Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis

Gregory Y.H. Lip (Chair)1*, Felicita Andreotti2†, Laurent Fauchier3†, Kurt Huber4*, Elaine Hylek5†, Eve Knight6†, Deirdre A. Lane1†, Marcel Levi7†, Francisco Marin8†, Gualtiero Palareti9†, and Paulus Kirchhof (Co-chair)10†

Document reviewers: Jean-Philippe Collet11, Andrea Rubboli12, Daniela Poli13, and John Camm14

1University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, UK; 2Department of Cardiovascular Medicine, A. Gemelli University Hospital, Rome, Italy; 3Cardiologie B, Centre Hospitalier Universitaire Trousseau et Université François Rabelais, Tours, France; 43rd Department of Medicine, Cardiology and Emergency Medicine, Wilhelminen Hospital, A-1160 Vienna, Austria; 5Department of Medicine, Research Unit-Section of General Internal Medicine, Boston University Medical Center, Boston, MA 02118, USA; 6AntiCoagulation Europe; 7Department of Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; 8Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; 9Department of Angiology and Blood Coagulation, University Hospital S. Orsola-Malpighi, Bologna, Italy; 10Department of Cardiology and Angiology, Universitätsklinikum Münster, D-48149 Münster, Germany; 11Groupe Hopitalier Pitie-Salpetriere, Paris, France; 12Maggiore Hospital, Bologna, Italy; 13Department of Heart and Vessels, Thrombosis Center, Florence, Italy; and 14Division of Cardiac and Vascular Sciences, St. George’s University of London, London, UK

Despite the clear net clinical benefit of oral anticoagulation (OAC) in atrial fibrillation (AF) patients at risk for stroke, major bleeding events (especially intra-cranial bleeds) may be devastating events when they do occur. The decision for OAC is often based on a careful assessment of both stroke risk and bleeding risk, but clinical scores for bleeding risk estimation are much less well validated than stroke risk scales. Also, the estimation of bleeding risk is rendered difficult since many of the known factors that increase bleeding risk overlap with stroke risk factors. As well as this, many factors that increase bleeding risk are transient, such as variable international normalized ratio values, operations, vascular procedures, or drug–drug and food–drug interactions.

In this Position Document, we comprehensively review the published evidence and propose a consensus on bleeding risk assessments in AF patients, with a view to summarizing “best practice” when approaching antithrombotic therapy in AF patients. We address the epidemiology and size of the problem of bleeding risk in AF and review established bleeding risk factors. We also summarize definitions of bleeding in the published literature. Patient values and preferences balancing the risk of bleeding against thrombo-embolism is reviewed, and the prognostic implications of bleeding are discussed. We also review bleeding risk stratification and currently published bleeding risk schema. A brief discussion of special situations [e.g. peri-ablation, peri-devices (implantable cardioverter-defibrillator, pacemakers) and presentation with acute coronary syndromes and/or requiring percutaneous coronary interventions/stents and bridging therapy], as well as a discussion of prevention of bleeds and managing bleeding complications, is made. Finally, this document also puts forwards consensus statements that may help to define evidence gaps and assist in everyday clinical practice.

Bleeding risk is almost inevitably lower than stroke risk in patients with atrial fibrillation. Nonetheless, identification of patients at high risk of bleeding and delineation of conditions and situations associated with bleeding risk can help to refine antithrombotic therapy to minimize bleeding risk.

**Keywords**
- Bleeding
- Oral anticoagulation
- Atrial fibrillation
- Risk assessment
- Stroke prevention
- Antithrombotic therapy
- Triple therapy

* Corresponding author. Tel: +44 121 5075080; Fax: +44 121 507 4907; Email: g.y.h.lip@bham.ac.uk
† Task Force Members.
‡ Representing the ESC Working Group on Thrombosis.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2011. For permissions please email: journals.permissions@oup.com.
Introduction and scope

Prevention of stroke and thrombo-embolism is one of the main therapeutic goals in atrial fibrillation (AF). Oral anticoagulation (OAC) is highly effective in preventing ischaemic strokes in patients with AF and conveys a clear net clinical benefit despite a potential risk for major bleeding events.

Currently, anticoagulation therapy mainly consists of vitamin K antagonists (VKAs), often warfarin or acenocoumarol or phenprocoumon, which are dose adjusted to achieve an international normalized ratio (INR) of 2.0–3.0. The VKAs have many limitations, including a significant inter- and intra-patient variability of effective dose, and various food and drug interactions. Thus, regular anticoagulation monitoring is required in all patients to keep the INR within the narrow therapeutic range of 2.0–3.0. Furthermore, this variability causes many patients to spend significant amounts of time outside the therapeutic INR window, and an important proportion of patients discontinue OAC therapy.

New OACs, broadly divided into two categories, the oral direct thrombin inhibitors and the oral direct factor Xa inhibitors, are in advanced clinical development, and may offer alternative therapies to patients who suffer from the limitations and dis-utility associated with VKAs. Indeed, indirect comparisons show how well these new OACs may perform relative to VKA, aspirin–clopidogrel combination therapy, aspirin monotherapy or placebo.

Anticoagulant therapy with VKAs carries a risk for bleeding, including severe bleeding events, but the clinical benefit of OAC clearly outweighs the risk of OAC therapy, especially in patients at high risk for stroke: bleeding events are five to eight times less likely than ischaemic strokes reported among AF patients from trials and registry data.

Estimation of the stroke risk in an individual patient with AF can be achieved using easily applicable clinical stroke risk estimators such as the CHADS2 score and an increasingly more refined score that considers additional stroke risk factors, the CHA2DS2–VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, previous stroke (doubled)—vascular disease, age 65–74, sex category] score. Patients at moderate–high risk for stroke are increasingly being considered candidates for OAC based on both an old and a new evidence base.

Despite the clear net clinical benefit of OAC to AF patients at risk for stroke, major bleeding events, especially intra-cranial bleeds, may be devastating when they do occur. The decision for OAC should therefore be based on a careful assessment of both stroke risk and bleeding risk. Unfortunately, clinical scores for bleeding risk estimation are much less well validated than stroke risk scales. Moreover, the estimation of bleeding risk is rendered difficult by other factors:

(i) many of the known factors that increase bleeding risk overlap with stroke risk factors;
(ii) many factors that increase bleeding risk are transient, such as variable INR values, operations, vascular procedures, and drug–drug or food–drug interactions.

In recognizing this problem, the European Heart Rhythm Association (EHRA) and the European Society of Cardiology (ESC) Working Group on Thrombosis convened a Task Force, which aimed to review the published evidence and to propose a consensus on bleeding risk assessment in AF patients, with a view to summarizing ‘best practice’. The present document summarizes the available evidence and put forwards consensus statements that may help to define evidence gaps and assist in everyday clinical practice.

The ultimate judgement regarding care of a particular patient must be made by the healthcare provider and the patient in light of all of the circumstances presented by that patient.

Literature searches were conducted in the following databases: PubMed/MEDLINE and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Registry). Searches focused on English-language sources and studies in human subjects. Articles related to animal experimentation were only cited when the information was important for understanding pathophysiological concepts pertinent to patient management and comparable data were not available from human studies. Additional information was requested from the authors where necessary.

Systematic review of evidence/data

Epidemiology and size of the problem of bleeding risk in atrial fibrillation

The risk of stroke attributable to AF increases with age. For example, among individuals aged 50–59 years old, ~1.5% of strokes are attributable to AF compared with 23.5% of strokes among individuals aged 80–89 years. Oral anticoagulation therapy greatly reduces the risk of stroke in AF, and the clinical dilemma faced by physicians and patients is anticoagulant-related haemorrhage, which also increases with age. It is of note that the rate of intra-cranial haemorrhage has quintupled in recent years, due to the expanded use of anticoagulants and antiplatelet therapy in older adults. Perceived bleeding risk and older age are potent negative predictors of receiving warfarin and partly explain the reported low rates of warfarin use in clinical practice. It is worth remembering that the risk of both haemorrhage and stroke are highest when AF is newly diagnosed and during the initiation of anticoagulant medication. Nonetheless, one recent study does not suggest that OAC naïve status conferred a disadvantage in relation to efficacy and bleeding endpoints.

Reported rates of major bleeding among individuals with AF taking oral VKAs vary widely ranging from 1.3 to 7.2% per year (Table 1). These disparate rates reflect the variability in patient population characteristics studied and the methodology employed. The early trials in AF that established the efficacy of warfarin excluded almost 90% of individuals screened. To establish drug efficacy, efforts to minimize trial drop-out and cross-over are imperative. Trial participants, therefore, are often selected based on a lower bleeding risk profile and higher likelihood of adherence. For these reasons, bleeding rates reported from randomized trials will often be lower than in clinical practice. Randomized controlled trials designed to evaluate the safety and efficacy of new anti-thrombotic agents should also include substantial numbers...
of patients without prior exposure to anticoagulation since these individuals are at the highest risk for bleeding and thrombo-embolism. Observational studies are also subject to selection bias and methodological differences.

Thus, to more fully interpret bleeding rates from real-world observational cohorts of AF patients, it is important to know the proportion of patients within the defined AF population taking warfarin. This proportion reflects individual physician judgement of VKA candidacy or eligibility, which is often subjective. Prospective registries that require written informed consent for participation are less likely to enroll the more acutely ill, medically complex, or frail individuals, and thus will also underestimate the bleeding that occurs in routine care. Indeed, rates reported from these studies are significantly lower than rates of haemorrhage found in the various definitions as regards the decrease in haemoglobin level required for a bleed to be considered as ‘major’.40

The various definitions appear to have different validities depending on the clinical situation in which the antithrombotic drug is being used, complicating the formulation of a single universal bleeding definition. This is particularly true now that several trials have incorporated the rate of major bleeding as a component of the primary study endpoints.

Heterogeneous definitions are frequently observed in the trials assessing the benefits of antithrombotic drugs in acute coronary syndromes (ACS), with the TIMI (thrombolysis in myocardial infarction) and GUSTO being the two bleeding definitions most commonly used in trials on ACS. Different definitions are also used in studies on patients with other clinical conditions (Table 2). The Academic Research Consortium has defined bleeding clinical endpoints in Coronary Stent Trials, as shown in Table 2. However, most studies focusing on bleeding events in AF patients have used broadly similar definitions for major bleeding, as follows: fatal bleeding, bleeding requiring hospitalization or transfusion of ≥2 units of packed red blood cells, or bleeding with involvement of a critical site (i.e. intra-cranial, retroperitoneal,

### Definitions of bleeding

The incidence of bleeding with OAC varies widely in published studies. Differences in study design, patient populations, and quality of monitoring seem to have the most important roles in explaining such differences. At least in part, the difference in reported rates, however, can also be attributed to the diverse classification of bleeding events (major, life-threatening, and minor) adopted in each study. For example, large differences are found in the various definitions as regards the decrease in haemoglobin level required for a bleed to be considered as ‘major’.40

