Oral anticoagulation (OAC) with vitamin K antagonists (VKA) is a highly effective way to prevent thromboembolic complications. During surgery or other invasive procedures it may, however, be necessary to temporarily discontinue VKA therapy, as it could increase the risk of bleeding during the procedure. In order to sustain the protective effect, temporary substitution (“bridging”) with heparin may be necessary. The periprocedural risk for hemorrhage or thromboembolism is higher in patients with an indication for OAC.

Methods: Selective literature review and taking into account the American College of Chest Physicians’ current guidelines.

Results and Discussion: Even though there is no formal labelling for the use of low molecular weight heparins (LMWH) in this indication, LMWH has been much better documented than unfractionated heparin (UFH). In planning appropriate perioperative management, patient specific thromboembolic risks must be balanced against the procedural risk for bleeding. In certain instances, OAC may be continued during the procedure. Bridging with LMWH is at least as safe and effective as UFH, and offers substantial advantages. There are however clear advantages in clinical application, side effects and ongoing management, and it reduces hospital stay and treatment cost.

Key words: oral anticoagulation, vitamin K antagonist, low molecular heparin, bridging, risk, recommendation

The classic approach to bridging anticoagulation is to give unfractionated heparin (UFH) from the moment that oral anticoagulation is no longer in the therapeutic range until it becomes therapeutic once again. The dose of UFH is titrated according to the activated partial thromboplastin time (APTT). Frequent laboratory testing (at least once per day) is necessary so that, as soon as the International Normalized Ratio (INR) has become subtherapeutic, this can be determined without excessive delay and UFH can be titrated in the appropriate dose. As UFH is usually given intravenously through an infusion pump, bridging anticoagulation with UFH requires several additional days of hospitalization beyond the time required for the surgical intervention itself.

This traditional concept of bridging with UFH is incompatible with the desire of patients and insurances alike to keep hospital stays as short as possible. Since the mid-1990's, therefore, low molecular weight heparins (LMWH) have increasingly been used for this purpose. Unless the patient's renal function is impaired, these can be given subcutaneously in a therapeutic dose without any laboratory testing or individual dose titration, and can thus
also be administered in an outpatient setting. Furthermore, the risk of heparin-induced thrombocytopenia (type II) is lower with LMWH than with UFH. At present, in Germany, oral anticoagulation therapy is probably bridged with LMWH, rather than with UFH, in a majority of cases.

None of the LMWH that are currently on the market are explicitly approved for the bridging of oral anticoagulation. This use of LMWH therefore constitutes a non-approved indication for an approved substance. In contrast, the use of UFH for bridging is covered by its broad and general approval “for the prophylaxis and treatment of arterial and venous thromboses and emboli.” This non-specific formulation of the indication for UFH originated decades ago, when suitable studies relevant to drug approval were scarce. This situation presents two different medicolegal difficulties. First, any complications (thromboembolism or hemorrhage) that should arise under treatment with LMWH might have serious medicolegal consequences for the ordering physician, even if the medication was used correctly, simply because it has not been approved for this particular indication. Second, German law specifies that a drug that has not been approved for a particular indication may not be reimbursed if there is an alternative drug that has been approved for the same indication.

The authors therefore consider it appropriate to summarize the currently available research data on the bridging of oral anticoagulation, the approach taken by international guidelines to this subject, and the current practical options for treating physicians.

The risk of thromboembolism without medication

The most common reasons for long-term oral anticoagulation are atrial fibrillation, mechanical artificial heart valves, and venous thromboembolism. Anticoagulation must be bridged for invasive procedures because of the risk of thromboembolism that would result if the oral anticoagulation were simply stopped. The magnitude of this risk varies, not only from one underlying disease to another, but also among individuals.

Diseases requiring oral anticoagulation can be classified into three categories according to the magnitude of the risk of thromboembolism: high-risk (more than 10% per year without OAC), intermediate-risk (4% to 10% per year), and low-risk (below 4%). Other factors may influence this risk: patients with atrial fibrillation, for example, face a higher risk if they

