European Heart Journal Advance Access published October 27, 2016

European Heart Journal (2016) **0**, 1–11
doi:10.1093/eurheartj/ehw454

CURRENT OPINION

Management of antithrombotic therapy after bleeding in patients with coronary artery disease and/or atrial fibrillation: expert consensus paper of the European Society of Cardiology Working Group on Thrombosis

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Received 29 December 2015; revised 29 July 2016; accepted 11 September 2016

Introduction

Bleeding is a frequent complication of the management of patients with coronary artery disease (CAD), especially those presenting with acute coronary syndromes (ACS) or undergoing percutaneous coronary intervention (PCI), and of patients with atrial fibrillation (AF). Randomized trials have shown a risk of major bleeding of 1–8% at 30 days in ACS patients,[1–5] and of 2–5% per year in patients with AF treated with oral anticoagulants (OACs).[6] Observational studies suggest that bleeding risk is even higher.[7] Major bleeding is associated with a subsequent increase in both short- and long-term mortality.[7–13] Even minimal bleeding may have prognostic importance because it frequently leads to disruption of antithrombotic therapy.[14,15]

Several mechanisms have been put forward to explain the relationship between major bleeding and increased mortality (*Figure 1*). The overlap in risk factors for bleeding and ischaemic events means that patients who are more likely to suffer from bleeding complications of antithrombotic therapy also tend to be at higher risk of thrombotic events.[16] Discontinuation of antithrombotic drugs may lead to an increased rate of thrombotic events due to the progressive recovery of platelet function and coagulation activity.[17–19] In addition, bleeding may provoke prothrombotic responses beyond those related to discontinuation of antithrombotic drugs.[20,21] Clearly, balancing the risks of further bleeding vs. potentially fatal thrombotic events is critical for decisions about if and when to restart antithrombotic therapy after bleeding.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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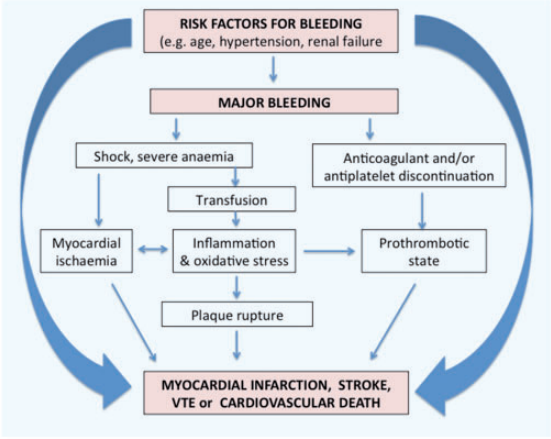

Figure 1 Hypothetical mechanisms linking bleeding to thrombotic events and death. Numerous risk factors for bleeding are also risk factors for myocardial infarction, stroke and death (large arrows).
VTE, venous thromboembolism.

Aim of consensus document

Although several recommendations have been published dealing with the acute management of bleeding in patients treated with antithrombotic drugs,[22–24] there is an unmet need for guidance on how to manage antithrombotic therapy *after* bleeding has occurred. Patients with recent bleeding have been excluded from most randomized trials of antithrombotic therapy and rigorous evidence to inform decisions is scarce. While waiting for observational and randomized data to accrue, this consensus paper offers a European perspective on managing antithrombotic therapy after bleeding in patients with CAD and/or AF, including which drugs to stop, which to restart, and *when*.

For the purpose of this document, major bleeding has been defined according to the Bleeding Academic Research Consortium (BARC)[25] as BARC type ≥ 3, minor bleeding as BARC type 2 and minimal as BARC type 1. Cessation of antithrombotic therapy has been defined according to Mehran *et al.*[19] as discontinuation (recommended, physician-directed withdrawal), interruption (temporary cessation of antiplatelet treatment due to surgical necessity with reinstitution within 14 days), or disruption (cessation of antiplatelet treatment due to bleeding or non-compliance).

Consensus definitions of thrombotic and haemorrhagic risks after bleeding

Tables 1 and *2* present the authors' consensus definitions of thrombotic and haemorrhagic risks for CAD and AF patients who develop a bleeding event. Risks are stratified into five categories: low, low-to-moderate, moderate, high, and very high. Definitions are based on simple clinical parameters and validated scores.[26,27] Although the value of platelet function testing for predicting ischaemic and bleeding risks was recently demonstrated in a cohort of >20 000 patients,[28] personalized treatment based on platelet function and/or genetic testing cannot be recommended in routine clinical practice due to insufficient prospective data.[29,30] Ongoing studies further investigate this issue (e.g. NCT01538446, NCT01959451).

