

Resumption of Antiplatelet Therapy after Major Bleeding

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Abstract

Keywords

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- ▶ gastrointestinal bleeding
- ▶ aspirin
- ▶ dual antiplatelet therapy

Major bleeding is a common threat in patients requiring antiplatelet therapy. Timing and intensity with regard to resumption of antiplatelet therapy represent a major challenge in clinical practice. Knowledge of the patient's bleeding risk, defining transient/treatable and permanent/untreatable risk factors for bleeding, and weighing these against thrombotic risk are key to successful prevention of major adverse events. Shared decision-making involving various disciplines is essential to determine the optimal strategy. The present article addresses clinically relevant questions focusing on the most life-threatening or frequently occurring bleeding events, such as intracranial hemorrhage and gastrointestinal bleeding, and discusses the evidence for antiplatelet therapy resumption using individual risk assessment in high-risk cardiovascular disease patients.

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Clinical Impact of Bleeding

Risk Factors for Bleeding on Antiplatelet Therapy

Bleeding under antiplatelet therapy (APT) can occur in the early phase postprocedure (e.g., after coronary or valve interventions), in the intermediate phase from discharge during the first year, or in the chronic phase after the first year of treatment. Major and minor risk factors for bleeding under APT have been recently issued by the Academic Research Consortium. A high bleeding risk (HBR) status is defined by the presence of at least one major or two minor risk criteria (►Fig. 1).¹

Incidence and Case Fatality of Bleeding on Antiplatelet Therapy

Bleeding is associated with higher short-term, i.e., in-hospital, intermediate (up to 12 months), and long-term (beyond 12 months) mortality after the event, which is either caused by case fatality of the bleeding event itself or by thromboembolic complications after temporary or permanent discontinuation/disruption or modification of APT.²⁻⁷ In many cases, treating physicians tend to discontinue APT even after nonmajor bleeding events. Cessation of antithrombotic therapy has been defined in the literature as *discontinuation* (physician-recommended withdrawal), *interruption* (temporary cessation of antiplatelet treatment due to surgical necessity with resumption within 14 days), or *disruption* (cessation of antiplatelet treatment due to bleeding or noncompliance).^{8,9} In the Patterns of nonadherence to Antiplatelet Regimens In Stented patients (PARIS) registry,⁸ the risk of major adverse cardiovascular events (MACE) was approximately sevenfold higher in the first week after disruption of dual antiplatelet therapy (DAPT). An

observational cohort study suggested that those who discontinued P2Y12 inhibitor after 3 months or had poor initial adherence had higher MACE risk compared with those with persistently good adherence over 12 months.¹⁰

If a patient has a bleeding tendency, the majority of major bleeding events occur early (within 3 months) after initiation of DAPT. Shortening of DAPT duration (from 3 to 1 month) is associated with a significant decrease of major bleeding in patients with a HBR (2.1 vs. 1.0%).¹¹ Although the rates of major bleeding decrease over time, there remains a persistent annual major bleeding rate of approximately 0.4% with low-dose acetyl salicylic acid (ASA) and 0.6 to 0.9% with DAPT in the chronic phase beyond 1 year.¹² Among patients treated with DAPT, gastrointestinal bleeding (GIB) accounts for about two-thirds of all bleeding events.¹³ GIB occurs in 3 to 4% of cases in the first year of DAPT.¹³ The bleeding rates reported in randomized trials need to be evaluated with caution when translating into the real world. In clinical trials, patients often either underwent a run-in period of event-free DAPT to be included or were excluded due to bleeding risk criteria (►Table 1). Precise numbers of major and clinically relevant nonmajor bleeding events in true all-comer populations are sparse but likely higher than in well-controlled clinical trials.¹⁴ In addition, bleeding rates differ with regard to bleeding definition, type of APT, and indication, timing and duration of APT (►Table 1). In the PLATelet inhibition and patient Outcomes (PLATO) trial, non-coronary artery bypass graft (non-CABG)-related major bleeding occurred at similar rates under ticagrelor and clopidogrel (2.47 vs. 2.21%) during the first 30 days, and at a significantly higher rate of 2.17% versus 1.65% after 30 days until the end of study treatment with ticagrelor.¹⁵ Similarly, in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing

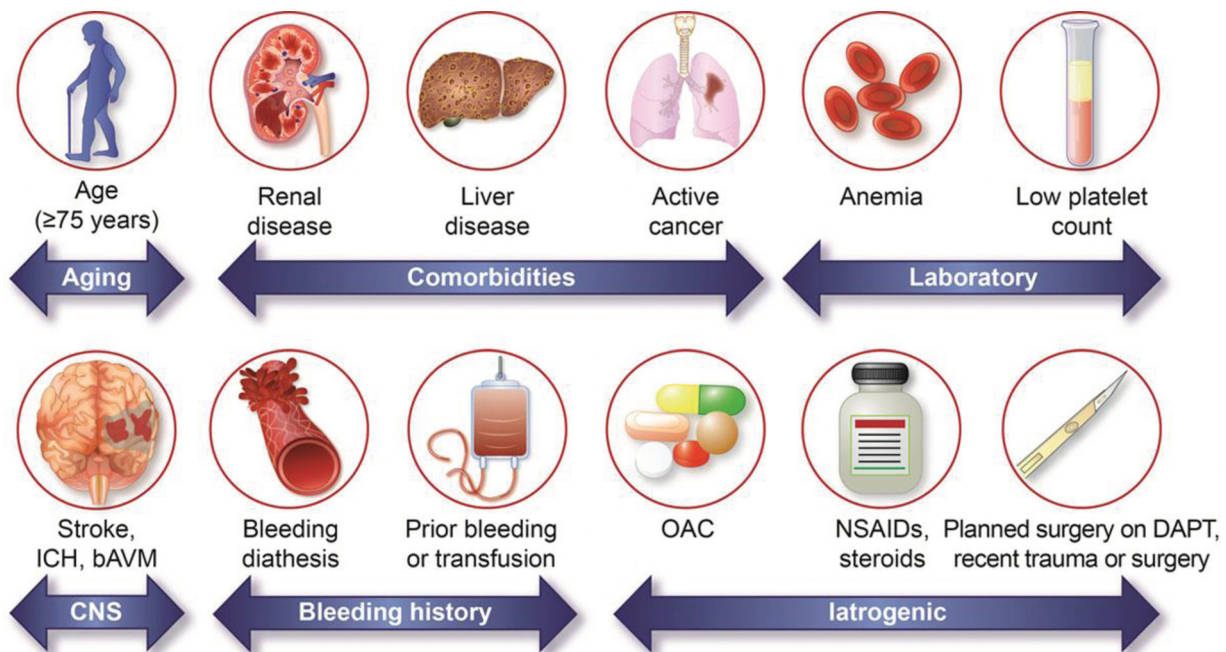


Fig. 1 Major and minor criteria for definition of high bleeding risk, modified according to the Academic Research Consortium.¹ High bleeding risk is defined by the presence of at least one major or two minor criteria.