Diagram representing bridging of chronic oral anticoagulation with vitamin K antagonists for a planned procedure on Day 0 with unfractionated or low molecular weight heparin. After the vitamin K antagonist (in Germany, usually phenprocoumone) is stopped, approximately one week before the planned procedure, the INR gradually falls and the degree of protection against thromboembolism lessens. Once the oral anticoagulation is no longer in therapeutic range, “bridging” anticoagulation is begun with unfractionated or low molecular weight heparin (arch). Heparin treatment is briefly interrupted for the procedure itself and then – depending on the procedure-associated risk of hemorrhage and the characteristics of the individual patient – started again afterward. Postoperatively, oral anticoagulation is started again and bridging with heparin is continued until the oral anticoagulation is once again in therapeutic range.
simultaneously suffer from heart failure. The same is true of patients with mechanical heart
valves who have atrial fibrillation in addition. The elapsed time after a prior venous or
arterial thromboembolic event also affects the risk of thromboembolism: it is much higher
in the first three months after such an event than at later times. The clinical assessment of
the risk of thromboembolism is summarized in box 1.

In patients with diseases associated with a low risk of thromboembolism, oral anticoagulation
does not need to be bridged when oral anticoagulation is briefly interrupted for a surgical
procedure. In such cases, the standard antithrombotic prophylaxis used for the procedure in
question suffices.

The risk of hemorrhage with various procedures
An individual patient’s risk of hemorrhage depends both on patient-specific factors such as
congenital or acquired abnormalities of hemostasis, earlier episodes of perioperative
hemorrhage, and the use of aspirin or non-steroidal anti-inflammatory drugs, and on the
nature of the procedure, e.g., with respect to the anatomy of the operative site, the surgeon’s
opportunity (or lack of opportunity) to control bleeding, the urgency of the procedure, and
the degree of the surgeon’s experience. Procedures can be roughly subdivided into those
with a high risk of bleeding and those without a high risk of hemorrhage (1, 2, 3).

In general, minor surgical procedures are associated with a low risk of hemorrhage, while
major procedures are associated with a higher risk, e.g., cancer surgery (e2), urological
procedures (e3), interventional cardiological procedures, and open heart surgery (e4, 4, 5),
as well as multiple tooth extractions and extensive oral surgical procedures (6). Gastrointestinal
polypectomy is considered to be associated with a low risk of hemorrhage (1, 7), but this is
not necessarily true of all types of polypectomy. Complications of elective, minimally
invasive procedures may unexpectedly necessitate open surgery and thereby lead to a
higher risk of hemorrhage. The risk of hemorrhage is highest in neurosurgical procedures,
mainly because of the serious consequences of hemorrhage in the area of operation (3). Hip
and knee replacement surgery is associated with a high risk of venous thromboembolism,
but also with a high risk of hemorrhage (8). Ophthalmologic procedures that do not require retrobulbar anesthesia (except for complex procedures), laparoscopic surgery or cholecystectomy (7), dermatological surgery (3), and most dental procedures (6, 9) are not associated with a high risk of hemorrhage. In oral surgery, persistent bleeding can usually be stopped with local treatment or with the administration of an antifibrinolytic agent, such as tranexamic acid (9).

A classification of procedures according to their presumed risk of hemorrhage, as used in a prospective registry, is shown in Box 2 (1).

Clinical data on the traditional concept with unfractionated heparin
The scientific evidence supporting bridging oral anticoagulation with UFH is inadequate, consisting of only two very small, open studies involving a total of 59 episodes (table 1), one of which dates back to 1978, before the Good Clinical Practice Standards were introduced. As far as can be determined from the limited number of cases, the classic approach to bridging anticoagulation with UFH leads to a rate of thromboembolism under 1% (95% confidence interval: 0.0% to 6.0%), with a rate of severe hemorrhage of approximately 1.7% (95% confidence interval: 0.0% to 9.1%). The latter rate was lower when the UFH dose was titrated with the aid of a nomogram.

**BOX 2**

**Clinical risk assessment for hemorrhagic events**

**Examples of high risk of hemorrhage**
- Cardiac surgery
- Abdominal aortic aneurysm surgery
- Neurosurgical operations, laminectomy
- Complex tumor surgery
- Transurethral prostatectomy
- Bilateral knee replacement
- Kidney and liver biopsy
- Extensive oral surgery, multiple tooth extractions
- Interventional cardiology