Consensus on the general management of antithrombotic therapy after bleeding

The concomitance of very high thrombotic *and* very high haemorrhagic risks in a patient with bleeding poses the most difficult treatment decisions. Given the increased risk of thrombotic events after premature cessation of antithrombotic drugs, our consensus is to consider resumption of oral antithrombotic therapy in all situations where there is a clear indication, even in case of major bleeding, as long as the bleeding event is not a life-threatening intracranial or extracranial bleed. When the thrombotic risk is higher than the risk of recurrent bleeding (according to *Tables 1* and *2*), we suggest continuing antithrombotic therapy. When thrombotic risk is in equipoise with bleeding risk, we suggest only brief or temporary interruption of antithrombotic therapy. When bleeding risk outweighs thrombotic risk, we suggest considering, on a case to case basis, reducing the number and/or dose of antithrombotic drug(s). Whenever possible we strongly suggest recruiting patients into randomized trials or registries designed to address the many dilemmas discussed below. When this is not possible, we suggest applying the guidance provided by this consensus paper.

Antiplatelet therapy after extracranial bleeding

Patients with a recent acute coronary syndrome and/or percutaneous coronary intervention (<12 months)

The risk for new cardiovascular events is increased in patients with a recent ACS, especially during the first 3 months, and remains elevated up to 1 year after the acute event.[31] The importance of dual antiplatelet treatment (DAPT) with aspirin and a $P2Y_{12}$ inhibitor up to 1 year for these patients is well established.[32]

After bleeding, no randomized trials have assessed whether stopping or restarting one or both antiplatelet agents is the best choice. In patients with a recently implanted coronary stent, premature disruption of one or both antiplatelet agents (especially the $P2Y_{12}$ inhibitor) has been shown to be the strongest predictor of stent thrombosis.[33–35] The risk of stent thrombosis increases with longer time off treatment, particularly more than 5 days, and if treatment is stopped within the 1st month after the procedure.[33,34,36,37] One-year mortality rates for stent thrombosis remain as high as 10–14%.[38,39] In a contemporary registry of over 5000 patients treated with PCI, cardiovascular risk was significantly increased when DAPT cessation was due to non-compliance or bleeding.[19] The risk was highest for the first 7 days after the start of disruption, but still high within 30 days.[19] Thus, it is important for clinicians to clearly appreciate the heightened risk of ischaemic events following premature cessation of antiplatelet therapy in patients with coronary stents.

Table 1 Consensus definitions of thrombotic risk categories

Risk category	Risk of athero-thrombotic events (stable CAD, ACS or after PCI)	Risk of cardio-embolic events (AF or mechanical valves)
Very high	ACS or PCI with newer generation DES <8 days BVS <30 days	AF with CHA_2DS_2-VASc > =6 Mechanical mitral valves Cardiac assist devices.
High	ACS or PCI with newer generation DES 8–30 days ago. BVS 1–12 months ago	AF with CHA_2DS_2-VASc 4–5 Mechanical aortic valves (bileaflet)
Moderate	ACS or PCI with newer generation DES 1–12 months ago	AF with CHA_2DS_2-VASc 2–3
Low-to-moderate	Stable CAD (>12 months after ACS or PCI with newer generation DES), but complex cases (left main, bifurcations, recurrent ACS)	AF with CHA_2DS_2-VASc 1 (male) or 2 (female)
Low	Stable CAD (>12 months after ACS or PCI with newer generation DES) without additional risk factors	AF with CHA_2DS_2-VASc 0 (male) or 1 (female)

ACS, acute coronary syndrome; AF, atrial fibrillation; BVS, biovascular scaffolds; CAD, coronary artery disease; CHA_2DS_2-VASc, Cardiac failure, Hypertension, Age ≥75 (2 points), Diabetes, Stroke (2 points)—Vascular disease, Age 65–74, Sex category; DES, drug eluting stent; PCI, percutaneous coronary intervention.

Table 2 Consensus definitions of recurrent bleeding risk categories

Risk category	Bleeding source and severity	Clinical setting	Patients clinical risk factors for bleeding
Very high	Intracranial bleeding where no treatment is possible or effective. Life-threatening extracranial bleeding where the source is either not identified or identified but not treated effectively	No precipitating or reversible factor identified (e.g. trauma, invasive procedure, hypertension, drug overdosing) Cessation of antithrombotic therapy discouraged because of very high-thrombotic risk, e.g. mechanical heart valve	HAS-BLED ≥5
High	Major extracranial bleeding where the source is identified but not treated effectively.	No reversible factor identified. Cessation of antithrombotic therapy discouraged because of very high thrombotic risk.	HAS-BLED 3–4
Moderate	Intracranial bleeding where cause of bleeding and relevant risk factors have been treated. Extracranial major bleeding where the source has been identified and treated effectively.		HAS-BLED =2
Low-to-moderate	Extracranial minor bleeding	Bleeding caused by antithrombotic drugs which can be discontinued	HAS BLED = 1
Low	Extracranial minimal bleeding	Bleeding caused by antithrombotic drugs which can be discontinued	HAS BLED = 0

To be in the low-risk category for recurrent bleeding, both bleeding source/severity, clinical setting and patient risk factors for bleeding must be low. To be in the high-risk category, it is sufficient that one variable is high risk.
HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65), Drugs/alcohol concomitantly; PCI, percutaneous coronary intervention.