Table 1. Annual rates of major haemorrhage among patients taking warfarin

<table>
<thead>
<tr>
<th>Study</th>
<th>Year published</th>
<th>Population (n)</th>
<th>Major haemorrhage, % per year</th>
<th>ICH % per year</th>
<th>New to warfarin, %</th>
<th>Age, mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFI</td>
<td>1994</td>
<td>AF (n = 3691)</td>
<td>1.3</td>
<td>0.3</td>
<td>100</td>
<td>69</td>
</tr>
<tr>
<td>SPAF II</td>
<td>1994</td>
<td>AF (n = 715)</td>
<td>1.7</td>
<td>0.5</td>
<td>100</td>
<td>69</td>
</tr>
<tr>
<td>AFFIRM</td>
<td>2002</td>
<td>AF (n = 4060)</td>
<td>2.0</td>
<td>0.6</td>
<td>NR</td>
<td>70</td>
</tr>
<tr>
<td>SPORTIF III</td>
<td>2003</td>
<td>AF (n = 3407)</td>
<td>2.2</td>
<td>0.4</td>
<td>27</td>
<td>70</td>
</tr>
<tr>
<td>SPORTIF V</td>
<td>2005</td>
<td>AF (n = 3422)</td>
<td>3.4</td>
<td>0.1</td>
<td>15</td>
<td>72</td>
</tr>
<tr>
<td>ACTIVE W</td>
<td>2006</td>
<td>AF (n = 6706)</td>
<td>2.2</td>
<td>NR</td>
<td>23</td>
<td>71</td>
</tr>
<tr>
<td>RE-LY</td>
<td>2009</td>
<td>AF (n = 18006)</td>
<td>3.4</td>
<td>0.74</td>
<td>51</td>
<td>72</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Presented 2010</td>
<td>AF (n = 14264)</td>
<td>3.5</td>
<td>0.7</td>
<td>37</td>
<td>73</td>
</tr>
<tr>
<td>Landefeld and Goldman</td>
<td>1989</td>
<td>All (n = 565)</td>
<td>7.4</td>
<td>1.3</td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td>Steffensen et al.</td>
<td>1997</td>
<td>All (n = 682)</td>
<td>6.0</td>
<td>1.3</td>
<td>100</td>
<td>59F/66M</td>
</tr>
<tr>
<td>Beyth et al.</td>
<td>1998</td>
<td>All (n = 264)</td>
<td>5.0</td>
<td>0.9</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>Pengo et al.</td>
<td>2001</td>
<td>AF (n = 433)</td>
<td>Age ≥ 75: 5.1</td>
<td>NA</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>Hylek et al.</td>
<td>2007</td>
<td>AF (n = 472)</td>
<td>Age &lt; 75: 1.0</td>
<td>2.5</td>
<td>100</td>
<td>77</td>
</tr>
<tr>
<td>Van der Meeret et al.</td>
<td>1993</td>
<td>All (n = 6814)</td>
<td>2.7</td>
<td>1.3</td>
<td>NR</td>
<td>66</td>
</tr>
<tr>
<td>Fihn et al.</td>
<td>1996</td>
<td>All (n = 528)</td>
<td>1.0</td>
<td>1.3</td>
<td>NR</td>
<td>58</td>
</tr>
<tr>
<td>ATRIA</td>
<td>2003</td>
<td>AF (n = 6320)</td>
<td>1.52</td>
<td>0.46</td>
<td>NR</td>
<td>71</td>
</tr>
<tr>
<td>Poli et al.</td>
<td>2009</td>
<td>AF (n = 782)</td>
<td>1.4</td>
<td>2.5</td>
<td>NR</td>
<td>75</td>
</tr>
<tr>
<td>Rose et al.</td>
<td>2009</td>
<td>AF (n = 3396)</td>
<td>1.9</td>
<td>NA</td>
<td>5</td>
<td>74</td>
</tr>
</tbody>
</table>

### Table 1. Annual rates of major haemorrhage among patients taking warfarin
Table 2 Major bleeding definitions in clinical trials

<table>
<thead>
<tr>
<th>Study or author, year</th>
<th>Reference</th>
<th>Definition of major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI, 1987</td>
<td>41</td>
<td>Fatal, intra-cranial, bleeding associated with a decrease in Hb of at least 5 g/dL, transfusions are factored in 1 unit = 1 g/dL Hb, and cardiac tamponade</td>
</tr>
<tr>
<td>GUSTO, 1993</td>
<td>42</td>
<td>Intra-cerebral, bleeding associated with blood transfusion, or bleeding resulting in haemodynamic compromise requiring treatment</td>
</tr>
<tr>
<td>ACUITY, 2004</td>
<td>45</td>
<td>Intracranial or intra-ocular, drop in Hb of at least 4 g/dL without an overt source of bleeding, or of at least 3 g/dL with an overt source of bleeding. Bleeding associated with blood transfusion. Haematoma ≥ 5 cm in diameter, bleeding requiring re-operation, or access site haemorrhage requiring intervention</td>
</tr>
<tr>
<td>PLATO, 2009</td>
<td>47</td>
<td>Fatal bleeding, intra-cranial bleeding, intra-peri-cardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding, bleeding requiring pressors or surgery, bleeding associated with a drop in haemoglobin of at least 5 g/dL or more, or associated with transfusion of 4 units of blood; or bleeding either associated with a drop in haemoglobin of 3–5 g/dL, bleeding associated with transfusion of 2–3 units of red blood cells</td>
</tr>
<tr>
<td>Landefeld and Goldman, 1989</td>
<td>26</td>
<td>Fatal, life threatening, potentially life threatening, leading to severe blood loss, to surgical treatment or to moderate blood loss (acute or subacute) not explained by trauma or surgery</td>
</tr>
<tr>
<td>Palareti, 1996</td>
<td>73</td>
<td>Fatal intra-cranial (documented by imaging); ocular (with blindness); articular; retroperitoneal; if surgery or angiographic intervention are necessary to stop bleeding; haemoglobin drop of 2 g/dL or need for transfusion of ≥ 2 blood units</td>
</tr>
<tr>
<td>Beyth et al., 1998</td>
<td>28</td>
<td>Overt bleeding leading to a drop in haemoglobin of 2 g/dL in 7 days or less, or life threatening</td>
</tr>
<tr>
<td>Kuijer et al., 1999</td>
<td>49</td>
<td>Clinically overt and associated with a decline in haemoglobin concentration of at least 2 g/dL, transfusion of 2 units or more of red blood cells, retroperitoneal or intra-cranial, warranted permanent discontinuation of treatment</td>
</tr>
<tr>
<td>Wells et al., 2003</td>
<td>48</td>
<td>Loss of 2 units of blood in a 7-day period or bleeding otherwise life threatening</td>
</tr>
<tr>
<td>ISTH, 2005</td>
<td>58</td>
<td>Fall in haemoglobin of 2 g/dL or transfusion of 2 or more units of blood, bleeding that is symptomatic in a critical organ (intra-cranial, intra-spinal, intra-ocular, retroperitoneal, intra-articular or peri-cardial, or intra-muscular with compartment syndrome) or fatal</td>
</tr>
<tr>
<td>Aspinall et al., 2005</td>
<td>51</td>
<td>Haemodynamic instability, association with transfusion of blood, intra-cranial haemorrhage, or death (e.g. a gastrointestinal bleed in a hypotensive patient, subdural haematoma)</td>
</tr>
<tr>
<td>Gage et al., 2006</td>
<td>52</td>
<td>International classification of disease-9th version codes for bleed in any location</td>
</tr>
<tr>
<td>Shireman et al., 2006</td>
<td>53</td>
<td>Hospitalization for ‘major acute bleeding’ (including gastrointestinal haemorrhage or intra-cranial haemorrhage)</td>
</tr>
<tr>
<td>Ruiz-Gimenez et al., 2008</td>
<td>54</td>
<td>Overt, requiring a transfusion of 2 or more units of blood, retroperitoneal, spinal, intra-cranial, fatal</td>
</tr>
<tr>
<td>Poli et al., 2009</td>
<td>34</td>
<td>Fatal, intra-cranial (documented by imaging), ocular causing blindness, articular, or retroperitoneal; when surgery or transfusion of more than two blood units were required or with haemoglobin drop of 2 g/dL or more</td>
</tr>
</tbody>
</table>

(c) BARC (Bleeding Academic Research Consortium) bleeding definitions:

Type 0 No bleeding

Type 1 Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional

Type 2 (minor) Any overt sign of haemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not meet criteria for Type 3 BARC bleeding, Type 4 BARC bleeding (CABG-related), or Type 5 BARC bleeding (fatal bleeding) that is actionable

Type 3 (major) a. BARC Type 3a bleeding

Intracranial haemorrhage (does not include microbleeds; does include intra-spinal). Subcategories; confirmed by autopsy or imaging or LP

Intra-ocular compromising vision (even temporarily)

Overt bleeding plus haemoglobin drop > 5 g/dL (provided haemoglobin drop is related to bleed)
The subcommittee on control of anticoagulation of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis (ISTH) proposed a definition of bleeding complications in non-surgical patients that was recently revisited. Most of the contemporary AF studies have been performed according to this standardized definition. Although the adoption of a single standardized definition would facilitate comparison of bleeding events across studies, it remains to be established whether the proposed ISTH definition is more reliable than other existing definitions for identifying clinically relevant bleeding episodes. Even the ISTH definition suffers from the inclusion of a wide range of events with variable clinical relevance to the patient, ranging from death or severely life-threatening events to ‘laboratory indices of bleeding’ (2 g/dL Hb drop), which may well be a normal variant, for example, in well-hydrated ACS patients undergoing percutaneous coronary interventions (PCI) with a small access site haematoma.

**How to interpret major bleeding rates in clinical practice**

Clearly, there is a need to record major bleeds in order to assess the safety of a new antithrombotic therapy. Especially prior to regulatory approval, counting major bleeds will allow to detect a signal for enhanced bleeding risk early during the course of clinical development of a new antithrombotic regime. On the other hand, many of the events that are counted as major bleeds in large trials are clinically less significant: in addition to life-threatening bleeds, events that cause permanent organ damage, and bleeds requiring acute intervention or operation to stabilize the patient, major bleeds also comprise asymptomatic haemoglobin drop of 2 or 3 g/dL combined with a small access site or nasal bleed. Furthermore, modern management of gastrointestinal bleeds has helped to contain long-term consequences of such bleeds for patients. For decision making in clinical practice, it may therefore be helpful to distinguish major bleeding events into clinically relevant major bleeds and clinically less relevant major bleeds. The former would include life-threatening events, symptomatic intra-cerebral bleeds and other bleeding events resulting in permanent organ damage and bleeds that require an acute operation to stabilize the patients. Clinically less relevant major bleeds would be less acute events, e.g. an asymptomatic haemoglobin drop and bleeding events that result in a temporary cessation of antithrombotic therapy. From a clinical perspective, many bleeding events appear minor, as evidenced by continuous antithrombotic therapy. Clinical decision making may be made easier if such subgroups of major bleeding events were reported in clinical trials.

**Prognostic implications of bleeding**

Despite the varying clinical impact of different subtypes of ‘major’ bleeds, major bleeding events are associated with a several-fold risk of death for up to 1 year compared with non-bleeders, at least in patients with acute coronary syndromes.

Although extensive information regarding the prognostic impact of bleeding in patients with AF is lacking, the mechanisms underlying the adverse prognosis associated with bleeding are likely to be similar (at least in part) to those observed among ACS patients who develop a major bleed. Severe bleeding events may be a marker of adverse outcomes, as well as a cause of poor outcomes.

The short-term adverse prognosis of patients with bleeding events compared with patients without such events may stem not only from the critical location of blood loss (intra-cranial, peri-cardial, and haemothorax) or the development of haemorrhagic shock, but also from the negative impact of transfusions and from the frequent discontinuation of antithrombotic therapy, with the ensuing enhanced risk of thrombo-embolic events. Additionally, in the short term, reduced tissue oxygenation through declining haemoglobin concentrations, increased cardiac work, haemodynamic compromise, and activation of sympathetic, vasoconstrictive and prothrombotic mechanisms may all concur to produce adverse outcomes (Table 3).