Table 1 Risk and fatality of major bleeding events in clinical trials and large observational studies of oral antiplatelet therapy

Type of APT	Indication	Incidence/risk increase of major bleeding events	Incidence of intracranial hemorrhage/fatal bleedings
SAPT			
Low-dose ASA	Primary prevention	0.23 per 100 patient-years ⁸⁶ ; 29% increased risk of major bleeding (mostly gastrointestinal) in diabetics, ³⁵ 87% increased risk of upper GIB in healthy elderly, ³⁶ 37% increased risk for ICB versus control ⁸⁷	0.3%, no increase versus control ³⁶
	Secondary prevention in CVD patients	Major bleeding 1.9% ⁸⁸ ; ~60% increased risk of major extracranial bleeds (mostly gastrointestinal) compared with placebo ⁸⁹⁻⁹¹	FB: 0.1% ⁸⁸
Clopidogrel monotherapy	Secondary prevention in patients with a history of ischemic stroke, myocardial infarction, or symptomatic atherosclerotic peripheral arterial disease.	Severe bleeding with clopidogrel versus ASA monotherapy: 1.38 versus 1.55% (nonsignificant); severe GIB (0.49 vs. 0.71%, $p < 0.05$) ³⁸	Nonfatal primary ICH or FB: 0.39% in the clopidogrel group versus 0.53% in the aspirin group ³⁸
	Secondary prevention after PCI (event free under DAPT for 6–18 months)	1.2% over 2 years (vs. 2.0% compared with ASA monotherapy) ³⁹	ICH: 0.2% over 2 years FB: not reported separately
Ticagrelor monotherapy	PCI with high-risk criteria (event free under DAPT for 3 months)	BARC bleeding 3–5 1.0% over 12 months ⁴¹ BARC 3 or 5 bleeding 1.6% over 12 months in HBR patients ⁸²	ICH/FB: not reported separately
DAPT			
ASA + clopidogrel	ACS ± PCI	Non-CABG PLATO-major bleeding 3.8%, non-CABG TIMI-major bleeding 2.2% ¹⁵	FB: 0.3% ¹⁵
	Chronic coronary syndromes	Major bleeding 0.2 to 1.3% with short duration and 0.2 to 2.3% with long duration DAPT ⁹²	
	Secondary prevention in patients with documented CAD, cerebrovascular disease, PAD, or multiple atherothrombotic risk factors	GUSTO severe bleeding according 1.7% in the ASA + clopidogrel group and 1.3% in the ASA + placebo group (relative risk: 1.25; 95 CI: 0.97–1.61; $p = 0.09$) ⁹³	Primary ICH 0.3 in both ASA + clopidogrel and ASA + placebo-treated patients FB: 0.3 (ASA + clopidogrel) versus 0.2% (ASA + placebo) ⁹³
	Extended therapy	BARC 3 bleeding 2.6% during 18 months extended treatment ⁹⁴	FB: 0.1%, no increase versus placebo ¹⁸
ASA + prasugrel	ACS + PCI	Non-CABG TIMI-major bleeding 2.4% ⁹⁵	FB: 0.4%, increased versus ASA + clopidogrel (HR: 4.19) ⁹⁵
ASA + ticagrelor 90 mg/bid	ACS ± PCI	Non-CABG major bleeding 4.5% ¹⁵	

(Continued)

Table 1 (Continued)

Type of APT	Indication	Incidence/risk increase of major bleeding events	Incidence of intracranial hemorrhage/fatal bleedings
			FB: 0.3%, no increase versus ASA + clopidogrel ¹⁵
ASA + ticagrelor 60 mg/bid	Extended therapy (beyond 12 months, post-MI)	Year 1: 0.86%; year 2: 0.86%; year 3: 0.6% ¹²	ICH: year 1: 0.15%; year 2: 0.18%; year 3: 0.28% FB: year 1: 0.11%; year 2: 0.04%; year 3: 0.11% ¹²

Abbreviations: ACS, acute coronary syndrome; ASA, acetyl salicylic acid; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass graft; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; FB, fatal bleeding; HR, hazard ratio; ICH, intracranial hemorrhage; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; UGIB, upper gastrointestinal bleeding.

Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON)–Thrombolysis In Myocardial Infarction (TIMI) 38 trial, TIMI major non-CABG-related bleeding rates with prasugrel were similar to clopidogrel during the first 3 days (0.74 vs. 0.61%) but were significantly higher with the use of prasugrel from 3 days to the end of study drug treatment (1.71 vs. 1.23%).¹⁶ In the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction (PEGASUS)–TIMI 54 trial, long-term DAPT with ticagrelor beyond 1 year post-myocardial infarction (MI) was associated with a 3-year major bleeding rate of 2.6% (90 mg bid) and 2.3% (60 mg bid) versus 1.1% with ASA alone and intracranial hemorrhage (ICH) rates of 0.56% (90 mg bid) and 0.61% (60 mg bid) versus 0.47% with ASA alone.¹⁷ Similarly, moderate-to-severe bleeding events occurred in 2.0% of cases under long-term treatment with clopidogrel plus ASA in the DAPT trial. Case fatality was high with an annualized mortality rate after a bleeding event of 21.5 (95% confidence interval [CI]: 15.4–29.1) per 100 person-years.¹⁸

Trade-Off between Bleeding and Ischemic Risk

Clear classification of the bleeding severity according to established bleeding risk classifications (i.e., Bleeding Academic Research Consortium [BARC], International Society of Thrombosis and Haemostasis [ISTH] bleeding classification; ► **Table 2**) and the individual assessment of bleeding recurrence and thrombotic risk are of utmost importance. In a retrospective study of the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial, the risk for mortality after major bleeding (BARC 3b + c) was almost equal to the mortality risk after MI. However, compared with bleeding with lower severity (BARC 2 and 3a), the mortality after MI clearly outweighed the bleeding-associated mortality risk.¹⁹ Thus, the trade-off between cardiovascular versus bleeding-associated mortality needs to be clearly defined (► **Fig. 2**). Although scores that weigh the antithrombotic benefit against the bleeding risk of continued DAPT have not been evaluated up to now in acute bleeding situations, they might aid decision-making about the net benefit of prolonged APT in HBR patients.