Duration of dual antiplatelet treatment according to stent type in high bleeding risk patients with percutaneous coronary intervention <12 months

Recent randomized trials using newer-generation (everolimus- or zotarolimus-eluting) drug-eluting stents (DES) support shortening DAPT duration in patients at high risk of bleeding; in some of these studies, there was no evidence of lower efficacy with 3–6 months of DAPT than with 12 months.[32,40,41] Thus, when major bleeding occurs after 3–6 months of DAPT, these studies lend support to discontinuing the $P2Y_{12}$ inhibitor and continuing aspirin alone, particularly in patients without a prior history of ACS.[32] Furthermore, the Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent vs. the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS FREE) trial suggested that a polymer-free

biolimus-coated stent may allow even shorter duration of DAPT (1 month).[42] Therefore, decisions of whether and when to resume antiplatelet treatment after bleeding should also consider the type of stent(s).

While the overall risk of stent thrombosis is lowest with the newest generation DES, the thrombotic risk appears higher with the new bioresorbable vascular scaffolds (BVS), owing to thrombogenicity related to strut thickness and extent of blood contact surface.[43,44] Therefore, a longer DAPT duration and a more urgent need for resuming antiplatelet agents after bleeding may be needed with BVS,[45] although further studies specifically with this device are required to explore the optimal DAPT duration.

Patients on prasugrel, ticagrelor, or vorapaxar

In ACS patients treated with the newer $P2Y_{12}$ inhibitors prasugrel or ticagrelor, there are no data available for resumption after bleeding. The risk of non-CABG related bleeding with these agents is significantly higher compared to clopidogrel. Although the evidence is weak, clopidogrel (which results in less platelet inhibition and a lower risk of spontaneous bleeding) may be used as $P2Y_{12}$ inhibitor after bleeding has occurred during treatment with prasugrel or ticagrelor, as soon as re-initiation of antiplatelet therapy is possible. The irreversible binding of prasugrel and the reversible binding of ticagrelor should be taken into consideration when deciding *when* to restart $P2Y_{12}$ inhibitors in these patients. Dose reduction from 10 to 5 mg od prasugrel or from 90 mg to 60 mg bid ticagrelor is not recommended due to lack of evidence of efficacy in patients with a recent ACS. Of note, however, the two doses of ticagrelor provided similarly high levels of platelet inhibition.[46]

The bleeding risk is also increased with the thrombin receptor antagonist vorapaxar,[47] having an extremely prolonged half-life. Our consensus is that this drug should be discontinued permanently in patients after bleeding has occurred.

Medically managed patients with acute coronary syndromes

Trials and registries show that a significant proportion of patients with ACS are treated medically without revascularization for various reasons.[48] Such patients on average have worse cardiovascular outcomes compared to those that undergo revascularization.[49] The suggestions for antithrombotic therapy after bleeding, outlined for patients treated invasively, largely apply also to patients receiving medical treatment alone, except for the lack of stent thrombosis risk.

Patients with stabilized coronary artery disease (>12 months after percutaneous coronary intervention or acute coronary syndromes)

Two meta-analyses, based mainly on observational data, suggest that single antiplatelet therapy prescribed for secondary prevention in stable CAD patients should be reinitiated within a few days after bleeding. The first analysis includes 50 279 patients receiving aspirin: cessation of, or non-adherence to, aspirin were associated with a three-fold higher risk of major adverse cardiac events compared to its continued use [OR = 3.14 (1.75–5.61), $P = 0.0001$].[50] The risk was magnified in patients with coronary stents.[50] The second meta-analysis evaluated patients with perioperative aspirin interruption.[51] The mean time to coronary events after withholding aspirin was 8.5 days, with events occurring as early as 5 days after withdrawal. On the other hand, a large randomized trial (POISE-2),[52] comparing perioperative aspirin vs. placebo among patients considered at risk of cardiovascular events and undergoing non-cardiac surgery, showed no significant effect of aspirin on the 30-day rate of death or non-fatal myocardial infarction but an increased risk of major bleeding vs. placebo. Of note, less than one third of the POISE-2 population had prior vascular disease and only 23% had CAD.