Importantly, both the short- and long-term prognoses of patients with bleeding events (even of those who develop minor bleeding events) may relate to an unfavourable cluster of baseline characteristics, typical of ‘high-risk’ patients; indeed, patients with bleeding events are older and with more co-morbidities (e.g. renal failure, hypertension, history of prior bleed, or stroke) compared with non-bleeders. In fact, the CHADS2 score is a valid indicator not only for stroke risk, but also for bleeding risk, and sums the known

<table>
<thead>
<tr>
<th>Study or author, year</th>
<th>Reference</th>
<th>Definition of major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamponade</td>
<td></td>
<td>Bleeding requiring surgical or percutaneous intervention for control (exclude dental/nose/skin/haemorrhoids) or inotropes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. BARC Type 3b bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any transfusion with overt bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overt bleeding plus haemoglobin drop 3 to 5 g/dL</td>
</tr>
<tr>
<td>Type 4 (CABG)</td>
<td>BARC CABG-related bleeding definitions must include the same criteria for fatal bleeding, intra-cranial haemorrhage, need for intervention to control bleeding and the number of transfusions as for BARC non-CABG related bleeding</td>
<td></td>
</tr>
<tr>
<td>Type 5 (Fatal)</td>
<td>Fatal bleeding is bleeding that directly causes death with no other explainable cause. BARC fatal bleeding is categorized as either definite or probable</td>
<td></td>
</tr>
</tbody>
</table>

CABG, coronary artery bypass graft surgery; PLATO, PLATelet inhibition and clinical Outcomes.
Table 3 Factors by which bleeding may negatively impact short- and long-term outcome

<table>
<thead>
<tr>
<th>Short-, mid- and long-term prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Accumulation of risk factors for cardiovascular events in patients with bleeding events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Short- and mid-term prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Critical location, e.g. intra-cranial, peri-cardial, haemothorax</td>
</tr>
<tr>
<td>• Impaired tissue perfusion, e.g. by hypotension, shock, hypoxemia</td>
</tr>
<tr>
<td>• Withdrawal of anti-thrombotic agents, with resultant increased risk of ischaemic complications</td>
</tr>
<tr>
<td>• Activation of sympathetic, vasoconstrictive, and prothrombotic mechanisms</td>
</tr>
<tr>
<td>• Increased cardiac work through increased heart rate and output</td>
</tr>
<tr>
<td>• Negative impact of transfusions, especially of older blood</td>
</tr>
<tr>
<td>• Prolonged hospitalisation and bed rest, with increased risk of venous thrombo-embolism</td>
</tr>
</tbody>
</table>

Table 4 Factors affecting bleeding risk when using oral anticoagulant therapy

<table>
<thead>
<tr>
<th>Intensity of anticoagulation Management modality</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Usual care vs. dedicated anticoagulation clinic or increased monitoring frequency or self management</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age</td>
</tr>
<tr>
<td>• Genetics (may also be assessed by the INR response in the initial period of VKA therapy initiation)</td>
</tr>
<tr>
<td>• Prior stroke</td>
</tr>
<tr>
<td>• History of bleeding</td>
</tr>
<tr>
<td>• Anaemia</td>
</tr>
<tr>
<td>• Co-morbidity (hypertension, renal insufficiency, liver disease)</td>
</tr>
<tr>
<td>Use of concomitant medication or alcohol</td>
</tr>
<tr>
<td>• Antiplatelet agents</td>
</tr>
<tr>
<td>• NSAIDs</td>
</tr>
<tr>
<td>• Medication that affects the intensity of anticoagulation</td>
</tr>
<tr>
<td>• Alcohol abuse</td>
</tr>
</tbody>
</table>

risk factors for cardiovascular events. Thus, the occurrence of any bleeding event identifies individuals as belonging to a high-risk subset. Not surprisingly, the baseline features of patients who bleed largely overlap with those of individuals at high risk of thrombo-embolic events, thereby denoting a general condition of vascular frailty. Intra-cranial and spontaneous bleeds carry worse prognosis than procedure-related or extracranial bleeds.

The Task Force recognizes that there is a need to better understand the causes of adverse outcomes in patients who bleed during OAC (Table 4). This may be approached by analysing existing databases and by prospective ‘real-world’ registries of patients who bleed.

Established bleeding risk factors

Intensity of anticoagulation, management modality, and patient characteristics constitute an important determinant of bleeding risk (Table 4). Drug compliance and maintenance of a therapeutic INR range are other considerations.

Age

Older age, in the majority of studies, has been shown to increase the risk of major haemorrhage. Elderly patients have a two-fold increased risk of bleeding and the relative risk of intra-cranial haemorrhage (in particular at higher INRs) was 2.5 (95% CI 2.3–9.4) in patients >85 years old compared with patients 70–74 years old. In the AFFIRM trial (Atrial Fibrillation Follow-up Investigation of Rhythm Management), the risk of major bleeding increased by ~5% per year of age.

International normalized ratio range

The most important risk factor for haemorrhage is the intensity of the anticoagulant effect (Table 4). Studies indicate that with a target INR of >3.0 the incidence of major bleeding is twofold greater compared to those with a target INR of 2.0–3.0, at least in some patient groups. In studies of patients with prosthetic heart valves, a lower INR target range resulted in a lower frequency of major bleeding and intra-cranial haemorrhage with a similar antithrombotic efficacy. One retrospective analysis of outpatients using warfarin who presented with intra-cranial haemorrhage demonstrated that the risk of this complication doubled for each 1 unit increment of the INR. Not only the target INR but also the actual individual INR is strongly associated with the risk of bleeding.

Time spent in the therapeutic range (TTR) is also a marker of risk. Among individuals randomized to warfarin in the SPORTIF (Stroke Prevention Using an Oral Direct Thrombin Inhibitor in Atrial Fibrillation) trials, those with TTR <60% experienced higher rates of major haemorrhage compared with those with TTR >75%, 3.85%/year vs. 1.58%/year, P < 0.01. A similar trend was found in the ACTIVE W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events). It is likely that this association reflects the increased bleeding risk during times spent with supra-therapeutic INR values.

It has been clearly shown that structured and well-organized management of anticoagulant treatment, e.g. by specialized anticoagulation clinics, results in higher proportions of patients in the therapeutic target range. Point of care testing as well as patient self-management has also been shown to improve TTR compared with conventional care in older studies, but not in a more recent large trial. Careful INR monitoring by experienced personnel, e.g. in anticoagulation clinics, results in similar rates of bleeding and thrombosis as self-monitoring.

Genetic factors affecting vitamin K antagonists metabolism and their antithrombotic effect

Recently, genetic factors have been identified that may affect the risk of bleeding. Common polymorphisms in the cytochrome P450 2C9 gene were found to be associated with slow metabolism of VKAs and (possibly) a higher risk of bleeding. Other genetic factors that may influence the requirement of VKAs are variants in the vitamin K epoxide reductase complex subunit 1 gene (VKORC1).

Indeed, the combined analysis of VKORC1, CYP2C9 SNPs, and age may account for >50% of the individual variability in the warfarin maintenance dosage, and based on this, prediction models of
warfarin maintenance dosage taking into account these individual parameters have been developed.84 While available data from trials suggest that patients carrying such variants require a lower daily dose of VKAs to achieve therapeutic INR values, the clinical relevance of these genetic polymorphisms is still controversial.

Co-morbidities including uncontrolled hypertension, hepatic, and renal insufficiency

History of bleeding and anaemia are risk factors for subsequent bleeding,56,57 being part of various bleeding risk prediction models (see later). Also, anaemia is frequent in patients with renal failure, who are at high risk of bleeding complications when anticoagulated.85

Prior stroke is a potent risk factor for thrombo-embolic stroke in AF, but it is also a risk factor for intra-cerebral haemorrhage.56,57 Other co-morbidities, such as hypertension, renal, or hepatic insufficiency, also significantly increase the risk of bleeding. A systolic blood pressure of 140 mmHg or greater has been shown to increase the risk of both haemorrhagic and ischaemic stroke among patients with AF56,57. A case-control study in 1986 patients on VKAs showed that renal impairment and hepatic disease each independently more than doubled the risk of bleeding.86 These associations were confirmed in the AFFIRM study, in which hepatic or renal disease conferred a two-fold increase in risk (hazard ratio, 1.93; 95% CI, 1.27–2.93).

The AFFIRM investigators also found that heart failure and diabetes increase bleeding risk, with hazard ratios of 1.43 and 1.44, respectively.20 However, diabetes has been a less consistent risk factor for bleeding in other overviews.56,57

Concomitant medications

Another critically important determinant of bleeding risk is the use of concomitant medications, especially antiplatelet drugs. Two meta-analyses, comprising 6 trials with a total of 3874 patients and 10 trials with a total of 5938 patients, found a relative risk of major bleeding when VKAs were combined with aspirin of 2.4 (95% CI 1.2–4.8) and 2.5 (95% CI 1.7–3.7), respectively.87,88 A population-based case-control study confirmed the high risk of upper gastro-intestinal bleeding in patients using VKAs in combination with aspirin and/or clopidogrel.89,90

Non-steroidal anti-inflammatory drugs (NSAIDs) and alcohol abuse are also associated with an enhanced risk of gastro-intestinal bleeding. The combined use of VKAs and NSAIDs may result in an 11-fold higher risk of hospitalization for gastro-intestinal bleeding as compared with the general population.90–92 This risk is not significantly lower when using selective inhibitors of cyclo-oxygenase.2,91,92

Clearly, frailty is an important consideration and biological age rather than calendar age is perhaps a better marker of bleeding risk. Falls may be overstated as a risk factor for bleeding, and based on a decision analysis model, a patient with AF would need to fall 295 times per year for the benefits of stroke prevention with warfarin to be outweighed by the risk of intra-cranial haemorrhage.93

Implications for clinical practice

The assessment of the absolute risk of bleeding in an individual patient may be difficult when using data from published clinical studies. In six pivotal trials that demonstrated the superiority of warfarin over placebo in the prevention of thrombo-embolic complications in patients with AF, 28 787 patients were screened but only 12.6% of these patients were included in the study.94 In a case-control study in 993 patients on VKAs with major bleeding and 993 non-bleeding controls, <70% of patients using VKAs would have been eligible for the clinical trials.95 In the group of patients that presented with haemorrhage, the proportion with any exclusion criteria was considerably greater (40%; 95% CI 37–43%) than in the control group (23%; 95% CI 21–26%). Bleeding risk increased sharply with the number of exclusion criteria: two vs. none increased the risk four-fold (odds ratio, 3.8; 95% CI 2.7–5.2) and three or more vs. none increased the risk 15-fold (odds ratio, 14.9; 95% CI 4.7–46). The fact that many patients were not included in the clinical trials may have a major impact on the external validity of these trials, in particular regarding safety.94

Recent trials of stroke prevention in AF have reported rates of major haemorrhage of 3%/year among patients randomized to warfarin.22,24 Bleeding rates did not differ markedly between open and double-blind trials.94 Rates as high as 7% have been reported in the first year of warfarin therapy among unselected patients with AF in routine practice.29 Hence, in patients not fulfilling the criteria for randomized controlled trials, a more individualized approach may be necessary to weigh the expected risks and benefits of VKA therapy. Furthermore, warfarin-naive patients may carry a higher risk for severe bleeding events than other patients. Taken together, clear risk factors for bleeding in patients using VKAs can be identified. Systematic reviews56,57 have concluded that the following patient characteristics had supporting evidence for being risk factors for anticoagulation-related bleeding complications in AF patients: advanced age, uncontrolled hypertension, history of myocardial infarction or ischaemic heart disease, cerebrovascular disease, anaemia or a history of bleeding, and the concomitant use of other drugs such as antiplatelet agents. The presence of diabetes mellitus, controlled hypertension, and gender were not identified as significant risk factors.

Appreciation of bleeding risk factors will help to inform decision making and will also identify higher risk patients for whom management strategies to mitigate bleeding risk should be implemented.