Several contemporary scores evaluate the bleeding risk and trade-off between bleeding and ischemic risk, and weigh the net benefit of prolonged versus shortened DAPT. Their utility in clinical routine is limited by their inability to discriminate between bleeding and ischemic risks as well as by the characteristics of the patient population and APT in the derivation cohorts.^{1,20–25} (► **Table 3**).

Evaluation before Resumption of Antiplatelet Therapy

Has the Bleeding Stopped?

Determining whether a major bleeding event has stopped depends on the source and severity of the bleeding and may require multidisciplinary evaluation. Repeated diagnostic assessment might be required to determine cessation of a bleeding event, including close measurements (daily or even hourly depending on urgency of bleeding) to document hemoglobin drops. Repeated computed tomography (CT) scans can help to determine the time point of cessation of ICH and complications of the bleeding potentially requiring neurosurgical intervention (e.g., hydrocephalus). In addition, CT angiography and post-contrast CT may aid in identifying patients at high risk of hematoma expansion according to the presence of contrast within the bleed, defined as “spot signs,” or brain vascular malformation.²⁶ Scores that included further information on number of spot signs, dimension, and attenuation have been shown to be predictive for mortality and poor outcome.²⁷ Evaluation of spot sign dynamics on CT perfusion source images might yield even better prognostic information with regard to hematoma expansion.²⁸

In case of GIB, repeated endoscopy may provide information about the localization and cause of the bleeding. The use of endoscopy can effectively contribute to treatment of the bleeding lesion, e.g., by epinephrine injection, cauterization, variceal band ligation, and metal clip placement. Endovascular angiography²⁹ and medical options such as octreotide infusions may also be considered for bleeding from angioectasia,³⁰ when endoscopic therapies fail or when bleeding originates from less accessible locations such as the small bowel. Thus, in many situations, GIB can be effectively controlled to allow a timely resumption of APT if indicated.

Table 2 Definition of major (non-fatal, non-surgical) and clinically-relevant non-major bleeding events, according to ISTH and BARC definitions

	ISTH96,97	BARC98
Major bleeding	<ul style="list-style-type: none"> • Fatal bleeding, and/or • Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or • Bleeding causing a fall in hemoglobin level of 2 g/dL or more or leading to transfusion of two or more units of whole blood or red cells. 	Type 3a <ul style="list-style-type: none"> • Overt bleeding plus hemoglobin drop of 3 to 5 g/dL (provided hemoglobin drop is related to bleed) • Any transfusion with overt bleeding Type 3b <ul style="list-style-type: none"> • Overt bleeding plus hemoglobin drop of 5 g/dL (provided hemoglobin drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) • Bleeding requiring intravenous vasoactive agents Type 3c <ul style="list-style-type: none"> • Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) • Subcategories confirmed by autopsy or imaging or lumbar puncture • Intraocular bleed compromising vision
Clinically relevant nonmajor bleeding	Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: <ul style="list-style-type: none"> • requiring medical intervention by a health care professional • leading to hospitalization or increased level of care • prompting a face-to-face (i.e., not just a telephone or electronic communication) evaluation 	Type 2 <p>Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:</p> <ul style="list-style-type: none"> • requiring nonsurgical, medical intervention by a health care professional, • leading to hospitalization or increased level of care, or • prompting evaluation.

Abbreviations: BARC, Bleeding Academic Research Consortium; ISTH, International Society on Thrombosis and Haemostasis.

Is Antiplatelet Therapy Still Needed?

The question whether APT is still needed after a bleeding event and, if so, at what potency and duration is subject to individual risk–benefit assessment. In many cases, antithrombotic therapy can be shortened according to recent guideline recommendations.³¹ Individualized strategies to reduce the bleeding risk by mitigating APT should include the type of intervention and the initial drug strategy. Thus, use of an abbreviated DAPT duration with ultrathin stents has been shown to reduce bleeding risk in HBR patients without substantially increasing ischemic risk, including stent thrombosis.³² Recently, recommendations to guide the design of clinical trials of devices and drugs in HBR patients undergoing percutaneous coronary intervention (PCI) have been proposed.³³

ASA Used for Primary Prevention in Individuals with Low or Moderate Risk for Ischemic Events

ASA may be considered for primary prevention in high- and very high-risk individuals according to the SCORE2 and SCORE2-OP risk classifications³⁴ given its unfavorable net benefit versus placebo in moderate risk or diabetic

patients.^{35,36} Resumption of ASA used for primary prevention after a bleeding event should therefore be avoided in low-risk patients and discussed on a case-by-case approach in high- and very high-risk patients given its accumulating benefit over time.³⁷

SAPT for Secondary Prevention

The most common single antiplatelet therapy (SAPT) for secondary prevention in cardio-, cerebrovascular, and peripheral artery disease is aspirin. However, there are cumulative data demonstrating clopidogrel monotherapy to be as effective and safer than aspirin for chronic maintenance monotherapy.^{38,39}

Dual Antiplatelet Therapy

Duration of DAPT can be reduced down to 1 month in patients undergoing elective PCI with modern stents and to 1 to 3 months after acute coronary syndrome (ACS) in high and very high bleeding risk patients according to recent guidelines.^{31,32,40} De-escalation to less potent P2Y₁₂ inhibitors or early switching to P2Y₁₂ inhibitor monotherapy has