Resuming antiplatelet therapy after gastrointestinal bleeding

The gastrointestinal (GI) tract is one of the most frequent bleeding sources in patients with CAD.[53] A small randomized controlled trial evaluated the effect of early resumption of aspirin, 80 mg daily, compared to placebo among 156 patients presenting with peptic ulcer bleeding while on aspirin.[54] Recurrent ulcer bleeding within 30 days occurred in 10.3% of patients receiving aspirin and 5.4% receiving placebo ($P = 0.25$). However, all-cause mortality at 8 weeks was markedly lower in the aspirin group than the placebo group (1.3 vs. 12.9%, $P = 0.005$). In patients receiving low-dose aspirin for secondary cardiovascular prevention who develop peptic ulcer bleeding, the European Society of Gastrointestinal Endoscopy (ESGE) recently recommended aspirin to be resumed immediately following index endoscopy if the risk of recurrent bleeding was low (low-risk endoscopic stigmata identified: Forrest classification IIc or III) (*Figure 2*).[55] In patients with high-risk peptic ulcer (Forrest Ia, Ib, IIa, IIb), early reintroduction of aspirin by day 3 was recommended, provided that adequate haemostasis had been established (*Figure 2*).[55] In patients on DAPT, it was recommended to continue DAPT without interruption if endoscopy showed low-risk stigmata. With high-risk stigmata, restarting single treatment with low-dose aspirin was recommended, followed by early consultation with a cardiologist for recommendation on resumption of the second antiplatelet agent. Since high-dose proton pump inhibitor (PPI) is recommended in all patients with bleeding peptic ulcer,[55,56] a rapid healing of the lesion is expected. A repeat endoscopy after the bleeding event might help to assure the safety of introducing clopidogrel in addition to aspirin.

Consensus summary on antiplatelet therapy after extracranial bleed

i. For patients at high or very high thrombotic risk (see *Table 1*: ACS or coronary stenting <30 days) who develop minor or major bleeding, we suggest continuation of low-dose aspirin without interruption. Restarting of the second antiplatelet agent should be considered as soon as possible after stabilization.

ii. For patients at moderate thrombotic risk (see *Table 1*: ACS or PCI with a second generation DES 1–12 months ago) who develop minor or major bleeding, we suggest resumption of low-dose aspirin as soon as bleeding is controlled, preferably within 3 days. Restarting a second antiplatelet agent should be considered if thrombotic risk outweighs recurrent bleeding risk. For patients who develop bleeding while on DAPT within 3 months of new generation DES implantation, we suggest resuming DAPT up to 3 months. If patients develop bleeding more than 3 months after new generation DES implantation and remain at risk of recurrent bleeding, we suggest resumption of only one antiplatelet agent (either aspirin or clopidogrel).

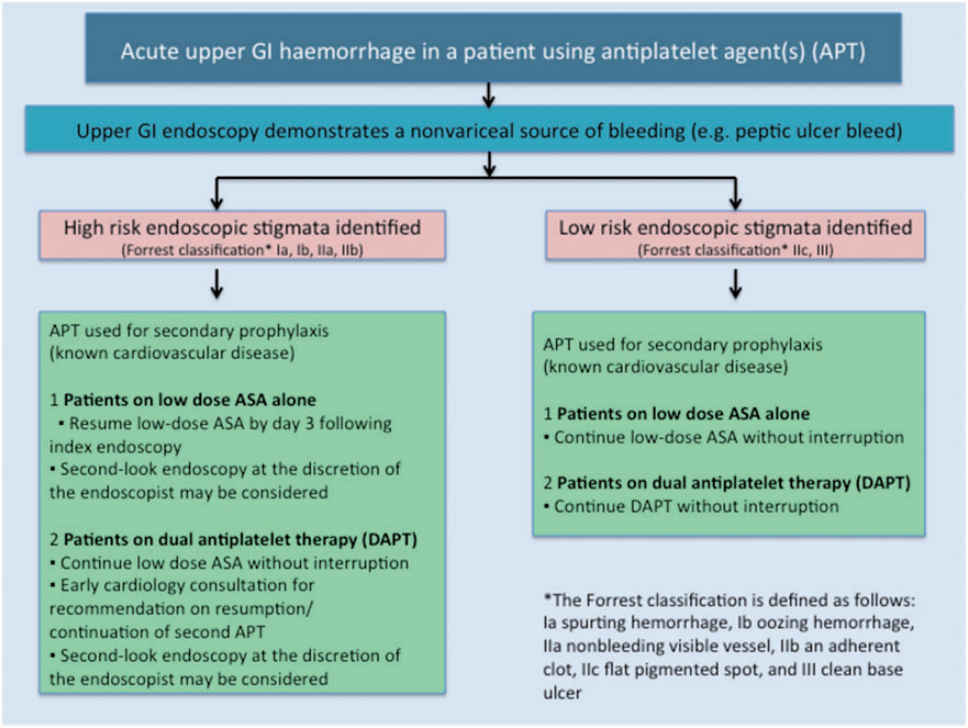

Figure 2 Algorithm for the management of patients with upper gastrointestinal haemorrhage who are using antiplatelet agent(s); modified with permission from Gralnek *et al.*[55]
APT, antiplatelet therapy; ASA, aspirin; DAPT, dual antiplatelet therapy; GI, gastrointestinal.

