Bridging

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Case Vignette

A 77-year-old female is scheduled for urgent coronary artery bypass graft surgery (CABG) due to an acute coronary syndrome caused by a multi-vessel disease involving all coronary arteries. Apart from this, a recent stroke (3 months before hospitalization) due to a non-valvular atrial fibrillation, a non-insulin dependent diabetes, hyperlipidemia, arterial hypertension, a moderate renal insufficiency with a creatinine between 1.5 and 2 mg/dL (i.e., 133 and 177 μmol/L), and an obesity with a body mass index of 37 kg/m^2 is known.

The patient is on warfarin with an INR of 2.3 on admission to hospital and 500 mg of aspirin was given intravenously before cardiac angiography. Due to the complex anticoagulation and the multi-vessel disease it was decided not to load her with a $P2Y_{12}$-inhibitor. The cardiac anesthesia team is approached on how to manage the warfarin anticoagulation in this patient.

Why Is It Important?

Many patients undergoing cardiac surgery are treated by an oral anticoagulant and/or antiplatelet therapy before surgery. These treatments are aimed at reducing the thromboembolic event risk, mainly stroke, or the ischemic risk, mainly myocardial infarction, in their daily life. However, continuation of these therapies increases the risk for perioperative bleeding. The benefit/risk ratio favors these treatments on daily care, but may be challenged in case of surgery, especially when the bleeding

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risk is high. In this respect, the challenge is to find the equilibrium between the indication of the medical treatment (prevention of the thromboembolic or ischemic risks) and the bleeding risk.

Bridging, which means switching an oral anticoagulant or antiplatelet drug to a more easily manageable drug, usually a parenteral one, is a possible option. If bridging is decided, it should result from an agreement between the cardiac surgeon, the cardiologist, and the anesthesiologist for an individual patient.

In general, the benefit of preventing a thromboembolic or ischemic event is considered to be higher than the risk of bleeding [1–7]. The objective of bridging should be to keep the same benefit, with both risks as low as possible. The main challenge is that surgery is not only associated with an increased risk for bleeding, but may also alter the risk of thromboembolic events due to the surgery-induced inflammatory response and surgical trauma. While the risk for bleeding is maximal during surgery or in the early postoperative period, the risk for thromboembolic or ischemic events peaks in the first days following surgery.

Furthermore, anticoagulant and antiplatelet drugs have a prolonged half-life, which influences the timing of discontinuation. Additionally, not all anticoagulant and antiplatelet drugs have appropriate antagonists. The concept of bridging therapy arose with the assumption that the bridging treatment has a titratable effect, with a predictable and quick reversal possibility. The switch to the bridging treatment needs to be timely managed, and careful attention is required since the effects of the primary drugs can overlap the therapy used for bridging. The purpose of this chapter is to provide insight in bridging options for oral anticoagulants and antiplatelet drugs in patients undergoing cardiac surgery.

Bridging of Oral Anticoagulation

Reduction of the Thromboembolic or Ischemic Risk

Oral anticoagulants are administered to reduce the risk for thromboembolic complications, especially in patients with atrial fibrillation, mechanical heart valves, or venous thromboembolism [8]. Table 8.1 shows the criteria for risk stratification for perioperative thromboembolism.

Even for these few indications the rate of periprocedural thromboembolism for unbridged oral anticoagulant interruptions is estimated at only 0.5% [9]. The perioperative risk of thromboembolism is higher for patients with a mechanical heart valve (1%) than for patients with atrial fibrillation or venous thromboembolism (0.5%) [8, 10]. In patients with left ventricular assist devices, the long-term thromboembolic risk is 1.5% per year. However, the timing of left ventricular assist device implantation is crucial, as the ischemic stroke rate peaks during the first post-implantation years, reaching 5.5% per year, irrespective of the type of implanted device [11, 12]. Despite the high risk for thromboembolic events, the bleeding risk is even higher, estimating 20–25% per year. In these patients, bridging may not be a good strategy [12].