**Examples where the risk of hemorrhage is not high**
- Laparoscopic surgery or cholecystectomy
- Bowel resection, hernia surgery, hemorrhoid surgery
- GI polypectomy
- Abdominal hysterectomy, dilatation and curettage
- Hand surgery, carpal tunnel surgery, foot surgery, shoulder surgery
- Knee and hip replacement
- Dermatological surgery
- Pacemaker and AICD implantation
- Ophthalmic surgery (e.g., cataract, trabeculectomy, vitreoretinal surgery); complex procedures (e.g., eyelid, lacrimal gland, orbital surgery) are associated with a higher risk of hemorrhage
- Endarterectomy
- Dental procedures (simple extractions, oral hygiene, prostheses)
- Diagnostic cardiac catheterization
- Gastrointestinal endoscopy with or without biopsy
- Bronchoscopy with or without biopsy
- Arthroscopy
- Biopsies (prostate, bladder, thyroid gland, breast, lymph nodes, pancreas, myocardium)
Cohort studies on low molecular weight heparin for bridging of anticoagulation

By the end of 2005, more than 10 prospective studies on the use of low molecular weight heparin for the bridging of oral anticoagulation had been published, including a total of more than 3000 patients (table 2). The patients in these studies were receiving permanent anticoagulation for all indications and underwent operative and non-surgical interventions from across the entire therapeutic spectrum. The most common reason for oral anticoagulation was chronic atrial fibrillation, but there were more than 900 patients receiving anticoagulation for mechanical heart-valve prostheses. The dosage schemes for LMWH varied widely across studies. The dose most commonly used was full therapeutic anticoagulation, i.e., LMWH was most often given in the dose recommended by the manufacturer for the acute treatment of deep venous thrombosis or pulmonary embolism. The rate of thromboembolic complications observed in these cohort studies ranged from 0% to 4%, and the rate of severe – usually postoperative – hemorrhage ranged from 0.2% to 6.7%. The cumulative event rates were 0.75% for thromboembolism (95% confidence interval: 0.5% to 1.1%) and 1.6% (95% confidence interval: 1.2% to 2.2%) for severe hemorrhage.

Comparison of UFH and LMWH with surrogate parameters

Two studies, one cohort study and one randomized study (4, 10) with a total of more than 500 patients, compared the bridging of oral anticoagulation with UFH and LMWH. If one takes the achievement and maintenance of anticoagulation in the therapeutic range (APTT for UFH, anti-Xa level for LMWH) as a measure of the quality of anticoagulation, then these studies revealed LMWH to be markedly superior to UFH: when LMWH are used, the therapeutic range is reached earlier and is more stably maintained.

Clinical comparative studies of UFH and LMWH

In addition to the studies just mentioned, two randomized studies with clinical endpoints have been published (11, 12) (558 patients), as well as 2 registry studies on bridging oral anticoagulation with UFH or LMWH (13, 14) (a total of 1388 episodes). Overall, no significant difference was found between the two forms of treatment with respect to the frequency of complications, whether hemorrhagic or thromboembolic. Hospital stays were significantly shorter when LMWH were used (table 3).

Current evidence

The data discussed above can be summarized as follows:

- The complication rate can be kept low by bridging oral anticoagulation with a method that is decided upon a priori. This is true for both UFH and LMWH, independent of the indication for oral anticoagulation with vitamin K antagonists and the type of intervention performed. In particular, currently available data reveal no significant differences between LMWH and UFH with respect to complication rates.
<table>
<thead>
<tr>
<th>Study</th>
<th>Indication for bridging</th>
<th>Operation</th>
<th>n</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thrombo-embolism</td>
<td>Hemorrhage (total)</td>
</tr>
<tr>
<td>Spandorfer (24)</td>
<td>Mechanical heart valves</td>
<td>Various major surgical procedures</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Spandorfer (25)</td>
<td>Mechanical heart valves</td>
<td>Non-cardiac surgery</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Johnson (26)</td>
<td>Mechanical heart valves</td>
<td>Major surgery, including cardiac surgery</td>
<td>143</td>
<td>0</td>
</tr>
<tr>
<td>Ferreira (27)</td>
<td>Mechanical heart valves</td>
<td>Major surgery Cardiac catheterization Minimally invasive surgery</td>
<td>82</td>
<td>0</td>
</tr>
<tr>
<td>Omran (28)</td>
<td>Mechanical heart valves</td>
<td>Aortic and mitral valve replacement surgery</td>
<td>362</td>
<td>0</td>
</tr>
<tr>
<td>Dunn (29)</td>
<td>VTE</td>
<td>Not specified</td>
<td>260</td>
<td>4</td>
</tr>
<tr>
<td>Turpie (30)</td>
<td>Mechanical heart valves</td>
<td>Elective surgery Invasive procedures</td>
<td>174</td>
<td>1</td>
</tr>
<tr>
<td>Hammer-stingl (31)</td>
<td>Atrial fibrillation</td>
<td>Operations with a high (n=34) and low (n=166) risk of hemorrhage</td>
<td>200</td>
<td>0</td>
</tr>
<tr>
<td>Tinmouth (32)</td>
<td>Atrial fibrillation</td>
<td>Cardiac catheterization Tooth extraction Biopsies</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Wilson (33)</td>
<td>VTE</td>
<td>Not specified</td>
<td>47</td>
<td>2</td>
</tr>
<tr>
<td>Kovacs (34)</td>
<td>Mechanical heart valves</td>
<td>Cardiac catheterization Urological surgery Dental surgery Orthopedic surgery Endoscopy</td>
<td>224</td>
<td>8</td>
</tr>
<tr>
<td>Douketis (1)</td>
<td>Mechanical heart valves</td>
<td>Operations with a high (n=108) and low (n=542) risk of hemorrhage</td>
<td>650</td>
<td>2</td>
</tr>
<tr>
<td>Baudo (35)</td>
<td>VTE</td>
<td>Major surgery n=68 Minor surgery n=409</td>
<td>394</td>
<td>2</td>
</tr>
<tr>
<td>Halbritter (17)</td>
<td>Venous thromboembolism</td>
<td>Catheterization, pacemaker implantation, endoscopy, general surgery, orthopedic surgery, cardiovascular surgery</td>
<td>286</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>2,961</td>
<td>22 (0.75 %) CI 0.5–1.1</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism; CI, confidence interval; NS, not specified
During the bridging of anticoagulation and immediately after the procedure, the risk of hemorrhage is higher than that of thromboembolism in all of the cohort studies that have been published. Hemorrhagic complications may necessitate further therapeutic interventions in the coagulation system, which may themselves, in turn, lead to thromboembolic events.

In all of these studies, LMWH was always given to patients with mechanical mitral or aortic valve prostheses in what was considered to be the fully therapeutic dose, i.e., the dose recommended by the manufacturer for the acute treatment of venous thromboembolism. It is not known whether it is better to give the drug once or twice daily. Initial data from registry studies suggest that patients with modern mechanical aortic-valve prostheses, unlike patients with older types of mechanical valve (ball-and-cage prostheses), might also be adequately anticoagulated with half of the therapeutic dose, as long as there is sinus rhythm and there is no heart failure (13).

There is no consensus regarding the dosage for bridging oral anticoagulation with LMWH in patients with atrial fibrillation or in patients who have previously sustained a venous thromboembolism. Most of the available data relate to the administration of the full therapeutic dose, but there is evidence that half of the therapeutic dose may be just as effective.

There has not yet been any systematic study on the optimal timing for the last dose of LMWH before the intervention. At issue here is not just the risk of hemorrhage from the procedure itself, but also that from spinal anesthesia. Most of the available data relate to a dosage schedule in which the last dose of LMWH was given 24 hours before the procedure. This interval appears not to increase the risk of thromboembolic complications, even in patients with prosthetic heart valves, and also seems to be the best way of dealing with the problem of spinal anesthesia.

**Guidelines**

The current guidelines of the American College of Chest Physicians (15) (www.chestnet.org/education/guidelines/currentGuidelines) for the bridging of oral anticoagulation concern oral anticoagulation with warfarin, which has a considerably shorter half-life than phenprocoumon. These guidelines classify patients receiving oral anticoagulation into three groups according to the magnitude of the risk of thromboembolism, similarly to the classification shown in box 1, above. In patients at high risk, warfarin should be stopped 4 days before a planned intervention. As soon as the INR falls, unfractionated or low molecular