iii. In patients with bleeding after BVS implantation, DAPT may be necessary up to 12 months after implantation.
iv. Clopidogrel, as less effective but also with a tendency for less bleeding rates, may be used as $P2Y_{12}$ inhibitor of choice after bleeding has occurred on prasugrel or ticagrelor. The duration of the effect of prasugrel (7–10 days) or ticagrelor (3–5 days)[32] should be taken into consideration when deciding *when* to restart $P2Y_{12}$ inhibitors in these patients.
v. In patients who develop major bleeding under vorapaxar, we suggest permanent discontinuation of the latter.
vi. In medically managed ACS patients who develop major bleeding on DAPT, single antiplatelet therapy may be considered, given the lack of stent thrombosis risk.
vii. For patients with stable CAD or ACS who develop upper GI (non-variceal) bleeding, antiplatelet therapy (single or dual) can be continued without interruption if endoscopy identifies low-risk bleeding stigmata (*Figure 2*). If high-risk bleeding stigmata are identified and bleeding has been controlled by interventional endoscopy, aspirin can be restarted within 3 days.[55] If high-risk stigmata are identified in patients on DAPT, resuming the second antiplatelet agent should be on an individual basis after careful weighing potential thrombotic and bleeding risks.
viii. Addition of a PPI is recommended in all cases of upper GI bleeding.[55,56] PPI should also be used in patients on DAPT at higher than average risk of GI bleeds.[32] The pharmacodynamic interaction between PPIs (especially omeprazole) and clopidogrel has not so far been clearly associated with worse clinical outcome, but it is preferred to use PPIs with weaker CYP2C19 inhibition (e.g. pantoprazole).[56]

Oral anticoagulant therapy after extracranial bleeding

Treatment with OACs reduces the risk of stroke and systemic embolism in patients with AF. Cessation of OACs has been shown to be associated with an increased risk of stroke even after short interruptions.[57,58]

Vitamin K-antagonists (VKA)

A recent meta-analysis of studies in patients on long-term VKA demonstrated that resumption of warfarin following interruption due to GI bleeding was associated with a reduction in thromboembolic events and mortality without any significant increase in recurrent GI bleeding.[59] In a retrospective study of patients with non-valvular AF, restarting warfarin after major GI bleeding was independently associated with decreased mortality as compared to permanent warfarin cessation.[60] No significant difference in the incidence of new GI bleeding was found when warfarin was resumed after 1 week vs. 1 month; however, when warfarin was restarted before the 1st week after GI bleeding had passed, the risk of recurrent bleeding was significantly enhanced. Based on these data, in the presence of a clear indication, VKA therapy should be resumed within 1 week following major GI bleeding.[60–62]

In patients with mechanical heart valves, discontinuation of VKA is associated with a high risk of thrombosis and is generally discouraged.

Non-vitamin K antagonist oral anticoagulants (NOAC)

The NOACs have not been tested in AF patients with recent bleeds and the optimal time for restarting NOAC after bleeding is unknown. In a recent study with the antidote idarucizumab for patients on dabigatran presenting a life-threatening bleed or requiring urgent surgery, thrombotic events occurred within 6 days after idarucizumab administration when anticoagulation was not reinitiated.[17] It may be reasonable to follow the same advice as for VKA, being aware that the full anticoagulant effect of NOAC occurs sooner (within 1–4 h)[63] than with VKA (several days).

When (re)starting a NOAC, renal function should be carefully assessed and monitored to avoid drug accumulation. The recommended time interval during follow-up for monitoring of renal function depends on the level of renal function: If creatinine clearance (CrCl) is less than 60 mL/min, then recheck renal function every x months, where x = CrCl/10.[63] After major bleeding, however, this interval should be reduced.

Some of the NOACs are associated with an increased risk of GI bleeding compared to warfarin.[16,64] Switching to warfarin or to a NOAC without an increased risk of GI bleeding compared to warfarin (e.g. apixaban)[16,64] may be considered.