Table 8.1 Risk stratification for perioperative thromboembolism

Indication for anticoagulation			
Risk group	Mechanical heart valve	Atrial fibrillation	VTE
High[a]	• Mitral valve prosthesis • Cage-ball or tilting disc aortic valve prosthesis • CVA/TIA <6 months prior	• CHA_2DS_2-VASc >6 • CVA/TIA <3 months prior • Rheumatic valvular heart disease prior	• VTE <3 months • Severe thrombophilia[b]
Moderate	• Bi-leaflet aortic valve and other risk factors[d]	• CHA_2DS_2-VASc 4–5	• VTE 3–12 months prior • Non-severe thrombophilia[c] • Recurrent VTE • Active cancer
Low	• Bi-leaflet aortic valve without other risk factors	• CHA_2DS_2-VASc 2–3 without prior CVA/TIA	• VTE >12 months prior without other risk factors

Data from the American College of Chest Physicians (ACCP) guidelines [8]
CVA cerebrovascular accident, *TIA* transient ischemic attack, *VTE* venous thromboembolism
CHA_2DS_2-VASc score: congestive heart failure, hypertension, age ≥75 years or 65–74, diabetes mellitus, stroke, vascular disease, female sex
[a]A true high-risk category may be difficult to objectively define in the absence of trials demonstrating benefit of heparin bridging in such patients
[b]Deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities
[c]Heterozygous factor V Leiden or prothrombin gene mutation
[d]CVA risk factors include: atrial fibrillation, prior CVA/TIA, hypertension, diabetes, congestive heart failure, age >75 years

The non-vitamin K oral anticoagulants (NOACs) are increasingly prescribed in the prevention of thromboembolic events in patients with atrial fibrillation or venous thromboembolism. In large trials and registries it was shown that these patients did not experience an increased thromboembolic rate in the perioperative period, irrespective whether they were bridged or unbridged [13, 14]. The rather low incidence of thromboembolic events observed in the literature explains why there is no scientific evidence to support bridging in case of these novel anticoagulants, even in high-risk patients.

Reduction of the Bleeding Risk

Bridging is undoubtedly associated with a higher risk of bleeding [15–17]. A meta-analysis of 34 observational studies of bridging anticoagulation found an odds ratio of 3.6 (95% CI 1.52–8.50) for major bleeding with bridging versus non-bridging, and no significant difference in thromboembolic events or mortality [18]. These results are observed whatever the invasive procedure considered,

and are consistent with the more recent data of the ORBIT-AF study [10]. In this study it was shown that bleeding events in cardiac surgery occurred more frequently after bridging compared to no bridging (7.1% vs. 4.2%) [10]. Similar results were found for NOACS, showing that continuation or short-term interruption of these drugs is safe for most invasive procedures, and bridging should only be considered in patients at cardiovascular risk undergoing major procedures [19].

In summary, there are no solid data supporting bridging of oral anticoagulants, and bridging, therefore, remains based on a case-by-case multidisciplinary decision [6]. However, in specific cases, bridging might be considered in order to prevent further thromboembolic complications, such as patients with a high risk of recurrent VTE, patients with atrial fibrillation and an ischemic event in the last 3 months, or patients with a mechanical heart valve other than a bileaflet valve [20].

Bridging of Antiplatelet Drugs

In analogy with oral anticoagulants, preoperative discontinuation of antiplatelet therapy requires balancing of the embolic and bleeding risks that are associated with cessation or discontinuation. Bridging should only be considered in patients on dual antiplatelet therapy (DAPT), or when high dose aspirin or $P2Y_{12}$-receptor inhibitors are used. Patients requiring coronary artery bypass grafting within the time of dual antiplatelet therapy administration are specifically concerned due to their high risk for ischemic events [21].

Current European Society of Cardiology guidelines state that bridging strategies should only be considered in patients at a very high risk for ischemia (active ischemia, high-risk coronary anatomy, and surgery performed very early after stent implantation) in whom temporary discontinuation of antiplatelet therapy is considered inevitable because of elevated hemorrhagic risk [22]. When patients face a high risk for bleeding, perioperative continuation of dual antiplatelet therapy is inappropriate, whereas the concomitant presence of high ischemic risk mandates the minimization of the total time without antithrombotic protection. In this case, it is recommended to measure the biological effect of antiplatelet therapy on platelet function before surgery. Various platelet function tests are available, and may be used to determine the extent of platelet dysfunction in a point-of-care setting [23]. There are however no data available that support the use of these platelet function tests in the decision to bridge patients. In summary, bridging of antiplatelet therapy is not supported by scientific evidence. Besides low dose aspirin continuation, adding parenteral antiplatelet drugs to maintain antiplatelet activity just before surgery remains discussed. The management of antiplatelet therapy currently consists of maintenance of a low dose aspirin, and to reduce the time, as short as possible, without dual antiplatelet therapy or $P2Y_{12}$-receptor inhibitors.

