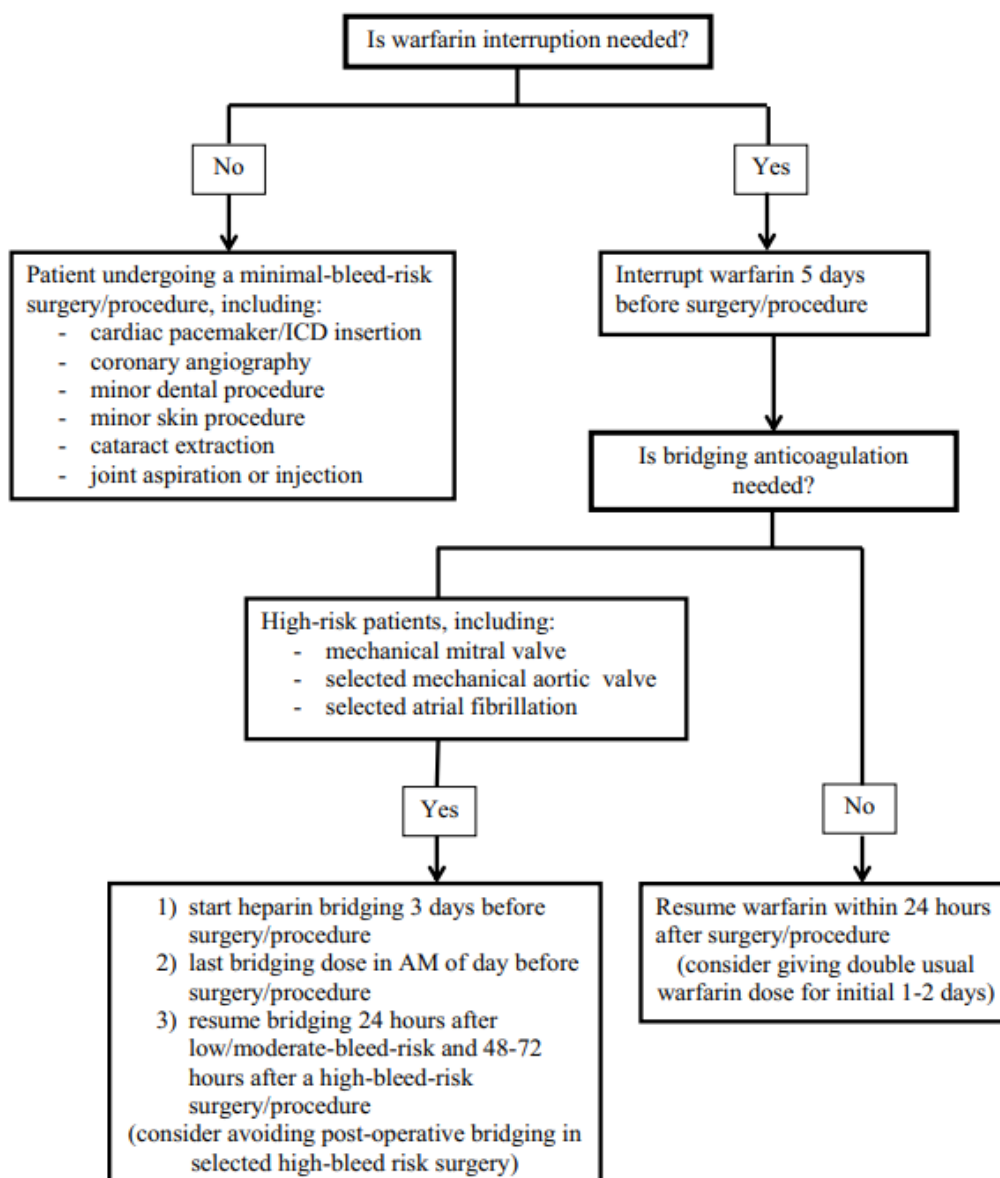


Figure 2: Perioperative Management of Patients on Warfarin [14]

Time of restarting oral ATC after intracerebral haemorrhage

Intracerebral haemorrhage is the fatal complication associated with anticoagulation, with an estimated 6-month mortality of 67% [16]. In this case, The management of oral anticoagulants with mechanical heart valves pose great difficulties because of significant thromboembolic and valve dysfunction risk. The decision on when to appropriately restart anticoagulation needs to be balanced with the risk of precipitating further cerebral haemorrhage.