Consensus summary on anticoagulant therapy after extracranial bleed

i. After extracranial bleeding, OAC should be reinitiated as soon as the cardiovascular thrombotic risks associated with discontinuation are thought to outweigh the risk of re-bleeding with reinitiation, in most cases within 1 week.
ii. When (re)starting a NOAC, renal function should be carefully assessed and monitored to avoid drug accumulation.
iii. If an antidote (idaruzicumab) has been used to reverse the anticoagulant effect of a NOAC, it is suggested to restart OAC as soon as possible, preferably within 3–4 days if the individual bleeding risk allows.
iv. In patients with mechanical heart valves, discontinuation of VKA is associated with a high risk of thrombosis and is discouraged, particularly for valves in the mitral position. NOACs are currently contraindicated for patients with mechanical heart valves.

Resuming antithrombotic therapy in patients with an indication for both antiplatelets and oral anticoagulant

A particular challenge in terms of antithrombotic treatment is patients who present with both AF and ACS/coronary stenting, most of them having an indication for both DAPT and OAC. A period of triple therapy is recommended in most patients, followed by double therapy (OAC plus single antiplatelet) up to one year; thereafter OAC alone is considered sufficient.[32,63] Combining DAPT with OAC (VKA or NOAC) significantly increases bleeding risk,[65] regardless of any of the large variety of possible combinations.

The What is the Optimal antiplatElet and anticoagulant therapy in patients with OAC and coronary StenTing (WOEST) pilot trial of 573 patients demonstrated that double therapy (VKA plus clopidogrel) was safer with respect to BARC bleeding compared to triple therapy (VKA plus clopidogrel and aspirin),[66] and registries have shown similar findings.[65,67] The recent Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR TRIPLE) study enrolled 614 patients receiving VKA who underwent DES implantation and showed that outcomes were similar if clopidogrel, on top of VKA and aspirin, was administered for 6 weeks or 6 months.[68] Both these trials were too small to reliably assess ischaemic outcomes, and the patients were stable and had not suffered a bleed. Nevertheless, as an extrapolation from these studies, we suggest stopping either aspirin or clopidogrel when a patient develops major bleeding during triple oral antithrombotic therapy. In patients who develop major bleeding on double therapy (OAC plus single antiplatelet), discontinuation of the antiplatelet agent may be considered before 1 year has passed, as long as the athero-thrombotic risk is moderate or less (*Table 1*).[63]

There is yet no randomized study comparing VKA vs. NOAC in the setting of AF with ACS/PCI, and the guidelines suggest that either can be used in combination with antiplatelet therapy.[32] With respect to choice of antiplatelet therapy, the ESC guidelines recommend avoiding the use of prasugrel or ticagrelor as part of triple therapy.[32] The use of ticagrelor in combination with a NOAC is currently being tested in prospective randomized trials (NCT02164864, NCT02415400).

When NOACs are combined with antiplatelet drugs, the lowest effective dose for stroke prevention should be used, meaning dabigatran 110 mg bid (rivaroxaban 15 mg od, apixaban 2.5 mg bid, or edoxaban 30 mg od, only when criteria for dose lowering are present).[32,69,70] The efficacy of rivaroxaban 2.5mg bid has not been demonstrated for stroke prevention in AF patients and cannot be recommended for this indication.

Consensus summary on indication for both antiplatelets and oral anticoagulant after bleeding

i. When PCI-treated patients with non-valvular AF develop bleeding during triple oral antithrombotic therapy, we suggest stopping either aspirin or clopidogrel (the latter not within the first month of stenting). For OAC, we suggest a target INR of 2.0–2.5 with VKA and the lowest effective dose for stroke prevention for NOACs.
ii. In patients who develop major bleeding on double therapy (OAC plus single antiplatelet), discontinuation of the antiplatelet agent may be considered before 1 year has passed.[63]
iii. We suggest DAPT alone (without OAC) for 1 year after ACS/PCI when a patient with non-valvular AF and a low risk of stroke (CHA_2DS_2-VASc score[27] 1 for men, 2 for women) develops bleeding during triple or double antithrombotic therapy.

Antithrombotic therapy after intracranial haemorrhage

Antiplatelet therapy

Approximately 0.2–0.6% of ACS patients develop intracranial haemorrhage (ICH) annually while on antiplatelet therapy.[71] There is limited evidence on whether to stop indefinitely or resume antiplatelet therapy.