Implications for Daily Practice

The decision to bridge a patient before surgery is based on the specific condition of the patient, since the therapeutic solutions are rather limited. Postponing surgery would be the first option in some patients. There are various bridging protocols available, which all take the anticoagulant effect duration into account and offer a progressive switch to parenteral anticoagulation [9, 20]. Bridging should only be considered in patients where the risk of thromboembolic events is high. Parenteral anticoagulation includes subcutaneous low molecular weight heparin (LMWH) or unfractionated heparin (UFH). The objective is mainly therapeutic, which means that the LMWH dose is adapted to the weight of the patient or is 1.5–2.5 times the control activated partial thromboplastin time for UFH. Parenteral anticoagulants are started 2 days after the withdrawal of oral anticoagulant, 3 days before surgery, and stopped 12–24 h before surgery. Parenteral anticoagulants are resumed at 6–48 h after surgery according to the bleeding risk [20]. For more detailed information regarding bridging protocols we refer to reference 24.

The perioperative use of LMWH or UFH in patients with coronary stents shows no consistent protective effect against stent thrombosis, while bleeding events increase [4]. European guidelines therefore discourage the use of heparins as bridging treatment for antiplatelet therapy [4]. Indeed, heparin pharmacodynamics are relatively ineffective in the prevention of platelet aggregation, and unfractionated heparin may even activate platelet aggregation [25].

Among parenteral antiplatelet therapy, short acting glycoprotein IIb/IIIa inhibitors (tirofiban or eptifibatide) could be considered as bridging agents [4, 22]. For example, for bridging clopidogrel, tirofiban infusion can be started 5 days before surgery, stopped 4 h before surgery, and resumed at the same schedule at 2 h after the end of surgery, and continued for up to 6 h after the resumption of clopidogrel, unless oral administration could be resumed on the same day of surgery [26].

Cangrelor is a novel non-thienopyridine intravenous antiplatelet agent with a very short plasma half-life (3–5 min), which reversibly blocks the $P2Y_{12}$ receptor. These properties result in a rapid offset of action, within 1 h of cessation of administration, while the onset of action is immediate. The use of cangrelor for bridging $P2Y_{12}$ inhibitor-treated patients to CABG surgery was evaluated against placebo [27]. Cangrelor resulted in a higher rate of maintenance of platelet inhibition and did not increase major bleeding before surgery. Although its characteristics theoretically approach the ideal of an antiplatelet-bridging drug, cangrelor is not yet commercially available everywhere.

After surgery, antiplatelet therapy should be resumed as soon as possible, not only with respect to aspirin to all patients having CABG but also $P2Y_{12}$-receptor inhibitors [22, 23] provided there is no concern of bleeding.

The indication for concomitant oral anticoagulant and antiplatelet therapy makes the perioperative management of patients more complicated. The combination of both thromboembolic and ischemic risks suggests that these patients would probably require a bridging strategy, but there are no scientific data to support clinical

decision-making. A combination of a single antiplatelet agent plus a parenteral anticoagulant (UFH/LMWH) might be considered as a perioperative bridging strategy to protect against both stent thrombosis and embolism [21].

For the 62-year-old lady of the case vignette the decision whether to bridge or not needs an individualized weighing of the risks and benefits. An interdisciplinary consensus recommends for this patient to interrupt warfarin until an INR of <1.5 is reached. Due to the rather high thromboembolic and the moderate bleeding risk with a primary CABG procedure a bridging protocol involving either the intravenous administration of unfractionated heparin (aPTT-guided) or the subcutaneous application of a half (some institutions may prefer full dose) therapeutic dose of low molecular weight heparin (LMWH) is advised for the interruption period until surgery. The half dose LMWH protocol should stop at 12 h (24 h for the full dose protocol) before cardiac surgery to prevent excessive blood loss. Unfractionated heparin may be continued until the start of surgery.

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