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**TABLE 3**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montalescot (10)</td>
<td>Heart-valve surgery, UFH n=106, LMWH n=102</td>
<td>Day 2: 87% of LMWH patients were in therapeutic range, but only 9% of UFH patients had a therapeutic PTT. End of treatment: 19% of LMWH patients were overanticoagulated, as compared to 62% of UFH patients; 2 severe hemorrhages in each group.</td>
</tr>
<tr>
<td>Stellbrink (11)</td>
<td>Atrial fibrillation n = 496</td>
<td>End point death, severe hemorrhage, or embolism: 2.8% LMWH vs. 4.8% UFH</td>
</tr>
<tr>
<td>Omran (22)</td>
<td>Atrial fibrillation, heart-valve replacement, or both, n = 68</td>
<td>The time till effective anticoagulation was reached was significantly shorter with LMWH; the percentage of days on which anticoagulation was effective was significantly higher with LMWH</td>
</tr>
<tr>
<td>Spyropoulos (11)</td>
<td>1,077 patients who were chronically anticoagulated with vitamin K antagonists</td>
<td>Shorter hospital stay with LMWH; no difference in frequency of undesired events</td>
</tr>
<tr>
<td>Spyropoulos (14)</td>
<td>246 patients with synthetic heart valves</td>
<td>LMWH just as safe and effective as UFH but with a shorter hospital stay</td>
</tr>
<tr>
<td>Fanikos (12)</td>
<td>63 patients for whom heart-valve replacement was planned (LMWH n=29, UFH n=34)</td>
<td>LMWH just as safe and effective as UFH but with a shorter hospital stay</td>
</tr>
</tbody>
</table>
weight heparin is given (15). After the procedure, bridging treatment is given in overlapping fashion until an INR of 2.0 to 3.0 is reached. According to these guidelines, either UFH or LMWH can be used for bridging; neither one is preferred over the other.

The guidelines of the European Society of Cardiology on the bridging of oral anticoagulation in patients with atrial fibrillation and mechanical heart-valve prostheses are now available (www.escardio.org/knowledge/guidelines, 2001). The joint guidelines of the European and American cardiology societies (www.guideline.gov; www.circulationaha.org) recommend bridging oral anticoagulation in patients with atrial fibrillation whenever the oral anticoagulation is to be interrupted for more than 7 days, which is the case for most patients. LMWH and UFH are recommended in similar fashion; the dose of heparin is not specified.

Summary for clinical practice

- The periprocedural risk of an invasive procedure (hemorrhage and/or thromboembolism) is greater in chronically anticoagulated patients than in those who are not chronically anticoagulated. This is independent of which drug is used to bridge oral anticoagulation. This fact must be discussed with the patient beforehand so that he or she can give properly informed consent to the procedure.
- In the current guidelines that are cited in this article, LMWH and UFH are recommended in similar fashion because of the lack of relevant and informative studies directly comparing these two types of medication. Nonetheless, LMWH is currently used far more often than UFH for the bridging of oral anticoagulation, even though UFH is approved for this indication, while LMWH is not.
- To the extent that a comparison is possible given the non-uniform state of the data, using LMWH to bridge oral anticoagulation seems to be at least as safe and effective as using UFH. This is true regardless of the condition for which oral anticoagulation is indicated, and regardless of the type of procedure for which it must be interrupted and bridged.
- In this context, it must also be mentioned that oral anticoagulation with vitamin K antagonists does not always need to be discontinued. Oral anticoagulation can continue to be given during most dermatological and dental procedures (except extensive oral procedures), as well as many ophthalmological procedures in the anterior chamber of the eye.
- Independently of the state of regulatory approval, the following considerations should be borne in mind when oral anticoagulation is bridged:
  - The benefit of surgery must be weighed against the risk of altering the anticoagulation regimen (hemorrhage versus thromboembolic events).
  - The patient should be enabled to weigh the risks and benefits for himself or herself (adequate patient information).
  - The dose of bridging medication should be chosen in accordance with the available scientific data.
- All of the above points are just as important if oral anticoagulation is to be bridged with UFH or LMWH. A particular concern when LMWH are used is their lower rate of elimination in patients with renal insufficiency.
- UFH and LMWH have both been found to be effective in practice; however, neither can yet be considered standard therapy for the bridging of oral anticoagulation. UFH cannot, because the required degree of comprehensive scientific evidence supporting its use for this indication is currently lacking; LMWH cannot, because they have not been in use for a long enough time.
- The use of LMWH rather than UFH is far less costly because of the shorter hospital stay required. This fact must be taken into consideration by payers reimbursing health care costs, in accordance with the general requirement of German law that medical care be delivered at minimal total cost, as far as possible.
- This review article does not address the issue of using LMWH for anticoagulation in pregnant women with mechanical heart valves. For these patients, special consultation should be obtained from an expert in hemostasis.

Conflict of Interest Statement

Prof. Riess has received lecture and consultancy fees from manufacturers of unfractionated heparin, low molecular weight heparin, and vitamin K antagonists (Braun, GSK, Leo, Novartis, Pfizer, Roche, Sanofi-Aventis) as well as research support from GSK, Leo, Novartis, and Sanofi-Aventis.

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REFERENCES
For e-references please refer to the additional references listed below.


ADDITIONAL REFERENCES


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