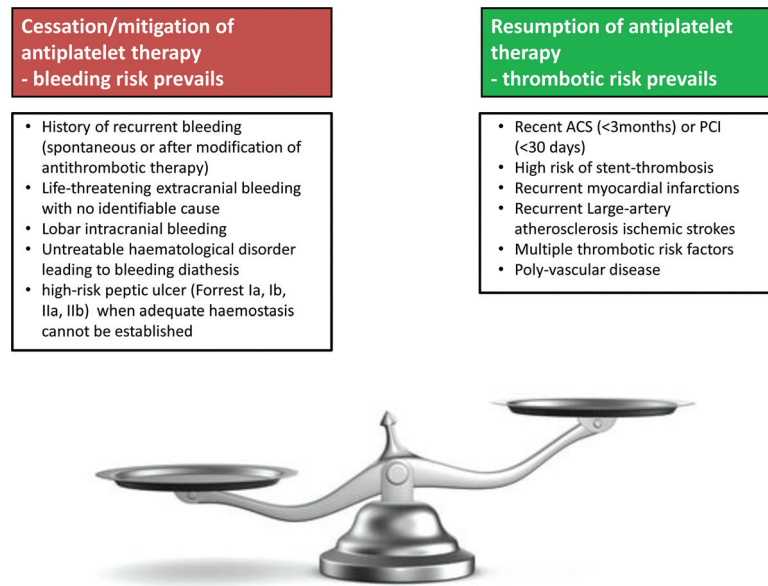


Fig. 2 Weighing of ischemic versus bleeding risk (figure was composed by using Adobe Stock vectors).

been established as effective strategies to prevent bleeding in HBR patients and in patients in whom the trade-off prevails on the bleeding risk side (► **Table 3**).^{41–46}

What Caused the Bleeding?

Risk factors for bleeding can be classified into reversible and irreversible factors (► **Table 4**). The question of what caused the bleeding is closely linked to the question of which modifiable factors may have contributed to the bleed and whether definitive treatment of these factors has been achieved. Identification of reversible/modifiable and irreversible factors as well as the risk for recurrence is important to provide an individual strategy to resume APT.

Recurrence of Bleeding after Resumption of Antiplatelet Therapy

The dilemma of weighing the benefit against the harm of resumption of antithrombotic therapy warrants interdisciplinary discussion for defining both severity of bleeding and risks of bleeding recurrence and thromboembolic events. ► **Table 4** summarizes risk factors for bleeding recurrence after ICH and major GIB. In addition, bleeding event history and comorbidities add to the bleeding risk recurrence and should be carefully included in the risk assessment, especially if risk factors cannot be controlled. Additional bleeding risk factors include those listed in the ARC-HBR classification scheme (► **Fig. 1**).¹ The use of biomarkers like growth differentiation factor-15 has been investigated to determine recurrent bleeding risk and recurrent events in post-hoc analyses of large clinical trials.⁴⁷ However, its use in clinical routine is still limited.

Risk of Recurrence of Gastrointestinal Bleeding

Predictors of recurrent GIB risk and bleeding fatality depend on the cause of bleeding. Thus, worse outcomes are associated with chronic alcoholism and active cancer.²² Risk scoring

systems have been evaluated to predict the risk of mortality and rebleeding after GIB. The Rockall scoring system⁴⁸ and the Glasgow–Blatchford Scale⁴⁹ are scoring systems that include clinical, laboratory, and/or endoscopic findings. These risk scores are used to predict the mortality associated with GIB, the urgency of endoscopy, and likelihood of endoscopic intervention, but they have not been validated for guidance regarding resumption of APT. The endoscopic appearances of a peptic ulcer, as described by the Forrest classification,⁵⁰ may be used to predict the risk of rebleeding in the period soon after an endoscopy. Patients with actively bleeding ulcers or ulcers with a visible blood vessel have a much greater risk of rebleeding than ulcers with a clean base.⁵¹ It is important to evaluate whether the GIB occurred during proton-pump inhibitor (PPI) treatment or not. If the upper GIB happens under effective PPI treatment, this might be an indicator to stop or reduce APT on an individual basis if there are no other reversible factors (*Helicobacter pylori* [HP], nonsteroidal anti-inflammatory drug, endoscopic therapy). Initiation of effective gastroprotection is a way to prevent recurrent bleeding. A randomized placebo-controlled trial showed that high-dose intravenous PPI treatment (omeprazole 80 mg bolus then 8 mg/h infusion for 72 hours after endoscopic therapy)⁵² in patients who had undergone endoscopic treatment of peptic ulcers effectively reduced the risk of rebleeding compared with endoscopy and placebo. Recent meta-analyses support the use of PPI therapy to promote healing of peptic ulcers thus reducing bleeding and mortality in patients at risk for upper GIB.^{53,54} There is no randomized controlled trial (RCT) that has evaluated the use of different PPI regimens and durations in patients that require resumption of antithrombotic therapy after major GIB. The common-sense view of the authors is that PPI therapy should be continued indefinitely at standard dose in patients with major upper GIB unless there are clear contraindications. Active HP infection is frequent with a

Table 3 Contemporary risk scores to define bleeding risk and trade-off between bleeding and ischemic risk in patients treated with APT