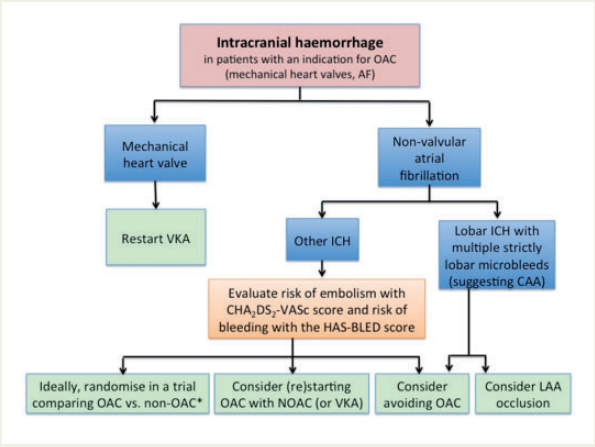

Figure 3 Flowchart for the initiation or re-initiation of oral anticoagulation after intracranial haemorrhage.
AF, atrial fibrillation; CAA, cerebral amyloid angiopathy; ICH, intracranial haemorrhage; LAA, left atrial appendage; NOAC, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulation; VKA, vitamin K antagonist.
*Non-OAC = any strategy that does not involve oral anticoagulation (i.e. no antithrombotic at all; antiplatelet agent(s); LAA occlusion etc).

Careful consideration of thrombotic and bleeding risk is needed. In general, restarting therapy after temporary discontinuation should be considered if thrombotic risk, as defined in *Table 1*, is very high or high. One randomized controlled trial of restarting vs. avoiding antiplatelet drugs after antithrombotic-associated ICH is ongoing (ISRCTN71907627).

Oral anticoagulants

ICH is one of the most feared complications of OAC, occurring in 0.5–1.0% of OAC-treated patients annually.[72] In patients surviving anticoagulation-associated ICH (< 60%),[13] the question is whether to restart OAC. A systematic review of observational studies of patients with prosthetic heart valves developing an ICH concluded that, in patients with mechanical heart valves, anticoagulation with heparin can safely be restarted as early as 3 days after ICH and switched to VKA at 7 days without major concerns of bleeding.[73] For patients without mechanical valves, the dilemma is whether to (re)start OAC at all after ICH.[74–77] Despite summaries of product characteristics stating that ICH constitutes a contraindication to OAC, several observational studies have compared (re)starting vs. avoiding OAC after ICH.[61,76,78–80] The three most informative studies included adults with various types of ICH and a variety of indications for OAC (mainly AF), and quantified the risks of recurrent ICH or ischaemic events for patients who avoided or restarted warfarin.[61,76,78] Data from these studies suggest a reduction in ischaemic events, in recurrent ICH and in death rates associated with restarting warfarin, although confounding by indication is likely, given the non-randomized designs.[61,76,78]

The thromboembolic potential of the underlying condition demanding OAC, as stratified in *Table 1*, the site of the ICH, the presence of brain microbleeds on magnetic resonance imaging, and the patient's general bleeding risk (*Table 2*) should all be considered (*Figure 3*).[74,75] Recurrent ICH is more common with cortical ICH, multiple lobar microbleeds, family history of ICH, amyloid angiopathy, and lack of reversible/precipitating factors. Reversible or treatable causes of ICH, or the urgent need for anticoagulation in patients with a mechanical valve (*Figure 3*), favour restarting, whereas recent PCI and need for DAPT favour temporary discontinuation of anticoagulation. If the decision is to restart anticoagulation, the optimal timing of resumption is uncertain:[16,73,75,76,81] the guidelines of the major American societies suggest to avoid OAC for at least 4 weeks after ICH in patients without mechanical heart valves.[81]

All of the existing evidence involves VKAs. The NOACs appear promising because of the lower risks of ICH than warfarin in trials of patients with non-valvular AF, but these drugs have not been tested in patients with prior ICH. All NOACs are currently contraindicated in the presence of mechanical heart valves given the negative results of the Dabigatran Etexilate in Patients with Mechanical Heart Valves (RE-ALIGN) trial.[82] In AF patients with lobar ICH and/or multiple lobar microbleeds and/or CHA_2DS_2-VASc score $\geq$4, left atrial appendage occlusion is an option.[83,84]

One randomized trial of apixaban vs. no anticoagulation after anticoagulation-associated ICH is ongoing (NTR4526).

Consensus summary on oral anticoagulant after intracranial haemorrhage

i. Whether and when to restart OAC after an ICH should be decided on an individual basis, depending on the patient's thrombotic risk and the risk of recurrent bleeding (*Figure 3*). Close collaboration between neurologists and cardiologists is needed to make individualized decisions.
ii. In the absence of mechanical valves, NOACs may be preferable to warfarin after ICH, given their lower incidence of ICH among non-valvular AF patients in phase III trials, but their efficacy and safety have still to be established in this setting. If one of the NOACs is chosen, the lowest effective dose for stroke prevention in AF should be preferred. Renal function, body weight, age, and drug interactions should be carefully considered to avoid drug-overdosing.

The future

Need for randomized evidence

There is a shortage of observational data, and even more so of randomized trials, describing the risks and benefits of when and how to resume antithrombotic drugs after bleeding in patients with CAD and/or AF. Current antithrombotic management is largely derived from randomized trials conducted in patients *without* a history of bleeding. Although the benefits observed in these trials are likely to apply also to patients who have a history of bleeding, the trade-off between the absolute reduction in thrombotic events and any absolute increase in recurrent bleeding events, as well as the net functional consequences for the patient, remain to be determined. The results of ongoing trials for this important group of patients are eagerly awaited.