Bleeding risk stratification and current published bleeding risk schema

Several distinctive clinical prediction rules have been proposed for the assessment of the individual risk for bleeding during OAC in patients with AF, based on a combination of treatment- and person-associated factors.56,57 These prediction rules may help physicians stratify patients into categories of increasing risk of bleeding so as to evaluate the individual risk/benefit ratio of an oral anticoagulant, either prior to starting or during treatment. The characteristics of the available clinical prediction rules specifically addressing AF patients are reported in Table 5.

The modified Outpatient Bleeding Risk Index (mOBR)28 has been prospectively derived and validated28,48 in patients with different indications for OAC, including AF patients.51 Another strength of the mOBR schema was the blinded outcome assessment of bleeding.28 In addition, the settings of the anticoagulation
<table>
<thead>
<tr>
<th>Schema, acronym, author</th>
<th>Reference</th>
<th>Population Design, n, mean (SD) age, % male; indication for anticoagulation; length of follow-up</th>
<th>Definition of major bleeding event adjudication</th>
<th>Calculation of risk score</th>
<th>Bleeding risk classification n (%) patients in each risk category</th>
<th>Major bleeding events by risk category in validation cohort, n (%)</th>
<th>Validated in other cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOBRI Beyth et al. 1998</td>
<td>28</td>
<td>Prospective inception cohort</td>
<td>Overt bleeding that resulted in the loss of ≥2.0 units in ≤7 days, or was otherwise life threatening</td>
<td>Age ≥65 years, previous stroke, GI bleed in last 2 weeks, ≥1 of the following comorbidities (recent MI, haematocrit &lt;30%, creatinine &gt;1.5 mg/dL, or diabetes mellitus) with 1 point for presence of each risk factor and 0 if absent</td>
<td>Low: 0</td>
<td>Cumulative incidence of major bleeding (95% CI) at 3/12/48 months</td>
<td>Aspinall et al.2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Derivation</td>
<td>Intermediate: 1–2</td>
<td>Intermediate: 5 (1–8)/12 (5–19)</td>
<td>Validation—n = 3971, 80.2; AF7 3138 patient years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Certification of risk</td>
<td>High: ≥3</td>
<td>High: 6 (0–17)/30 (0–62)/53 (11–97)</td>
<td>Validation—n = 556, 61 (14): 46.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calculation of risk score</td>
<td>Low: 186 (33.5%)</td>
<td>Low: 1 (0–8)/3 (0–4)/3 (0–8)</td>
<td>Validation—n = 264, 60 (16): 47.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calculation of risk score</td>
<td>Low: 80 (30.3)</td>
<td>Intermediate: 166 (62.9)</td>
<td>Validation—n = 3971, 80.2; AF7 3138 patient years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calculation of risk score</td>
<td>Low: 18 (6.8)</td>
<td>High: 18 (6.8)</td>
<td>Validation—n = 3971, 80.2; AF7 3138 patient years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calculation of risk score</td>
<td>Low: 0–1</td>
<td>Low: 15 (2.1%)</td>
<td>Validation—n = 3971, 80.2; AF7 3138 patient years</td>
</tr>
<tr>
<td>HEMORR2HAGES</td>
<td>52</td>
<td>Retrospective analysis of NRAF cohort</td>
<td>ICD-9-CM codes for major bleeds except those unrelated to antithrombotic therapy</td>
<td>Hepatic or renal disease, ethanol abuse, malignancy, older (aged &gt;75), reduced platelet count, re-bleeding risk, uncontrolled hypertension, anaemia, genetic factors (CYP 2C9 single nucleotide polymorphisms), excessive fall risk, previous stroke/TIA, 1 point for each risk factor present, and 2 points for previous bleed</td>
<td>Intermediate: 2–3</td>
<td>Intermediate: 35 (5.0%)</td>
<td>Validation—n = 3971, 80.2; AF7 3138 patient years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calculation of risk score</td>
<td>High: ≥4</td>
<td>High: 17 (8.8%)</td>
<td>Validation—n = 3971, 80.2; AF7 3138 patient years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calculation of risk score</td>
<td>Low: 717 (44.7%)</td>
<td>Low: 717 (44.7%)</td>
<td>Validation—n = 3971, 80.2; AF7 3138 patient years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calculation of risk score</td>
<td>Low: 694 (43.3%)</td>
<td>Low: 694 (43.3%)</td>
<td>Validation—n = 3971, 80.2; AF7 3138 patient years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calculation of risk score</td>
<td>High: 193 (12.0%)</td>
<td>High: 193 (12.0%)</td>
<td>Validation—n = 3971, 80.2; AF7 3138 patient years</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Methodology</td>
<td>Cohort</td>
<td>Hospitalisation Criteria</td>
<td>Risk Points</td>
<td>Low</td>
<td>Intermediate</td>
</tr>
<tr>
<td>-------</td>
<td>------</td>
<td>-------------</td>
<td>--------</td>
<td>--------------------------</td>
<td>-------------</td>
<td>-----</td>
<td>-------------</td>
</tr>
<tr>
<td>Shireman et al. 2006</td>
<td>2006</td>
<td>Retrospective chart review of NRAF cohort and Medicare data</td>
<td>Hospitalisation within 90 days of hospital discharge following index AF for GI haemorrhage (diagnosis-related group code 174 or 175) or intra-cranial haemorrhage (ICD-9 430–432)</td>
<td>(0.49 × age ≥ 70) + (0.32 × female gender) + (0.58 × remote bleed) + (0.62 × recent bleed) + (0.71 × alcohol/drug abuse) + (0.27 × diabetes) + (0.86 × anemia) + (0.32 × antiplatelet)</td>
<td>Low: ≤ 1.07</td>
<td>Intermediate: &gt; 1.07 to &lt; 2.19</td>
<td>High: ≥ 2.19</td>
</tr>
<tr>
<td>HAS-BLED Pisters et al. 2010</td>
<td>2010</td>
<td>Retrospective analysis of Euro Heart Survey cohort</td>
<td>Requiring hospitalisation and/or causing ↓ Hb ≥ 2g/L, need for blood transfusion that was not a haemorrhagic stroke</td>
<td>Hypertension (uncontrolled SBP &gt; 160 mm Hg), Abnormal renal and/or liver function, Stroke, bleeding history, Labile INR, elderly (age ≥ 65 years), drugs (antiplatelets/NSAIDS)/concomitant alcohol (≥ 8 units/week), with 1 point for the presence of each risk factor (maximum of 9 points)</td>
<td>Low: 0–1</td>
<td>Intermediate: 2</td>
<td>High: ≥ 3</td>
</tr>
<tr>
<td>Fang et al. 2010 (in abstract form only)</td>
<td>2010</td>
<td>Retrospective analysis of the ATRIA cohort</td>
<td>Anaemia, severe renal disease (GFR &lt; 30 mL/min or dialysis dependent), age ≥ 75 years, previous bleed, hypertension, with 1 point each for presence of previous bleed and hypertension, 2 points for age ≥ 75, and 3 points each for presence of anaemia and renal disease</td>
<td>Low: 0 to 3</td>
<td>Moderate: 4</td>
<td>Moderate: 5–10</td>
<td>Moderate: 6–10</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; ATRIA, AnTicoagulation and Risk Factors In Atrial fibrillation; DVT, deep vein thrombosis; GFR, glomerular filtration rate; GI, gastrointestinal; HAS-BLED, Hypertension, Abnormal renal &/or liver function, Stroke, Bleeding history, Labile INR, Elderly (age ≥ 65 years), Drugs (antiplatelets/NSAIDS)/concomitant alcohol (≥ 8 units/week); Hb, haemoglobin; HEMORR2HAGES, Hepatic or renal disease, Ethanol abuse, Malignancy, Older (aged ≥ 75), Reduced platelet count, Re-bleeding risk, uncontrolled Hypertension, Anaemia, Genetic factors (CYP 2C9 single nucleotide polymorphisms), Excessive fall risk, previous Stroke/TIA; ICD-9-CM, international classification of disease-9th version, clinical modification; ICU, intensive/critical care stay; INR, international normalised ratio; MI, myocardial infarction; mOBRI, modified Outpatient Bleeding Risk Index; NRAF, National Registry of Atrial Fibrillation; NSAIDs, non-steroidal anti-inflammatory drugs; OAC, oral anticoagulation; OBRI, Outpatient Bleeding Risk Index; PE, pulmonary embolism; RCT, randomised controlled trial; SBP, systolic blood pressure; TIA, transient ischaemic attack; VTE, venous thrombo-embolism.

*Not reported.
control were the primary care physician or a pharmacist-run anticoagulation clinic, demonstrating derivation and validation in ‘real-life’ AF patients.

All the clinical prediction rules include age as a risk factor for bleeding, but each schema employs a different cut-off. In the mOBR, age ≥ 65 years scores one point. Given the advanced age of most AF patients, the majority of the evaluated patients would be assigned at least to the intermediate-risk classification (1–2 points) using the mOBR, which in the validation cohort was associated with an incidence of major bleeding of 5, 8, and 12% after 3, 12, and 48 months of treatment, respectively. In the independent validation of the mOBR among elderly AF patients by Aspinall et al., the mOBR discriminated significantly (p < 0.001) between those in the intermediate- and high-risk categories for major bleeding.

The remaining prediction schemas have a retrospective design, based on the review of data from the National Registry of Atrial Fibrillation, the same Registry plus Medicare data, the Heart Heart Survey cohort, and the Anticoagulation and Risk factors in Atrial fibrillation (ATRIA) study. The retrospective design may represent a limitation of the validity of these schemas since a potential loss of patients with complications in the early phase of treatment cannot be excluded.

The HEMORR\textsuperscript{H}AGES (Hypertensive or renal disease, Ethanol abuse, Malignancy, Older (aged > 75), Reduced platelet count, Re-bleeding risk, uncontrolled Hypertension, Anaemia, Genetic factors (CYP2C9 single nucleotide polymorphisms), Excessive fall risk, previous Stroke/TIA) score, which considers age > 75 years as a condition at risk, includes factors such as CYP2C9 single nucleotide polymorphism, which is rarely investigated, and reduced platelet count and anaemia that are not easily available, whereas important factors such as antiplatelet treatment or other co-medications are not included. The rate of patients at high risk of bleeding was 12.0%. The cumulative incidence of major bleeding by risk category in the validation cohort was 2.1, 5.0, and 8.8% patient-years in the low, intermediate, and high risk categories, respectively.

The schema by Shireman et al. incorporates eight risk factors for bleeding, including female gender and an antiplatelet treatment, as well as age. There was a relatively short (90 days) follow-up period and the rate of patients at a high risk was very low (3.4%). This schema requires a complex mathematical calculation to derive the individual patient bleeding risk score, thereby limiting its applicability. In general, some important factors related to bleeding risk, such as poor quality anticoagulation control and the presence of NSAIDs as concomitant medication, have not been included in four of the aforementioned schemas. Reliable ascertainment of aspirin therapy given its non-prescription status is problematic. Moreover, no blinded outcome assessment was conducted and no indication of the setting of anticoagulation control was provided in either the HEMORR\textsuperscript{H}AGES or Shireman et al. studies.