International guidelines state that early resumption of anticoagulation may be necessary [17, 18]. Even so, there is no guidelines when to start appropriately oral anticoagulation post intracerebral haemorrhage. Management in such situations is usually based to individual case- scenarios.

A systematic review of the literature published in 2009 by Romualdi *et al.*, concluded that stopping anticoagulant therapy for few days (even for 7–14 days)

after cerebral haemorrhage and restarting oral anticoagulant therapy a few days after are safe [16].

However, a recent consensus statement by the European Society of Cardiology Working Group on Thrombosis suggested that anticoagulation with heparin may be safely restarted 3 days after ICH and that vitamin-K antagonists (VKAs) may be initiated at Day 7 without any major concerns for bleeding complications.¹³ However, this conclusion was based on a meta-analysis of small observational studies, the largest including on 52 MHV-patients of which 22 died [20, 21].

In international multicentre study pooled individual data of patients with OAC-associated ICH

and MHV to investigate both anticoagulation reversal and anticoagulation-resumption by providing incidences of haemorrhagic vs. thromboembolic complications among patients with and without restarted therapeutic anticoagulation (TA). the main objective of the study was to determinate an optimal time-window for restarting TA in MHV-patients with acute ICH using time-dependent safety and risk-benefit analyses the results were as follows: restarting TA within 2 weeks after ICH in patients with MHV was associated with increased haemorrhagic complications. Optimal weighing—between least risks for thromboembolic and haemorrhagic complications—provided an earliest starting point of TA at Day 6, reserved only for patients at high thromboembolic risk (Figure 3) [22].

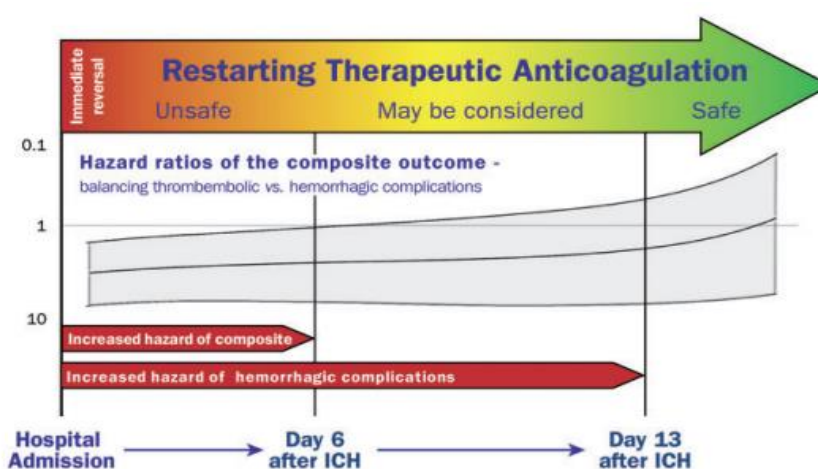


Figure 3: In-hospital management of therapeutic anticoagulation in patients with ICH and MHV – from reversal until restarting therapy [22]

Ultimately, all these studies contend against aggressive early anticoagulation and it seems acceptable to with hold that treatment in the acute phase of ICH in order to avoid severe bleeding complications outcome. The optimal time to restart anticoagulation should be discussed in relation to location of the bleeding event and interventions performed to stop bleeding and/or to treat an underlying cause. Furthermore, the early involvement of multispecialist input is recommended (specifically cardiology, hematology and neurosurgery) for similar cases to formulate efficient and appropriate management decisions, which will contribute towards successful patient.

CONCLUSION

Although thromboembolism may cause severe morbidity and mortality, it should be weighed against the bleeding risk of bridging anticoagulation. The clinicians should carefully consider the practice of routine bridging. Our case report is an impressive example of this strategy wrongfully applied causing a fatal bleeding complication. Incorporation of all the patient-related, procedural, and pharmacologic factors and good clinical judgment are required to select the

appropriate patients for an uninterrupted OAC strategy. Indeed, the decision to continue periprocedural VKA agents for CIED insertion is actually recommended.

At present, in patients with mechanical valve, there are no established guidelines regarding the optimal time to restart anticoagulation after acute intracerebral haemorrhage. Management of these patients necessitates a multidisciplinary approach in specialist centers.

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