Conclusion

The increasing use of potent antithrombotic drugs and drug combinations raises challenges for clinicians managing patients who develop

bleeding complications. It is essential that clinicians be aware of the heightened risk of ischaemic events following bleeding and tailor their decisions on continuation or reinitiation of antithrombotic therapy accordingly. Whilst the priority is to obtain further evidence from randomized trials, we propose guidance for managing antithrombotic therapy after bleeding when participation in a relevant clinical trial is not feasible, emphasising the frequent importance of continuation or early reinitiation of antithrombotic therapy.

Conflicts of interest: S.H. reports personal fees from AstraZeneca, Boehringer Ingelheim, Bayer, BMS/PFIZER, MSD, Sanofi, outside the submitted work. R.F.S. reports personal fees from Aspen, Correvio, PlaqueTec, The Medicines Company, ThermoFisher Scientific; grants, personal fees and other from AstraZeneca, outside the submitted work. B. R. reports personal fees from MSD. E.L.G. has received speaker honoraria from AstraZeneca, Baxter, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb and Pfizer and has participated in advisory board meetings for AstraZeneca, Bayer, Boehringer Ingelheim and Bristol-Myers Squibb. He is an investigator in THEMIS (AstraZeneca) and has received travel support (research meetings) from AstraZeneca, Boehringer Ingelheim and BMS-Pfizer. D.S. reports personal fees from Eli Lilly, Daiichi Sankyo, Roche Diagnostics, MSD, Bayer and grants from Roche Diagnostics, outside the submitted work. F.A. reports personal fees and support for essential travel from Amgen, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Eli Lilly and Pfizer. *R.A-S.S.* is the chief investigator of the REstart or STop Antithrombotics Randomized Trial (ISRCTN71907627), which is funded by the British Heart Foundation. A. L. has received an investigator-initiated grant from Bayer Pharma AG and has received fees for participating in Bayer-sponsored symposiums. T.W. has received lecture fees from AstraZeneca, Bayer, Boehringer-Ingelheim, Daiichi Sankyo, Eli-Lilly, Medtronic, the Menarini group, Novartis, Servier, and Vifor Pharma; advisory board and consultation fees from AstraZeneca, Boston Scientific, Daiichi Sankyo, Eli-Lilly, Medtronic, and Sanofi Aventis; and research grants from AstraZeneca, the Austrian Science Fund, the Austrian Cardiology Society, the Austrian Hypertension League, Boehringer-Ingelheim, Bristol-Meyer-Squibb, Daiichi Sankyo, and the Menarini group. J. B. reports grants from Astra outside the submitted work. G.Y.H.L. has served as a consultant for Bayer, Astellas, Merck, Astra Zeneca, Sanofi, BMS/Pfizer, Biotronik, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi-Aventis. J.M. reports personal fees for consulting activities and lectures for Bayer Healthcare; Astra Zeneca; Lilly Company; Daiichi Sankyo; Merck Sharp and Dhome; BMS; Pfizer. G.V. has nothing to disclose. F.W.A.V. reports personal fees from AstraZeneca, Boehringer-Ingelheim, BMS/Pfizer, Daiichi-Sankyo, Bayer Healthcare, outside the submitted work. P.G.S. reports personal fees from Amarin, AstraZeneca, Bayer, Boehringer-Ingelheim, Bristol-Myers-Squibb, Daiichi-Sankyo, GlaxoSmithKline, Lilly, Merck-Sharpe-Dohme, Novartis, Pfizer, Roche, Janssen, Regado, Regeneron, grants and personal fees from Sanofi, grants and personal fees from Servier, personal fees and non-financial support from The Medicines Company, outside the submitted work. D.G. reports non-financial support from Boehringer Ingelheim, personal fees from Bayer, Daiichi Sankyo, Eli Lilly, non-financial support and other from Pfizer, outside the submitted work. In addition, Dr. Gulba has a patent novel anticoagulant rodentizide pending. J.P.C. has received research grants from Bristol-Myers Squibb, Medtronic, Fédération Française de Cardiologie, and Société Française de Cardiologie; consulting fees from Sanofi -Aventis, Eli Lilly, and Bristol-Myers Squibb; and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, and AstraZeneca. S. Husted reports personal fees from AstraZeneca, BMS, Pfizer, Leo and Bayer, grants and personal fees from Boehringer Ingelheim, outside the submitted work. K.H. has received research support from AstraZeneca and lecture fees from Amgen, Astra Zeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, Sanofi-Aventis, and The Medicines Company.

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