More recently, a new clinical prediction rule for bleeding risk evaluation in AF patients, HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or pre-disposition, Labile INR, Elderly (≥ 65), Drugs/alcohol concomitantly), has been proposed by Pisters et al. The HAS-BLED score demonstrated a good predictive accuracy in the overall cohort (c-statistic 0.72) but performed particularly well in predicting bleeding risk when only antiplatelet therapy (c-statistic 0.91) or no antithrombotic therapy at all (c-statistic 0.85) were used. In the SPORTIF III and V cohorts, the HAS-BLED score was a good predictor of bleeding events among warfarin-naïve patients at baseline (c-statistic 0.66) and those patients receiving warfarin plus aspirin (c-statistic 0.60). The HAS-BLED score has been incorporated into the 2010 ESC guidelines for the management of AF2 and the Canadian guidelines. Preliminary data on a bleeding score from the ATRIA study have been presented in abstract form. This is a weighted score containing elements already contained within the HAS-BLED score, and gives 3 points for anaemia, 3 points for severe renal disease, 2 points for age ≥ 75, and 1 point each for prior bleeding and hypertension; essentially including similar components as the scores discussed above, but assigning a weight to the various risk factors (thus making it more complicated). The c-statistic for the continuous risk score was 0.74, but on collapsing points into a three-category risk index, the annual major haemorrhage rate was 0.8% in the low-risk group (0–3 points), 2.6% in medium risk (4 points), and 5.8% in high risk (5–10 points).

In summary, the four available published bleeding risk prediction rules demonstrate wide variation in the proportions of patients determined to be at low, intermediate, and high risk of bleeding, due to differences in the risk factors comprising each schema. Further, the four published schemas do not share a common definition of major bleeding and the length of follow-up of the cohorts differs between studies, which affects the event rate (but this can be easily corrected for). Despite the limitations of the available bleeding risk schema, they do offer a starting point for physicians to consider bleeding when initiating and/or continuing long-term OAC in AF patients, and to think about potentially correctable risk factors, for example, in the case of the HAS-BLED score, by treating uncontrolled blood pressure, improving anticoagulation control (lable INRs (if on VKAs) or stopping concomitant aspirin use.

Bleeding risk stratification should be considered as an integral part of anticoagulation treatment decision making, and this group recommends the use of the HAS-BLED score, in keeping with international guideline recommendations.

Patient values and preferences

Patients’ beliefs about their health, the medications and healthcare they receive are important determinants of whether or not they accept recommended treatments and adhere to therapy. Patients often have perceptions about VKAs, including the inconvenience of dosing adjustments, the need for daily medication and regular blood tests to monitor INR levels, reduction/abstinence from alcohol, dietary restrictions, the risk of minor and major bleeding, and under-appreciation or lack of knowledge regarding the risk of stroke that may influence their acceptance of warfarin and their ability to maintain good INR control. On the other hand, patients may feel protected by taking VKAs. Thus, patients’ preferences and their beliefs about their health are fundamental in determining whether anticoagulant treatment, particularly with warfarin, is adopted in the first place and maintained long term. Changes in health-care policy emphasize the need to achieve, and benefits of, patient involvement in the management of their own health and...
incorporation of patients’ preferences for anti-thrombotic therapy should be considered in the decision-making process.

To date, 15 studies have examined patient preferences for antithrombotic therapy in AF patients \(^{103–113}\) and in patients at high risk of developing AF, \(^{114–118}\) although one study is yet to report its results \(^{118}\) (Table 6). A variety of decision aids, such as audio-booklets \(^{108,112,116,117}\) decision boards \(^{105,108,110,114,115,117}\) (see Figure 1) and interactive videos/computer programs \(^{103,104,106,113,117}\) have been designed to enable patients to participate in the decision-making process with regard to their antithrombotic therapy, to ensure that treatment choices are consistent with their personal preferences, values, and beliefs. These decision aids provide written, visual, and verbal information on the likelihood of clinically important outcomes, such as stroke and major haemorrhage associated with antithrombotic therapy, present the treatment options (currently warfarin, aspirin, or no antithrombotic therapy), and ask patients to indicate their treatment choice.

Patients appear to trade-off the risks associated with antithrombotic treatment in order to avoid death. \(^{117,119}\) Overall, these studies appear to suggest that patients place greater emphasis on avoidance of stroke and are willing to accept a higher risk of bleeding to achieve this, although this may represent a lack of patient understanding of the disability associated with major bleeding, particularly intracranial haemorrhage. However, other studies suggest that the decision to accept OAC is attenuated by inclusion of information on intra-cranial haemorrhage risk, indicating that some patients place a greater importance on avoiding an event caused by anti-thrombotic therapy (i.e. major bleed) than a stroke caused by choosing not to take such therapy. \(^{110,115}\) Presenting patients with decision aids makes them more likely to be able to make a decision regarding antithrombotic therapy and improves their knowledge of AF and the need for such therapy. \(^{105,108,113,116,117}\) However, research suggests that the use of decision aids results in fewer patients choosing to take OAC \(^{108–110,113,115,117}\) and that incorporating patient preferences would lead to fewer patients choosing to take oral anticoagulants than the current guidelines would recommend. \(^{110,113}\)

It is hard to draw firm conclusions from the available studies as the sample sizes are often small, typically \(\leq 100\) patients, \(^{103–106,109–111,114,115,117}\) and there is significant heterogeneity between the studies (methods employed to elicit preferences, patients’ education, risks employed; inclusion of AF patients and those without AF, etc.). It is important to distinguish between

### Table 6 Patients’ preferences for antithrombotic therapy among atrial fibrillation patients and those at high risk of developing atrial fibrillation

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Study population. Number participants, mean (SD) age, years</th>
<th>Study design</th>
<th>Method of eliciting patient preferences</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gage et al. 1995, USA (^{103})</td>
<td>(n = 57; 70^a)</td>
<td>Cross-sectional, Markov decision model</td>
<td>Interviews, computer-based TTO</td>
<td>• High utility for daily aspirin (0.998) or warfarin (0.988) • Disutility associated with severe stroke (0.39) or extra-cranial haemorrhage (0.76)</td>
</tr>
<tr>
<td>Gage et al. 1996, USA (^{104})</td>
<td>(n = 70; 70.1 (7.3))</td>
<td>Cross-sectional, longitudinal</td>
<td>Interviews, computer-based TTO</td>
<td>• High utility for daily aspirin (1.0) or warfarin (0.997) • Disutility associated with moderate-to-severe stroke (0.07 and 0.0, respectively)</td>
</tr>
<tr>
<td>Man Son Hing et al. 1996, USA (^{105})</td>
<td>(n = 64; 68.9 (9.0))</td>
<td>RCT</td>
<td>Interviews, PTOT</td>
<td>• 52% willing to take warfarin for absolute risk reduction (\leq 1/100) • Disutility associated with stroke (^b)</td>
</tr>
<tr>
<td>Gage 1998, USA (^{106})</td>
<td>(n = 69; 70^a)</td>
<td>Cross-sectional, Markov decision model</td>
<td>Interviews, computer-based TTO</td>
<td></td>
</tr>
<tr>
<td>Sudlow et al. 1998, UK (^{107})</td>
<td>(n = 176; \geq 50) years (^a)</td>
<td>Cross-sectional</td>
<td>Questionnaire and interview</td>
<td>• 89% willing to take warfarin to prevent stroke • Proportion choosing warfarin greater in control group • PTOT ↑ ability to make decision choice</td>
</tr>
<tr>
<td>Man Son Hing et al. 1999, USA (^{108})</td>
<td>(n = 287; ) control 67, intervention 65(^a)</td>
<td>RCT</td>
<td>PTOT vs. usual care</td>
<td></td>
</tr>
<tr>
<td>Howitt and Armstrong 1999, UK (^{109})</td>
<td>(n = 56^a)</td>
<td>Cross-sectional</td>
<td>‘Qualitative’ interview, PTOT</td>
<td>• 20 choose not to take warfarin despite knowledge of stroke risk</td>
</tr>
<tr>
<td>Protheroe et al. 2000, UK (^{110})</td>
<td>(n = 97; 77 (3.9))</td>
<td>Observational, Markov decision model</td>
<td>Individualised decision analysis</td>
<td>• 61% preferred warfarin based on individualised stroke risk</td>
</tr>
</tbody>
</table>

Continued
studies of patients with AF and without AF as preferences may differ markedly between patients with AF who need to decide about lifelong therapy and those in a hypothetical situation who need to decide, if they had AF, which treatment they would choose. Patients’ previous or current antithrombotic use and their experiences (satisfaction with the antithrombotic regimen, adverse events, etc.) may dramatically influence choice, since many studies enrolled large proportions of people either currently taking warfarin or aspirin or those with previous experience of antithrombotic therapy. Patients tend to choose their current therapy over other treatment choices to prevent cognitive dissonance (i.e. distress/conflict between preferences and actual treatment choice). Further studies need to elicit patient preferences for antithrombotic treatment in warfarin-naive AF patients, with and without previous stroke, to remove these potential biases. In addition, perceptions of risk can be altered by the way in which information is presented—the effect of ‘framing’.

### Table 6 Continued

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Study population. Number participants, mean (SD) age, years</th>
<th>Study design</th>
<th>Method of eliciting patient preferences</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson et al. 2000, UK</td>
<td>n = 57; 73</td>
<td>Cross-sectional, Markov decision model</td>
<td>Interview, standard gamble</td>
<td>• High utility for daily warfarin (0.94) • Disability associated with severe stroke (0.19)</td>
</tr>
<tr>
<td>McAlister et al. 2005, USA</td>
<td>n = 434; 72</td>
<td>Cluster randomised trial</td>
<td>Self-administered, PTOT</td>
<td>• PTOT ↑ patient ability to choose ‘appropriate’ antithrombotic therapy in short-term only</td>
</tr>
<tr>
<td>Thomson et al. 2007, UK</td>
<td>n = 109; 73 (6)</td>
<td>RCT</td>
<td>Computerised decision aid vs. guideline evidence</td>
<td>• Computerised decision aid led to significantly fewer patients choosing warfarin</td>
</tr>
<tr>
<td>Devereaux et al. 2001, Canada</td>
<td>n = 61; aged 40–74 years</td>
<td>Prospective observational</td>
<td>Interview, PTOT</td>
<td>• 74% willing to take warfarin if just one stroke in 100 patients were prevented over 2 years • 57% willing to accept 22 extra bleeds in 100 patients over a 2-year period on warfarin • Most patients willing to take aspirin if it prevented just 1 stroke in 100 patients over 2 years</td>
</tr>
<tr>
<td>Fuller et al. 2004, UK</td>
<td>n = 81; 81</td>
<td>Cross-sectional</td>
<td>Qualitative interview and questionnaire, PTOT</td>
<td>• Avoidance of stroke paramount • &gt;50% would decline warfarin when presented with stroke risk information plus increasing ICH risk • Need for daily tablets, regular blood tests, and restrictions on alcohol, reduced number willing to take warfarin slightly</td>
</tr>
<tr>
<td>Man Son Hing et al. 2002, Canada</td>
<td>n = 198; 71 (7)</td>
<td>RCT</td>
<td>Qualitative vs. quantitative, PTOT</td>
<td>• Patients more likely to choose aspirin • Patients at moderate-stroke risk more likely to choose warfarin • No significant difference in treatment choice between groups</td>
</tr>
<tr>
<td>Holbrook et al. 2007, Canada</td>
<td>n = 98; 73.6 (6.1)</td>
<td>RCT</td>
<td>Interview, decision board vs. decision booklet with audiotape vs. interactive computer program</td>
<td>• When treatment names were blinded, 40% chose warfarin, 42% chose aspirin and 18% no treatment • Unblinding of treatment led to fewer people choosing warfarin or no treatment • Most people chose aspirin</td>
</tr>
<tr>
<td>Alonso-Coello et al. 2008, Spain</td>
<td>n ≥ 96; ≥ 60 years</td>
<td>Cross-sectional</td>
<td>Interview, PTOT and visual analogue scale</td>
<td>• Ongoing study data not yet available</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; SD, standard deviation; UK, United Kingdom; USA, United States of America; ICH, intra-cranial haemorrhage; PTOT, probability trade-off technique; RCT, randomised controlled trial; TTO, time-trade off; ↑, increased; ↓, decreased.