Score	Patient population/predominant type of APT	Risk factors in the primary model	Correlation with bleeding in the derivation cohort	Trade-off between bleeding and ischemic risk	Clinical utility/validity in real world
DAPT (total score range: -2 to 10) ²²	PCI patients completing 12-month DAPT (60% ASA + clopidogrel, 40% ASA + prasugrel)	Age (categorized) Smoking Diabetes mellitus MI at presentation Prior PCI or MI Pacitaxel-eluting stent Stent diameter < 3 mm CHF or LVEF < 30 Vein graft stent	AUC 0.68 for moderate to severe bleedings (GUSTO) between 12 and 30 months under of prolonged DAPT.	Score ≥ 2 is associated with a favorable benefit/risk ratio for prolonged DAPT, whereas a score < 2 is associated with an unfavorable benefit/risk ratio	Ability to stratify ischemic benefit across different DAPT patient cohorts ⁹⁹⁻¹⁰²
PARIS (range: 0-14) ²³	PCI + drug-eluting stent (>90% ASA + clopidogrel)	Score for bleeding (PARIS MB): age (percentiles > 50 years) BMI Current smoking Anemia CrCl < 60 mL/min Triple therapy on discharge	AUC for major bleeding (BARC 3 or 5) at 2 years: 0.72		AUC 0.64 validation cohort (ADAPT-DES) ¹⁰³
PRECISE-DAPT (range: 0-100) ²⁰	PCI + stent (ASA + clopidogrel (88%))	Age (continuous), creatinine clearance, hemoglobin, previous bleeding, and white blood cell count (simplified version excluding white blood cell count) ¹⁰⁴	AUC 0.71 for TIMI major bleedings within 12 months	Longer DAPT duration reduced the composite ischemic endpoint (MI, definite ST, stroke, or target vessel revascularization) in those at non-high bleeding risk	Recommended in current guidelines, ^{7,31} reproducible in real-world cohorts, limited usefulness in patients with MI and pre-existing risk factors for bleeding ^{103,105,106}
PRAISE ²⁴	ACS (ASA + clopidogrel (64%) + ticagrelor (21%), + prasugrel (15%))	16 clinical variables ^a , five therapeutic variables ^b , two angiographic variables ^c , and two procedural variables ^d	AUC for major bleeding within 12 months: 0.70 in the internal validation cohort	Robust hypothetical trade-offs in the occurrence of ischemic and bleeding events according to individual MI and major bleeding score classes ²⁴	High predictability and good discrimination of the trade-off (AUC > 0.8 for mortality, MI, and major bleeding in an external validation cohort) ²⁴ Allowing for differentiation of the use of potent P2Y12 inhibitors in different bleeding/thrombotic risk subsets. ¹⁰⁷ Further external validation required.
ARC-High Bleeding Risk Trade-off Model ¹²¹	Consensus definition of HBR in clinical trials evaluating the safety and effectiveness of devices and drug regimens for patients undergoing PCI	Combination of major and minor risk factors; see ► Fig. 1	No AUC in primary publication/consensus document	Eight independent predictors of MI and/or ST, 8 predictors for risk of BARC types 3 to 5 bleeding; both risk models showed moderate discrimination; AUC = 0.69 for predicting MI and/or ST and 0.68 for predicting BARC types 3 to 5 bleeding. ²¹	Recommended in current guidelines, ^{7,31} reproducible validation in external cohorts; high sensitivity, limited specificity ^{108,109}
BleeMACS (range: 0-80) ²⁵	Patients with ACS undergoing PCI (ASA + clopidogrel (91%), + ticagrelor (4%), + prasugrel (5%))	Age (categories), Hypertension, vascular disease, history of bleeding, Malignancy, creatinine (categories) hemoglobin	AUC: 0.71 for 1-year major bleeding in derivation cohort (0.72 internal validation) AUC: 0.65 (ACS + PCI); AUC: 0.63 (ACS)	Not validated	Acceptable performance in elderly ACS patients ¹¹⁰ ; further validation required

Abbreviations: ACS, acute coronary syndrome; ASA, acetyl salicylic acid; AUC, area under the curve; BARC, Bleeding Academic Research Consortium; CHF, congestive heart failure; DAPT, dual antiplatelet therapy; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

^aAge, sex, diabetes, hypertension, hyperlipidemia, peripheral artery disease, estimated glomerular filtration rate (eGFR); using the Modification of Diet in Renal Disease study formula), previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass graft, previous stroke, previous bleeding, malignancy, STEMI at presentation, hemoglobin, and left ventricular ejection fraction [LVEF].

^bTreatment with β blockers, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, statins, oral anticoagulation, and proton-pump inhibitors.

^cMultivessel disease and complete revascularization.

^dVascular access and percutaneous coronary intervention with drug-eluting stent.

Table 4 Risk of major bleeding recurrence in clinical trials and observational studies of antiplatelet therapy

Reversible causes of bleeding	Irreversible causes of bleeding
General factors	
Arterial hypertension Alcohol abuse Drug abuse	Older age (≥ 75 years) History of major spontaneous bleeding Malignancy Genetic factors Cirrhotic liver disease Uncontrollable arterial hypertension Hematologic abnormalities (e.g., low platelet count $< 50,000$ per μL) Dialysis-dependent kidney disease or renal transplantation ¹¹¹
Specific factors	
GI bleeding	
Small bleeding ulcer that can be treated by endoscopic therapy Bleeding from gastric ulcer associated with <i>Helicobacter</i> disease	Bleeding from sources that cannot be sufficiently treated by surgery or endoscopic procedures e.g., colonic tumor, angiodysplasia
Intracranial bleeding	
Traumatic cause of ICH Poor INR control, overdosing of antithrombotic therapies	Cerebral amyloid angiopathy Vascular abnormalities that cannot be treated by surgical or interventional procedures. Spontaneous ICH without identifiable risk factors (e.g., poor INR control)

Abbreviations: ICH, intracranial hemorrhage; INR, international normalized ratio.

reported prevalence of 20% in acute MI patients and still is an underestimated risk factor for GIB in patients treated with DAPT.^{55–57} Therefore, HP screening, eradication, and gastro-protective measures are important to minimize recurrent GIB risk.^{57–59}

Risk of Recurrence after Intracranial Bleeding

The REstart or STop Antithrombotics Randomized Trial (RESTART) evaluated the efficacy and safety of restarting APT after ICH. APT could be restarted in the interventional arm by using either one or a combination of ASA, dipyridamole, or clopidogrel at any time beyond 24 hours (median: 76 days) after randomization. In the comparator arm, no APT was allowed. However, it was permitted to start or discontinue APT or anticoagulant therapy if clinically indicated during follow-up, regardless of initial treatment allocation. Interestingly, RESTART demonstrated a reduced risk of both thromboembolic events and hemorrhagic strokes in patients restarting APT.^{60,61} These observations were recently confirmed in an extended follow-up at a median of 3.0 years.⁶² Given the variable time points of restarting APT in RESTART, the optimal time interval from ICH is still uncertain.

Arterial hypertension is a major cause underlying ICH, and consensus exists that blood pressure should be well controlled after ICH.⁶³ Also, other modifiable risk factors promoting continued stress to the already fragile vessel wall, or progressive endothelial damage such as in diabetes, should be treated before re-initiating any kind of antithrombotic regimen after ICH.^{64,65} Risk of ICH recurrence is higher in patients with lobar intracerebral bleeds compared with those with hemorrhage in

deep subcortical brain structures; nonetheless, resumption of APT seems beneficial with regard to mortality and functional outcome even in patients who suffered from a lobar bleed.⁶⁰ Superficial hemosiderosis and microbleeds are not visible on CT but their presence, number, and location can be visualized on magnetic resonance imaging (MRI) and have been linked to the risk of ICH.^{61,66} A nearly fivefold increased ICH risk has been observed in patients with five or more microbleeds.⁶⁷ However, even in patients with more than 20 microbleeds, the rate of ischemic stroke exceeded that of ICH.⁶⁷ Whereas microbleeds in the white matter or basal ganglia result from small vessel disease due to long-lasting arterial hypertension or diabetes, i.e., treatable conditions, cortical microbleeds are found in patients with (untreatable) cerebral amyloid angiopathy and are regarded as a precursor of atypical lobar bleeds. MRI might thus be superior to CT when it comes to selection of ICH candidates for restarting antithrombotic therapy (**► Fig. 3**).⁶⁸

Strategies to Resume Antiplatelet Therapy

What Are the Patients' Overall Goals of Care?

The main goal of restarting APT is to prevent ischemic events without increasing bleeding events and to reduce mortality and disability caused by recurrent stroke. For most patients, APT, if indicated, should be restarted after most bleeding events, considering that, for most of the therapies, fatal bleeding during APT is rare (**► Table 1**) and so the risk–benefit assessment does not favor permanent discontinuation of therapy. The mortality risk associated with major adverse events, e.g., MI or stroke, outweighs the risk of dying from

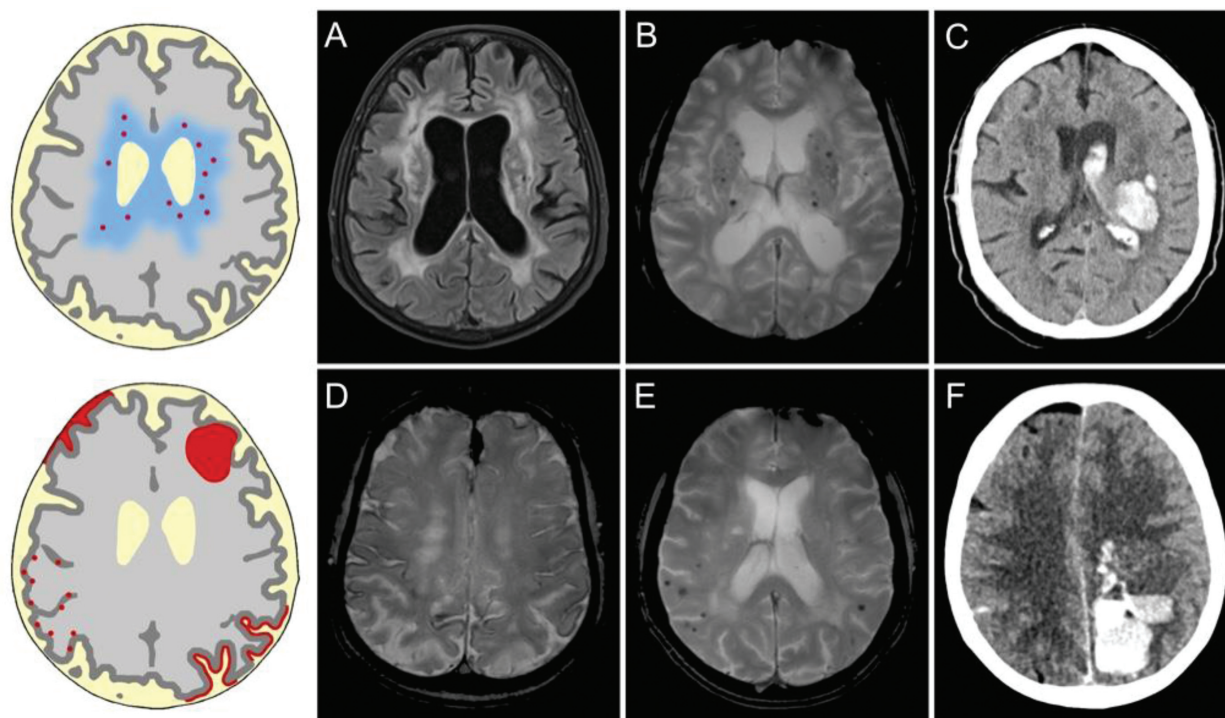


Fig. 3 Upper row: schematic drawing showing typical sequelae found in patients suffering from long-term arterial hypertension, i.e., leukoaraiosis and deep microbleeds. (A) Leukoaraiosis on fluid-attenuated inversion recovery (FLAIR) MRI, (B) deep microbleeds within the basal ganglia and thalami, and (C) a hypertensive basal ganglia hemorrhage with intraventricular extension. Other typical locations of hypertensive intracerebral hemorrhages are thalamic, pontine, and cerebellar hemorrhages. Lower row: schematic drawing showing bleeding lesions indicative for cerebral amyloid angiopathy, i.e., convexity subarachnoid hemorrhage (front left), lobar hemorrhage (front right), superficial hemosiderosis (back right), and cortical microbleeds (back left). (D) Superficial hemosiderosis, (E) cortical microbleeds, and (F) a hemorrhage within the left occipital lobe.