*aNot reported.

*bBased on data from only 14 patients.
persuading someone to take a ‘risky’ option, such as treatment, than negative framing (i.e. the chances of death). There is also tremendous disparity in perceptions of the impact of warfarin therapy on the lives of AF patients and this may influence the acceptance of such therapy, with many physicians tending to underestimate the level of patients’ satisfaction, whereas most patients report that warfarin did not precipitate any significant changes in their day-to-day lives other than minor inconveniences (such as regular blood tests, adjusting warfarin dose, and dietary restrictions) that they are willing to accept.

The novel OACs (direct thrombin inhibitors and factor Xa inhibitors) that do not appear to require regular monitoring, unlike VKA therapy, with few drug, food, and alcohol interactions, suggest that OAC will be available to a wider range of people in the future. It is conceivable that some patients will be more accepting of new OACs but we do not currently have data on the impact of such therapy on patients’ values and preferences.

In summary, patients’ preferences for antithrombotic treatment are largely influenced by the type and format of information provided to the patient by the care provider (physician, nurse, and other healthcare professionals), their level of education and understanding of the consequences of such treatment, and their previous experiences of antithrombotic therapy. Stroke is the most feared complication that patients wish to avoid, but bleeding risk with treatment attenuates the proportion of patients willing to take antithrombotic therapy. Patients need clear, simple, and individualized information (presented visually, verbally, and in writing) on their need for antithrombotic therapy and the potential complications.

Special situations with additional bleeding risk considerations

Periablation

Catheter ablation carries a small but relevant risk of severe bleeding, ~0.5% in older series, associated with vascular access—often with relatively large diameter sheaths and peri-interventional anticoagulation, increasing when ablation is performed in the left atrium or left ventricle. Interestingly, bleeding events do not

---

Figure 1  Example of a probability trade-off decision aid (reproduced from Man Son Hing et al. JAMA 1999;282:738, with permission. Copyright © (1999) American Medical Association. All rights reserved).
appear to be related to pre- and peri-procedural antithrombotic therapy (aspirin, VKAs, or others). The available data suggest that bleeding events during or shortly after catheter ablation procedures are largely due to mechanical factors such as vascular access, transseptal puncture, and the ablation lesions themselves.

Catheter ablation also carries a risk for thrombotic events to the scars created in the endocardial walls. Furthermore, an increasing number of patients undergoing catheter ablation are at long-term risk for embolic stroke and therefore require continuous OAC, e.g., most patients with AF or atrial flutter. Right-sided ablation procedures carry a relatively low risk of peri-procedural thrombotic events, and venous access required for such procedures appears to be securable without major bleeding risk when anticoagulation is continued using VKAs, at least in a relatively small series. Continuation of VKA therapy even demonstrated a trend towards less minor bleeding events.

Catheter ablation for AF combines the difficulties related to bleeding (from transseptal puncture and requirement for anticoagulation in many patients) and stroke risk (left atrial lesions, long periods with foreign material in the left atrium, and often long endocardial lesions in already diseased atria). The stroke and transient ischaemic attack (TIA) rate is 1% in recent surveys, while bleeding events occur at 1% for cardiac tamponade and 1–2% for access site bleeds. To avoid bleeding complications and to allow rapid adaptation of antithrombotic regimens, a consensus document from EHRA in 2008 recommended stopping warfarin 4–5 days before the ablation procedure and bridging with heparin.

In a large population of 3052 patients with continuation of VKA therapy at a therapeutic INR at the time of AF ablation without the use of heparin [unfractionated heparin (UFH) or low molecular weight heparin (LMWH)] for bridging, 1 patient had a haemorrhagic stroke but recovered completely and bleeding complications occurred in 34 (1.11%) patients. Major haemorrhagic complications (tamponade, haematomas requiring intervention, and necessity for transfusion) occurred in 10 (0.33%) patients. In a case-control analysis, no significant difference in terms of vascular events or bleeding was detected between patients with a therapeutic INR and the control group with normal INR. Thus, uninterrupted OAC is a potential alternative to strategies that use bridging with heparin or LMWH. In summary, recent data suggest that continuation of OAC during catheter ablation procedures for AF may be safe with respect to bleeding events and may help to prevent peri-procedural strokes.

A higher complication rate has been reported in the elderly (>65 years old) than in young patients undergoing electrophysiological study (2.2 vs. 0.5%) or radiofrequency ablation (6.1 vs. 2.0%). The incidence of vascular complications depends on the type of vascular access (arterial, venous, or both), site of vascular access (i.e., femoral vs. subclavian or jugular), number of introduced catheters, length of the procedure, patient profile (i.e., obesity and baseline coagulation parameters), type of anticoagulation used, management of catheterization site during the procedure (i.e., flush) and afterwards (immediate vs. delayed catheter removal, duration and strength of compression, and the use of protamine), and operator experience. The introduction of two sheaths through one puncture site probably increases the risk of haematoma, as does the use of wide-calibre sheaths for several simultaneous catheters.

The issue of bleeding with anticoagulation and catheter ablation is increased for patients treated with intra-coronary stents and with antiplatelet agents, such as clopidogrel and aspirin, which cannot be antagonized. For the introduction and manoeuvring of sheaths and catheters, the risk of peripheral bleeding or complications when using aspirin and clopidogrel is low. Additional use of effective UFH adds to the risk of bleeding. There are no relevant data in the literature on the specific question of the management of cardiac tamponade when the patient is on aspirin and clopidogrel. If life-threatening bleeding occurs, platelet transfusions may help.

The risk of perforation in catheter ablation is extremely low except in the ablation of AF, which carries higher incidences of tamponade, where tamponade is the cause of approximately half of the procedure-related deaths. It can be assumed that bleeding is more severe and more difficult to be managed when the patient is on aspirin and clopidogrel.

Most guidelines recommend continued anticoagulant therapy for 2–3 months following an AF ablation in all patients regardless of stroke risk factors. The optimal duration of this therapy has not been clearly established. Owing to the risk of relapse, the EHRA and ESC guidelines recommend that anticoagulation should be continued long term as per the original indication in subjects with stroke risk factors. This is in line with current recommendations for AF and with the observation that AF tends to recur in many patients, including late recurrences in patients after AF ablation.

**Peri-devices (implantable cardioverter-defibrillator, pacemakers)**

It may be necessary to interrupt oral anticoagulant therapy for elective implantation or replacement of a pacemaker or an implantable cardioverter defibrillator (ICD), although smaller procedures can often be performed without interrupting anticoagulation. In patients with mechanical prosthetic heart valves, it may be appropriate to substitute UFH or LMWH to prevent thrombosis. In patients with AF who do not have mechanical valves, however, based on extrapolation from the annual rate of thromboembolism in patients with non-valvular AF, it was the consensus of the Task Force for the 2010 ESC guidelines that anticoagulation may be interrupted temporarily for procedures that carry a risk of bleeding, such as ICD or pacemaker implantation, without substituting heparin. In high-risk patients (particularly those with prior stroke, TIA, or systemic embolism), UFH or LMWH may be administered. In the 2008 American College of Chest Physicians (ACCP) guidelines, bridging is ‘suggested’ for patients with a CHADS2 score of 3 or 4 (considered to be at moderate risk of thromboembolism after interruption of antithrombotic therapy) and ‘recommended’ for those with a CHADS2 score of 5 or 6 (considered at high risk, i.e., >10% risk per year). It is possible that such operations can in part be performed without interruption of anticoagulation, as for vascular procedures.

The use of LMWH instead of UFH in patients with AF is based on extrapolation from venous thromboembolic disease states and from limited observational studies or trials. LMWH has several pharmacological advantages over UFH including a longer half-life, more predictable bioavailability, and a predictable antithrombotic response based on body weight, which permits fixed-dose treatment.
without laboratory monitoring, except under special circumstances such as obesity, renal insufficiency, or pregnancy. Treatment with LMWH is associated with a lower risk of heparin-induced thrombocytopenia than treatment with UFH. The favourable properties of LMWH may simplify the treatment of AF in acute situations and may shorten the need for hospitalization. However, excess dosing of LMWH should be avoided in this vulnerable population (elderly and with frequent subclinical kidney impairment).

Haematoma in the region of the generator pocket mainly occurs in patients who are taking antiplatelet or anticoagulant medication. Haematoma formation after implantation remains rare among those who are anticoagulated with a rate that may be similar to that in patients with a normal INR. Indeed, there are probably more patients with haematoma on dual-antiplatelet therapy (incidence up to 20%) than on warfarin therapy (~5–10%). Pocket revision for evacuation may be needed in 20–50% of patients with this complication. In patients with non-valvular AF, post-operative high-dose heparinization or post-operative LMWH bridging substantially increases the haematoma rate (10–20 vs. 2–8%) without reducing the rate of arterial embolism within the first month after implantation.

In a systematic review of the literature including eight studies on the peri-operative management of anticoagulation in patients having implantation of a pacemaker or ICD, a strategy involving bridging anticoagulation with therapeutic-dose heparin was associated with an incidence of pocket haematoma of 12–20%, while a strategy involving peri-operative continuation of a coumarin was associated with an incidence of pocket bleeding of 2–7%. The incidence of thrombo-embolic events was 0–1%, irrespective of the peri-operative anticoagulation strategy used.

In a recent prospective randomized study including patients with high risk of thrombo-embolic events in whom 80% had AF, implant of devices while maintaining OAC was as safe as bridging with heparin infusion and allowed a significant reduction of in-hospital stay. When drainage systems are used, device implantation appears to be safe and can be performed without significantly increased risk of clinically relevant haematoma in patients on continued dual-antiplatelet therapy.

Thus, it has been recommended that for such implantations treatment be interrupted pre-operatively and replaced by heparin only if needed. If that is not feasible and implantation must be performed under anticoagulant (whether maintaining OAC or bridging with heparin) and/or antiplatelet therapy (see the section Patients with ACS and/or requiring PCI/stents), the procedure should be carried out by an experienced operator who will pay close attention to haemostasis in the area of the generator pocket.

**Acute coronary syndromes and coronary angiography/ intervention**

Several factors associated with coronary angiography or PCI bear an increased bleeding risk in patients with a need for OAC (for a detailed review see ). These include: ‘triple therapy’ using an oral anticoagulant and dual platelet inhibition, most often aspirin and clopidogrel; factors prolonging the duration of combined antithrombotic therapy (e.g. use of drug-eluting stents (DES)); OAC, when compared with non-anticoagulated patients; the additional use of a GPIIb/IIIa inhibitor (GPI; e.g. in bailout situations in elective patients or in very high-risk ACS patients); left main or three-vessel disease; older age (e.g. >75 years); female gender; smoking; chronic kidney disease; and high INR value (>2.6).

Some measures have been taken to reduce this increased bleeding risk: radial instead of femoral access was associated with fewer access site bleeding events in ‘all-comers’. The use of femoral closure devices, although believed to reduce bleeding risk when compared with manual compression, was not associated with reduced bleeding events.

Owing to the lack of prospective randomized investigations in this field, a group of experts recently published recommendations, which in the majority are level C, i.e. largely based on expert opinion (Table 7).

Our recommendations can be summarized as follows: (i) avoid the use of DES for patients who require triple antithrombotic therapy; (ii) when OAC is given in combination with clopidogrel and/or low-dose aspirin, the intensity must be carefully regulated, with a target INR of 2.0–2.5; and (iii) in the case of combined antithrombotic strategies, gastric protection is recommended at least for the duration of combination therapy.

In elective PCI for patients with chronic stable coronary disease, DES, which require a more prolonged antithrombotic combination therapy compared with bare metal stents (BMS), should be avoided or strictly limited to those clinical and/or anatomical situations, such as long lesions, small vessels, diabetes, etc., where a significant benefit is expected as compared with BMS. Triple therapy (OAC, aspirin, and clopidogrel) should be given for the duration and at the dosages shown in Table 7. After implantation of a BMS, clopidogrel needs to be given in combination with OAC plus aspirin only for 1 month after implantation, but at least 3 months after the use of a ‘-limus’ (sirolimus, everolimus, and tacrolimus) eluting stent and at least 6 months after a paclitaxel-eluting stent. For OAC patients at moderate-high risk of thromboembolism, an uninterrupted anticoagulation strategy can be followed, and radial access can be used as the first choice even during therapeutic anticoagulation (INR 2.0–3.0).

In patients presenting with NSTE-ACS (including unstable angina and non-ST elevation myocardial infarction [NSTEMI]) dual-antiplatelet therapy with aspirin plus clopidogrel (or other P2Y12 receptor blockers) is recommended for 12 months. Those with AF and a moderate-high risk of stroke should also receive or continue anticoagulation therapy. The majority of these patients will undergo cardiac catheterization and/or PCI with/without stenting. Again DES should be avoided or be strictly limited to those clinical and/or anatomical situations, such as long lesions, small vessels, or diabetes. Given the risk of bleeding with combination antithrombotic therapies, it may be prudent to temporarily stop OAC, and administer short-acting antithrombins or GPs only if the INR is ≤2. However, in anticoagulated patients at very high risk of thrombo-embolism, an uninterrupted strategy of OAC can be followed and radial access can be used as the first choice even during therapeutic anticoagulation (INR 2.0–3.0).

For longer-term management after an acute event, triple therapy (OAC, aspirin, and clopidogrel) should be used in the mid-term (3–6 months), or longer in selected patients at low bleeding risk (Table 7).
In patients with acute STEMI referred for primary PCI, usually unfractionated heparin or bivalirudin is used as an anticoagulant agent in combination with dual-antiplatelet therapy, but their use, however, should be ideally limited to patients with a known INR of ≤2. The use of more effective ADP receptor blockers in this setting (prasugrel, ticagrelor) may further increase peri-interventional bleeding rates. Accordingly, the additional use of GPIs in patients on OAC should be considered only in rare bailout situations and should not be part of a routine procedure. Also, potent P2Y12 inhibitors (prasugrel and ticagrelor) should not be used in combination with VKA until more data are available, unless there is an urgent clinical need. Again, radial access for primary PCI is probably the best option to avoid procedural bleeding in patients on OAC, depending on operator expertise and operator expertise and

---

Table 7 Recommended antithrombotic strategies following coronary artery stenting in patients with atrial fibrillation at moderate-to-high thrombo-embolic risk (in whom oral anticoagulation therapy is required)

<table>
<thead>
<tr>
<th>Haemorrhagic risk</th>
<th>Clinical setting</th>
<th>Stent implanted</th>
<th>Anticoagulation regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low/intermediate risk</td>
<td>Elective</td>
<td>Bare metal</td>
<td>1 month: triple therapy of VKA (INR 2.0–2.5)+aspirin ≤100 mg/day+Clopidogrel 75 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Up to 12th month: combination of VKA (INR 2.0–2.5)+aspirin ≤100 mg/day+Clopidogrel 75 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lifelong: VKA (INR 2.0–2.5) alone</td>
</tr>
<tr>
<td>Elective</td>
<td>Drug eluting</td>
<td>3 (olimus group) to 6 (palixial) months: triple therapy of VKA (INR 2.0–2.5)+aspirin ≤100 mg/day+Clopidogrel 75 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Up to 12th month: combination of VKA (INR 2.0–2.5)+aspirin ≤100 mg/day+Clopidogrel 75 mg/day</td>
</tr>
<tr>
<td>ACS</td>
<td>Bare metal/drug eluting</td>
<td>6 months: triple therapy of VKA (INR 2.0–2.5)+aspirin ≤100 mg/day+Clopidogrel 75 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lifelong: VKA (INR 2.0–2.5) alone</td>
</tr>
<tr>
<td>High</td>
<td>Elective</td>
<td>Bare metal</td>
<td>2–4 weeks: triple therapy of VKA (INR 2.0–2.5)+aspirin ≤100 mg/day+Clopidogrel 75 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lifelong: VKA (INR 2.0–3.0) alone</td>
</tr>
<tr>
<td>ACS</td>
<td>Bare metal</td>
<td>4 weeks: triple therapy of VKA (INR 2.0–2.5)+aspirin ≤100 mg/day+Clopidogrel 75 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lifelong: VKA (INR 2.0–3.0) alone</td>
</tr>
</tbody>
</table>

Gastric protection with a proton pump inhibitor (PPI) should be considered where necessary. ACS, acute coronary syndrome; AF, atrial fibrillation; INR, international normalized ratio; VKA, vitamin K antagonist.

In patients with acute STEMI referred for primary PCI, usually unfractionated heparin or bivalirudin is used as an anticoagulant agent in combination with dual-antiplatelet therapy, but their use, however, should be ideally limited to patients with a known INR of ≤2. The use of more effective ADP receptor blockers in this setting (prasugrel, ticagrelor) may further increase peri-interventional bleeding rates. Accordingly, the additional use of GPIs in patients on OAC should be considered only in rare bailout situations and should not be part of a routine procedure. Also, potent P2Y12 inhibitors (prasugrel and ticagrelor) should not be used in combination with VKA until more data are available, unless there is an urgent clinical need. Again, radial access for primary PCI is probably the best option to avoid procedural bleeding in patients on OAC, depending on operator expertise and operator expertise and
preference. The use of DES should be avoided. Long-term treatment after primary PCI follows similar recommendations to those in patients with NSTE-ACS (Table 7).

Surgical procedures and bridging therapy

Dual-antiplatelet therapy with aspirin and clopidogrel is a well-established strategy to prevent thrombotic complications in patients with high platelet reactivity following plaque rupture in ACS or PCI. Current practice guidelines for antiplatelet patients with high platelet reactivity following plaque rupture in established strategy to prevent thrombotic complications in Dual-antiplatelet therapy with aspirin and clopidogrel is a well-

Withdrawal of oral-antiplatelet drugs may cause a ‘rebound effect’ associated with the clustering of thrombotic events. Importantly, patients requiring early surgery after coronary artery stenting face an up to 30% incidence of in-hospital major adverse cardiac events. Although oral-antiplatelet therapy is associated with both short- and long-term clinical efficacy, platelet inhibition, especially when combined with anticoagulant therapy, carries a substantial risk of in-hospital and long-term bleeding and may be a particular limitation in patients presenting for cardiac and non-cardiac surgery. The risk of major bleeding has been demonstrated to be particularly pronounced in ACS patients treated with prasugrel, as compared with clopidogrel. Ticagrelor is an oral, reversible and more potent P2Y antagonist than clopidogrel and has shown better efficacy with a comparable bleeding risk including coronary artery bypass graft surgery (CABG)-related bleeding; however, similar to prasugrel, there was a statistically significant increase in spontaneous severe bleeding rate.

Patients on dual-antiplatelet therapy

Management of patients undergoing dual-antiplatelet therapy who are referred for surgical procedures depends on the urgency of the situation and the thrombotic and bleeding risk of the individual patient. Many surgical procedures are not immediately necessary and should be delayed until combination antithrombotic treatment is no longer necessary. If surgery, however, cannot be delayed, most surgical procedures can be performed under dual-antiplatelet therapy or at least under acetyl salicylic acid (ASA) alone with an acceptable rate of bleeding; a multidisciplinary approach is required (cardiologist, anesthesiologist, haematologist, and surgeon) to determine the patient’s risk and choose the best method of treatment. The assessment of these patients requires a balance between the risk of thrombo-embolic events such as stent thrombosis or stroke, and bleeding risk. Those at ‘high risk’ for thrombotic events include those with any stent <6 weeks; DES <6–12 months; NSTEMI < 6 weeks; and STEMI < 12 months. Those at ‘moderate risk’ include those with a BMS > 6 weeks, a DES > 12 months, and those presenting with an ACS from 6 weeks to 1 year.

Patients on triple therapy

In patients taking triple therapy, it is even more important to choose the right time point of surgery. For high-risk patients, OAC should be stopped 3–5 days before surgery and replaced by LMWH or UFH when the INR falls below the therapeutic range.

Practical approaches in patients taking dual-antiplatelet therapy

In surgical procedures with high to very high bleeding risk:

(i) stop clopidogrel 5 days before surgery and stay on ASA, unless very high bleeding risk surgery;
(ii) if prasugrel is used, therapy should be stopped 7 days before surgery based on its prolonged and less unpredictable action compared with clopidogrel;
(iii) the advantage of ticagrelor in patients referred for surgery would be its fast offset of action after stopping intake. In the PLATElet inhibition and clinical Outcomes (PLATO) trial, ticagrelor was stopped 3–5 days before CABG and peri-operative bleeding rate was broadly similar to that seen with clopidogrel.
(iv) the substitution of combined antiplatelet therapy with LMWH or UFH alone is ineffective;
(v) restart clopidogrel (prasugrel and ticagrelor) as soon as possible with loading dose (if possible <24 h after operation);
(vi) in very high-risk patients, in whom cessation of antiplatelet therapy before surgery seems to be dangerous (e.g. shortly after stent implantation), it has been suggested that to switch from clopidogrel 5 days before surgery to a short half-life antiplatelet agent, e.g. the GPIIb/IIIa-inhibitor tirofiban, and stop infusion of these agents 4 h before surgery. This strategy has, however, not been investigated in prospective randomized trials.

A summary of how to resume oral-antiplatelet drugs after an invasive procedure is summarized in Table 8.

In surgical procedures with low to moderate bleeding risk: consider operating on dual-antiplatelet therapy (ASA + clopidogrel) if the specific type of surgery would allow.

Practical approaches in patients taking oral anticoagulation

Tables 9 and 10 give an overview of bridging therapy in relation to the choice of antithrombotic regimen and related dosage, whereby the actual risk of developing a thrombotic complication and the actual bleeding risk determine the respective therapeutic approach. There may be evidence that continuation of OAC with an INR of 2 is better for the prevention of thrombo-embolism and bleeding events for PCI—but limited data are available concerning surgery while on therapeutic OAC.