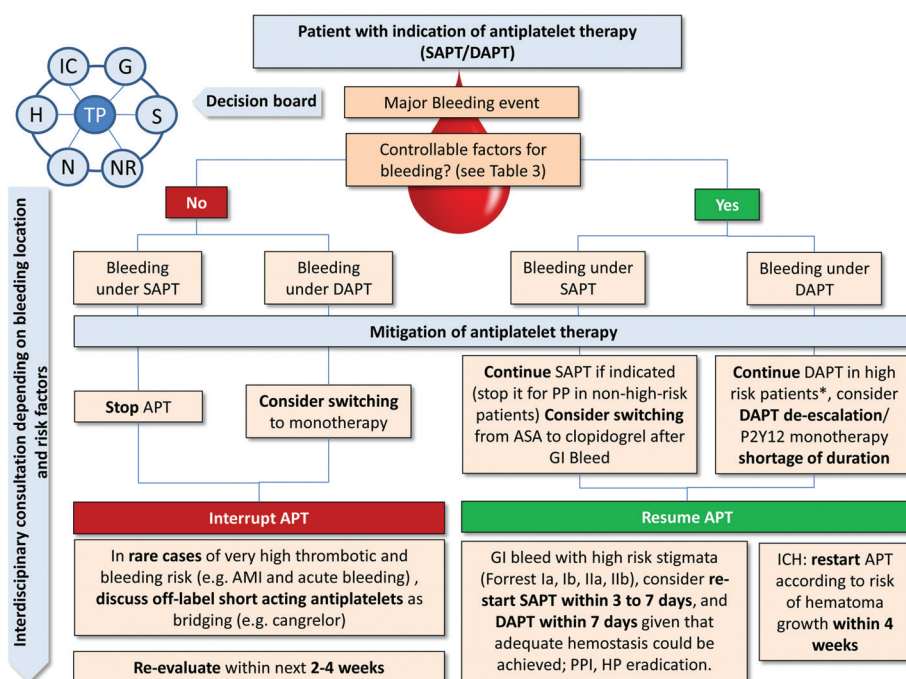


Fig. 4 Suggested algorithm for interruption of antiplatelet or anticoagulation according to bleeding severity type. AMI, acute myocardial infarction; G, gastroenterologist; H, hematologist; IC, invasive cardiologist; N, neurologist; NR, neuroradiologist; S, surgeon; TP, treating physician. *For example, patients with recurrent myocardial infarction (MI), patients with high risk of stent thrombosis or previous stent thrombosis, recent ACS (<3 months) or PCI (<30 days), recurrent MI, recurrent large-artery atherosclerosis, ischemic strokes, multiple thrombotic risk factors, polyvascular disease.

minor or moderate bleeding events (e.g., BARC 2 and 3a bleeding).¹⁹ Interruption and resumption of APT should be individually tailored according to bleeding severity/location, indication for antithrombotic therapy, risk for bleeding recurrence, and thrombotic risk. APT should only be interrupted in case of major/severe bleeding. In clinically relevant but not major bleeding events, therapy in patients with clear indication for APT can be safely continued in most cases after short interruption. There is no need for interruption of APT in patients with minor/trivial bleeding events.

Restarting/De-escalating Antiplatelet Therapy

The need for continuation of APT should be carefully assessed by weighing thrombotic versus bleeding risk. The impact of early resumption (immediately after endoscopic therapy) of low-dose ASA therapy was investigated in a small placebo-controlled trial in 156 patients presenting with bleeding from peptic ulcer during ASA treatment. Within 30 days, the incidence of recurrent ulcer bleeding was 10.3% of patients who continued ASA treatment versus 5.4% in patients receiving placebo ($p = 0.25$). All-cause mortality was markedly lower in the ASA group compared with the placebo group (1.3 vs. 12.9%, $p = 0.005$). The low statistical power does not allow definite conclusions to be drawn from this trial.⁶⁹ A recent meta-analysis including this RCT and observational studies reports inconsistent evidence for a protective effect of aspirin resumption soon after nonvariceal upper GIB.⁷⁰ Current guidelines recommend resumption of aspirin for secondary prevention within 3 to 7 days after upper GIB cessation.^{71,72} The European Society of Gastrointestinal Endoscopy recently recommended determining the time point of ASA re-initiation based on endoscopic classification of peptic ulcer classification. In patients with low-risk endoscopic stigmata identified by Forrest classification IIc or III, ASA should be restarted immediately. In patients with high-risk stigmata (Forrest Ia, Ib, IIa, IIb), ASA should be restarted at day 3, given that adequate hemostasis could be achieved.⁷³ Extrapolating data from patients undergoing polypectomy show a similar bleeding risk between patients discontinuing and those continuing ASA.⁷⁴ The American College of Gastroenterology (ACG) recommends not to discontinue ASA for secondary prophylaxis in patients with established cardiovascular disease in the setting of lower GIB.⁷⁵

In some situations, permanent cessation or de-escalation of DAPT may be considered. In patients with major bleeding, the duration of DAPT can be shortened to 1 month after elective PCI and to 6 months or less after ACS according to recent guidelines.^{7,31,40} There are accumulating data from trials indicating safety of 1 month DAPT in high-bleeding-risk patients treated with modern drug-eluting stents.^{32,44,76-78} In patients with ACS undergoing PCI, the highest risk for recurrent cardiovascular event lies within the first 3 months and cessation of DAPT within the first month is associated with high risk of MACE and stent thrombosis.⁹ Therefore, longer periods of discontinuation of DAPT (i.e., ≥ 5 days) should be avoided in this vulnerable phase. Of note, the bleeding event itself can trigger a prothrombotic condition by inflammatory processes, but also by the administration of

Table 5 Ongoing trials evaluating resumption of APT and interventional strategies in patients with major bleeding

Study	Study population	Sample size	Randomization arms	Estimated completion date
RESTART-Fr (NCT02966119)	ICH in patients on antiplatelet or anticoagulant therapy	292	ASA, clopidogrel, or dipyridamol according to treating physician's decision versus no treatment	December 2022
Study of Antithrombotic Treatment after IntraCerebral Hemorrhage (STATICH) (NCT03186729)	Spontaneous, primary ICH, and indication for antiplatelet or anticoagulant therapy	500	Anticoagulant or antiplatelet drugs versus no antithrombotics	June 2023
When Should Low-dose ASA be Resumed after Peptic Ulcer Bleeding? (NCT03785015)	Patients with active GIB or high-risk ulcers on ASA monotherapy or DAPT	436	Resume the standard treatment within 12 hours versus 72-84 hours after endoscopic hemostasis	February 2022

Abbreviations: ACS, acute coronary syndrome; ASA, acetyl salicylic acid; DAPT, dual antiplatelet therapy; ICH, intracranial hemorrhage.