Managing bleeding complications

Management of bleeding consists of measures to preserve adequate circulation, local control (e.g. endoscopic treatment or surgical haemostasis), and proper transfusion procedures. If serious bleeding occurs in a VKA user it may be necessary to reverse the anticoagulant effect of the agent. When interrupting the administration of VKAs important differences in the half-lives of the various agents (9 h for acenocoumarol, 36–42 h for warfarin, and 90 h for phenprocoumon, respectively) need to be taken into account.164 There is debate over the best management strategy when a patient on VKA bleeds, given the competing concern for thrombo-embolic risk. Adequacy of haemostasis and duration of VKA interruption would vary with different patient scenarios.
The most straightforward intervention to counteract the effect of VKAs is the administration of vitamin K. 164–167 There is some debate on the need for vitamin K in the management of a patient with a very high INR but with no signs of bleeding. A recent randomized controlled trial did not find any difference in bleeding or other complications in non-bleeding patients with INR values of 4.5–10 who were treated with vitamin K or placebo. 168,169 In patients with clinically significant bleeding, administration of vitamin K is crucial to reverse the anticoagulant effect of VKAs. Vitamin K can be given orally and intravenously (iv), but the bioavailability of vitamin K results in a less predictable effect. Theoretically, these factors are present in fresh frozen plasma; however, the amount of plasma that is required for correcting higher INRs. Higher doses of vitamin K are equally effective but may lead to VKA resistance for more than a week, which may hamper long-term management. 169

When the INR is <7, a dose range of 2.5–5 mg vitamin K has been advocated, whereas a dose of 5–10 mg may be required for correcting higher INRs. Intra-muscular injections of vitamin K should be avoided in patients who are anticoagulated, and subcutaneous administration of vitamin K results in a less predictable bioavailability. 164,169

In the case of very serious or even life-threatening bleeding, immediate correction of the INR is essential and can be achieved by the administration of vitamin K-dependent coagulation factors. Theoretically, these factors are present in fresh frozen plasma; however, the amount of plasma that is required for correcting

Table 9 A recommended approach to bridging therapy, in relation to risk of thrombo-embolism (adapted from ACCP8 guidelines, with permission133). Thrombo-embolic risk category of patient

<table>
<thead>
<tr>
<th>Risk stratum</th>
<th>Indication for vitamin K antagonist therapy</th>
<th>Atrial fibrillation</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Any mitral value prosthesis; older (caged-ball or tilting-disc) aortic valve prosthesis; recent stroke or transient ischemic attack (within 6 months)</td>
<td>CHADS2; score: 5 or 6; recent (within 3 months) stroke or transient ischemic attack; rheumatic valvular heart disease</td>
<td>Recent VTE (within 3 months); severe thrombophilia: e.g. deficiency of protein C, protein S or antithrombin, antiphospholipid antibodies or multiple abnormalities</td>
</tr>
<tr>
<td>Moderate</td>
<td>Bileaflet aortic valve prosthesis and one of the following atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure or age &gt;75 years</td>
<td>CHADS2; score: 3 or 4</td>
<td>VTE within the past 3–12 months: non-severe thrombophilic conditions (e.g. heterozygos. Factor V Leiden mutation or heterozygos. Factor II mutation); recurrent VTE</td>
</tr>
<tr>
<td>Low</td>
<td>Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke</td>
<td>CHADS2; score: 0–2 (and no prior stroke or transient ischemic attack)</td>
<td>Active cancer (treated within 6 months or palliative)</td>
</tr>
</tbody>
</table>

Table 10 A recommended approach to bridging therapy, in relation to risk of thrombo-embolism (adapted from ACCP8 guidelines, with permission133). Bridging anticoagulant therapy

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Bridging recommendation</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with an MHV or NVAF or VTE at high risk for thrombo-embolism</td>
<td>Bridging anticoagulation with therapeutic-dose subcutaneous LMWH or intra-venous UFH over no bridging during temporary interruption of OAC</td>
<td>Grade 1C</td>
</tr>
<tr>
<td>Patients with a MHV, NVAF, or VTE at moderate risk for ‘thrombo-embolism’</td>
<td>Bridging anticoagulation with therapeutic-dose subcutaneous LMWH, therapeutic-dose intra-venous UFH, or low-dose subcutaneous LMWH over no bridging curing. Temporary interruption of OAC (grade 2C)</td>
<td>Grade 2C</td>
</tr>
<tr>
<td>Patients with MHV, NFAV, or VTE at low risk for ‘thrombo-embolism’</td>
<td>Low-dose subcutaneous LMWH or no bridging over bridging with therapeutic-dose subcutaneous LMWH or intra-venous UFH</td>
<td>Grade 2C</td>
</tr>
<tr>
<td>Patients who are undergoing minor dental procedures and are receiving VKAs</td>
<td>Continuing VKAs at the time of the procedure and co-administering an oral prohaemostatic agent</td>
<td>Grade 1E</td>
</tr>
<tr>
<td>Patients who are undergoing cataract removal and are receiving VKAs</td>
<td>Continuing VKAs at the time at the procedure</td>
<td>Grade 1C</td>
</tr>
</tbody>
</table>

LMWH, low-molecular-weight heparin; MHV, mechanical heart valve; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulation; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thrombo-embolism.
the INR is very large, carries the risk of fluid overload, and will probably take hours to administer. Therefore, prothrombin complex concentrates (PCCs), most of which contain all vitamin K-dependent coagulation factors, are more useful, and individualized dosing regimens based on INR at presentation and body weight are more effective. The risk of disseminated intravascular coagulation (DIC) due to traces of activated coagulation factors in PCCs comes from the older literature and modern PCCs seem not to be associated with precipitating precipitating DIC. However, PCCs do confer a small thrombotic risk, and this needs to be weighed when considering their use.

**Left atrial appendage closure**

A substantial number of patients eligible for OAC will suffer bleeding complications that may be potentially life threatening. Patients at high risk of embolic stroke, but with contraindications for OAC are in need of an alternative strategy that is not associated with long-term bleeding risk. This is particularly true for those after an intra-cranial hemorrhage.

The high frequency of thrombus formation in the left ventricular appendage (LAA) of patients with AF and its role as a source of embolism have led to the hypothesis that resection or obliteration of the LAA may reduce the risk of stroke. Surgical closure of the LAA has been practiced, and indeed, current guidelines suggest obliteration of the LAA during mitral valve surgery. Currently, excision of the LAA at the time of mitral valve surgery is recommended for reduction of future stroke risk. Exclusion of the LAA during coronary artery bypass graft surgery has also been proposed, but with suboptimal results.

A reasonable alternative may be the exclusion of the LAA cavity from the circulation, using either surgical or percutaneous catheter-based procedures. The percutaneous left atrial appendage transcatheter occlusion device was the first to be successfully deployed. The second device specifically designed for percutaneous transcatheter LAA exclusion is the WATCHMAN left atrial appendage system. The WATCHMAN Left Atrial Appendage System for Embolic PROTECTION in Patients With Atrial Fibrillation (PROTECT AF) study was designed to demonstrate the safety, efficacy, and non-inferiority of the WATCHMAN device compared to chronic warfarin therapy in those patients with non-valvular AF who are eligible for long-term OAC. The rate of ischaemic stroke was higher in the intervention group than in the control group, whereas haemorrhagic strokes were less frequent in the intervention group than in the control group. Moreover, an important risk of serious procedural complications was observed (e.g., peri-cardial tamponade), perhaps related to a learning curve of device implantation. Several new devices, the AMPLATZER and Coherex WaveCrest, are a novel alternative, and initial results are encouraging. Major bleeding was higher with warfarin (4.1%) compared with the WATCHMAN device (3.5%).

Careful selection of patients and a meticulous technique are required to improve the risk–benefit ratio. Further data are required in order to recommend the use of LAA closure in our high-risk patients.

**A perspective on newer anticoagulants**

At the time of writing of this summary, the direct thrombin inhibitor dabigatran is approved for clinical use in the USA and in Canada, and is close to approval in Europe. The pharmacokinetics of the drug and its apparent safety compared with warfarin render dabigatran a potentially attractive therapeutic option in patients in need of anticoagulation and at risk for bleeding; at the lower dose tested [110 mg twice a day (bid)] the rate of intra-cerebral bleeding events was higher in the VKA group in the RE-LY trial than in the dabigatran group. At the higher tested dose (150 mg bid), dabigatran prevented ischaemic strokes more effectively than VKAs. It is conceivable that some of the other new anticoagulants may confer similar benefits, but large trials in AF patients are not available as full publications at the time of writing of this document. In addition to these long-term benefits, the shorter half-life of direct thrombin or factor Xa antagonists compared with VKAs suggests that the management of bleeding complications and the antithrombotic regimen during operations and invasive procedures could become simpler with those substances compared to VKAs. This assumption is supported by the orthopaedic experience, e.g. with dabigatran 110 mg bid which is often initiated 12–24 h after orthopedic surgery.

**Consensus statements**

**General atrial fibrillation populations**

(i) In most patients, thrombo-embolic rates without anticoagulation are markedly (five- to eight-fold) higher than bleeding rates. Therefore, most patients with AF—including the majority of patients at high bleeding risk—are in need of anticoagulant therapy.

(ii) For AF patients requiring permanent effective anticoagulation, it is recommended that the 2010 ESC Guidelines for the management of patients with AF be applied.

(iii) The bleeding risk with aspirin should be considered as similar to that with VKA, especially in the elderly.

(iv) Most patients with a high CHA2DS2-VASC score would benefit from OAC even if their bleeding risk is high. Only in rare patients with a relatively low stroke risk and an extremely increased risk of bleeding may the withholding of OAC be considered.

(v) An assessment of the (long-term) risk of bleeding in the general AF population is recommended.

(vi) In specific AF patient subsets (i.e. post-ablation, post-LAA closure, post-percutaneous coronary intervention/acute coronary syndrome, etc.), the assessment of bleeding risk is part of overall management, balancing this risk against the risk of thrombo-embolic complications.

(vii) The HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score of ≥3 indicates ‘high risk’ and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet drugs.
**Peri-ablation**

(i) Start OAC (e.g. VKA, such as warfarin INR 2.0–3.0) for at least 4 weeks prior to the ablation procedure.

(ii) In many cases, OAC can be continued throughout the ablation procedure.

(iii) Where a bridging strategy is planned, stop VKA 2–5 days before the ablation procedure and bridging therapy with heparin (either LMWH or UFH) until the day before the ablation procedure.

(iv) Peri-procedure anticoagulation: after sheath insertion and transseptal puncture, administration of a bolus of intravenous (IV) heparin (bolus dose empirically 5000–10,000 U or 50–100 U/kg) followed by continuous infusion of 1000–1500 U/h in order to achieve an ACT at least in excess of 300 s that is checked every 30–45 min. On the completion of the procedure, IV heparin is discontinued and sheaths removed when the ACT is subtherapeutic (<160 s) or if high, reversed by protamine. IV heparin to be resumed for 12–24 h at a maintenance dose of 1000 U/h without a bolus that will maintain activated partial thromboplastin time at 60–80 s or at least twice the baseline level. Oral anticoagulation to be resumed on the day of the procedure.

(v) Replace IV heparin with subcutaneous LMWH after 12–24 h and reintiate OAC. Stop LMWH when the target INR 2–3 is reached.

(vi) Continue therapeutic warfarin for a minimum of 12 weeks after the ablation procedure. Patients who have a CHA2DS2-VASC score of ≥2 should continue OAC long term.

**Peri-devices (implantable cardioverter-defibrillator, pacemakers)**

(i) Implant of devices maintaining OAC may be as safe as bridging with heparin infusion and should allow a significant reduction of in-hospital stay.

(ii) In some circumstances, anticoagulant treatment should be interrupted pre-operatively and be replaced by heparin.

(iii) If implantation must be performed while on anticoagulant (whether maintaining OAC or bridging with heparin infusion) and/or antiplatelet therapy, the procedure should be carried out by an experienced operator who will pay close attention to haemostasis in the area of the generator pocket.

**Presentation with ACS and/or requiring PCI/stents**

(i) For antithrombotic therapy management in anticoagulated AF patients presenting with an ACS and/or undergoing PCI/stenting, the recommendations in the 2010 ESC Guidelines for the management of patients with AF or the ESC thrombosis working group consensus document should be applied.

**The management of bleeding complications**

(i) Appropriate strategies should be implemented both in the long term and peri-intervention, in order to prevent bleeding.

(ii) Bleeding risk assessment should be regularly performed, during regular review of the patient. Correctable bleeding risk factors should be managed.

**References**


98. Levi M, Hovingh GK, Carnegeiter SC, Vermeerum M, Buller HR, Rosendaal FR. Bleeding in patients receiving vitamin K antagonists who would have been excluded from trials on which the indication for anticoagulation was based. Blood 2008;111:4471–6.
Bleeding risk assessment and management in atrial fibrillation patients

gastrointestinal complications of anticoagulant therapy.


122. Hirsh J, Bauer K, Donati MB, Gould M, Samama MM, Weitz JJ. Parenteral anticoagu-