blood products, coagulation factors, and antidotes. Therefore, in patients with temporary enhanced bleeding risk and high thrombotic risk requiring DAPT (e.g., patients with a recent major bleeding and acute MI), antiplatelet compounds with short offset of action, i.e., cangrelor might be a temporary option. However, there is only limited experience with regard to safety and efficacy profile in bleeding situations. According to the product labels, the use of cangrelor, eptifibatid, and tirofiban is off-label in bleeding situations. Based on previous consensus documents, it is advisable to restart DAPT within 3 days after moderate GIB.^{9,73} DAPT should be interrupted for a longer period after major GIB and may be resumed after 7 to 15 days in patients with low/moderate risk of recurrence.^{73,79} There is no clear consensus if early re-initiation of a P2Y₁₂ inhibitor and omission of ASA is associated with a favorable risk–benefit profile early after major GIB. The ACG guideline recommends that, in patients on DAPT or SAPT with clopidogrel, non-ASA-based APT should be resumed as soon as possible and at least within 7 days based on multidisciplinary assessment of cardiovascular and gastrointestinal risk. A second endoscopic examination may help to evaluate the further risk after initiation of DAPT. DAPT should not be discontinued in patients with an ACS within the past 90 days or coronary stenting within the past 30 days (strong recommendation, low-quality evidence).⁷⁵ SAPT should be maintained if possible in most instances. Concomitant long-term therapy with PPIs should be implemented if not already started.^{73,80} In addition, de-escalation therapy to DAPT with clopidogrel in post-ACS patients after a short period of DAPT with prasugrel or ticagrelor might be applicable to HBR patients, which has shown to be beneficial regarding reduction of bleeding in recent trials.^{42,46,81} This includes de-escalation guided by platelet function or genetic testing, which has demonstrated favorable effects in a recent meta-analysis⁴⁶ and could be particularly useful in patients with both high bleeding and ischemic risk. Early switching to monotherapy after 1 to 3 months of DAPT to ticagrelor^{41,45,82} or clopidogrel⁴⁴ monotherapy represents alternative strategies to reduce future bleeding events without losing efficacy in selected patients. Availability of the specific antidote (i.e., antibody-based antidote bentracimab [PB2452] for ticagrelor) may be relevant when choosing the oral P2Y₁₂ inhibitor for long-term

treatment in HBR patients. However, there are limited data on efficacy and safety in acute bleeding situations and the antidote is not yet available.⁸³

Restarting Combination Therapy (Anticoagulation + APT)

Triple therapy should be avoided in patients with atrial fibrillation (AFIB) undergoing PCI who experienced a prior major bleeding event. The better safety of dual antithrombotic therapy consisting of non-vitamin-K-antagonist oral anticoagulants (NOACs) plus a P2Y₁₂ receptor inhibitor compared with triple therapy^{2,84} is established and highly recommended.^{31,85} In HBR patients, switching from triple therapy (NOAC + DAPT) to dual therapy (NOAC + P2Y₁₂ inhibitor) and from vitamin-K antagonists to NOAC are possible strategies to reduce the bleeding risk. In case bleeding occurred under dual antithrombotic therapy (NOAC + SAPT), dose reduction of NOAC to the lowest effective dose should be considered.⁷ Although the preferred dosing for patients with AFIB undergoing PCI in general should be the highest approved NOAC dose, if indicated, the current guidelines recommend lowering the dose in HBR patients.⁸⁵ If risk for recurrent bleeding remains high even under a reduced NOAC dose, left atrial appendage occlusion may be considered in patients to get along with APT only for long-term treatment.

Conclusion

Growing use of antithrombotic drugs in the elderly and frail patients leads to more bleeding events and challenging situations with respect to resuming therapies. The clinician often faces the dilemma of whether and when to restart APT after a bleeding event. Risk estimation requires a multidisciplinary team discussion to adequately determine the risk for thrombosis and bleeding recurrence. Guidance on the optimal time point to resume APT is based on retrospective registry data analysis and expert consensus. The presented review and algorithm (►Fig. 4) provide guidance based on an individual dynamic risk assessment and advocate for enrollment of patients in one of the ongoing trials (►Table 5). Potential strategies to reduce future bleeding risk by modification of antithrombotic therapy are summarized in ►Table 6.

Table 6 Potential strategies to reduce future bleeding risk by modification of antithrombotic therapy

Bleeding occurred under treatment with	Possible strategies
SAPT	Consider cessation in particular in case of primary prevention, or if indicated switching from ASA to non-ASA (e.g., clopidogrel) treatment
DAPT	Consider cessation, switching to monotherapy (aspirin, clopidogrel, or ticagrelor), or de-escalation after ACS
Combination therapy	Consider switching from triple therapy to dual therapy, consider reducing the dose of NOAC in patients with HBR, consider LAA occlusion if high recurrent bleeding risk persists even under reduced NOAC dose

Abbreviations: ACS, acute coronary syndrome; ASA, acetyl salicylic acid; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; LAA, left atrial appendage; NOAC, non-vitamin-K-antagonist oral anticoagulant; SAPT, single antiplatelet therapy.

Conflict of Interest

T.G. reports personal fees from Astra Zeneca, Boehringer Ingelheim, Pfizer, Boston Scientific, and Abbott; grants and personal fees from Bayer Healthcare, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, and Medtronic outside of the submitted work. T.G. was supported by the German Research Foundation (DFG) KFO-274—Project number 190538538, by the German Research Foundation (DFG)—Project number 374031971-TRR 240, and funded by the German Research Foundation (DFG)—Project number 335549539-GRK2381. S.P. reports research grants from Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, the European Union (EU), and the Federal Joint Committee Innovation Fund (GB-A Innovationsfonds), and speakers' honoraria and consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, and Werfen outside of the submitted work. K.H. reports lecture fees from AstraZeneca, Bayer, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Portola, and Sanofi Aventis outside of the submitted work. D.R. has no conflicts to report. P.A. has no conflicts to report. S.D.K. has no conflicts to report. R.F.S. reports research grants and personal fees from AstraZeneca, Cytosorbents, GlyCardial Diagnostics and Thromboserin, and personal fees from Alnylam, Bayer, Bristol Myers Squibb/Pfizer, Chiesi, CSL Behring, HengRui, Idorsia, Intas Pharmaceuticals, Medscape, Novartis, PhaseBio, Portola, and Sanofi Aventis outside of the submitted work. A.B. has no conflicts of interest. J.P.C. reports personal fees and honoraria from AstraZeneca, Bristol-Myers Squibb, Lead-Up, Medtronic, and WebMD, and research grant to the institution from Medtronic and Boston Scientific. J.T.B. reports speaker and consultancy fees from AstraZeneca, Eli Lilly, Daiichi Sankyo, The Medicines Company, Accu-Metrics, Boehringer Ingelheim, BMS, Pfizer, Bayer, and Ferrer, and grants from ZonMw and AstraZeneca outside of the submitted work.

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