

JACC REVIEW TOPIC OF THE WEEK

Intracranial Hemorrhage During Dual Antiplatelet Therapy



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ABSTRACT

Dual antiplatelet therapy (DAPT) with acetylsalicylic acid and a P2Y₁₂ inhibitor is an established therapy for a broad spectrum of patients with cardiovascular disease. The ischemic benefit of DAPT is partially offset by its increased bleeding risk, with intracranial hemorrhage (ICH) being the most serious complication. Although uncommon (0.2%-0.3% annually), its cumulative burden can be substantial given the number of patients afflicted by cardiovascular disease worldwide. Patients with a history of stroke or transient ischemic attack harbor a particularly high risk for ICH when treated with DAPT. Prediction rules may assist clinicians when weighing the risk/benefit ratio of prescribing DAPT for patients with stroke/transient ischemic attack in the nonacute, ambulatory setting. Currently, there are no reversal agents that can rapidly and effectively reverse the effect of P2Y₁₂ inhibitors in routine practice, although a reversal agent for ticagrelor is under clinical investigation. (J Am Coll Cardiol 2021;78:1372-1384) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Dual antiplatelet therapy (DAPT) with an oral P2Y₁₂ inhibitor and acetylsalicylic acid (ASA) is a cornerstone treatment for a broad spectrum of patients with cardiovascular disease. Multiple randomized trials have established the superiority of DAPT over single antiplatelet therapy (SAPT) in reducing the risk of stroke and myocardial infarction in the following patient populations: percutaneous coronary intervention (PCI), acute coronary syndrome (ACS), high-risk chronic coronary artery disease, and those with a recent history of stroke or transient ischemic attack (TIA) (1-8). Extended DAPT (>12 months) for patients at high risk of coronary ischemia and with low or moderate risk of major

bleeding is a class IIa recommendation in the recent European Society of Cardiology guidelines for chronic coronary syndromes (3). However, gains in ischemic protection afforded by DAPT are somewhat offset by increased risk of major bleeding by up to 30% to 70% compared with SAPT (4,5,7,8). Faced with this trade-off, physicians must carefully weigh their decision to initiate and/or continue DAPT for patients who would benefit from this therapy, particularly those at high risk of serious or life-threatening bleeding.

Intracranial hemorrhage (ICH) is the most serious bleeding complication related to antiplatelet therapy. Fatality rates from ICH related to antiplatelet agents



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HIGHLIGHTS

- DAPT is associated with a 40% increased risk of ICH compared to aspirin alone.
- The risk of ICH during antiplatelet therapy can be estimated from validated prediction models.
- Development of reversal agents for P2Y₁₂ inhibitors may improve the safety of DAPT in patients with atherosclerosis.

remain very high, at up to 60% even during the current era (9). On an individual level, the incident risk of ICH is relatively low among patients treated with SAPT or DAPT, in the range of 2 to 3 cases per 1,000 person years (8,10). However, on a population level, the aggregate burden of DAPT-associated ICH is sizeable. Annually, 1 million hospitalizations related to ACS, 480,000 PCI procedures, 695,000 cases of ischemic stroke, and ≈5 million cases of TIA occurred in the United States alone (11). Because DAPT has clinically proven benefits in these patient populations, the total number of potential ICH cases related to antiplatelet therapy can be substantial. Furthermore, the unavailability of therapy to rapidly reverse the effect of antiplatelet agents may contribute to the significant morbidity and mortality associated with ICH in this patient population.

The objective of the current review was to bring attention to cardiovascular physicians that antiplatelet-associated ICH is not as uncommon as one may think. This review discusses the epidemiology of ICH associated with antiplatelet agents, risk factors, and prediction rules for antiplatelet-associated ICH, as well as treatment options for ICH in the context of antiplatelet use, including emerging data on reversal agents.

EPIDEMIOLOGY OF ICH

ICH can be classified according to the bleeding location (intracerebral, subarachnoid, subdural, and epidural) and the mechanism (traumatic vs non-traumatic). In 2019, an estimated 4.6 million cases of intracerebral and subarachnoid bleeding occurred worldwide (Central Illustration) (12). These 2 types of ICH accounted for ≈3.4 million deaths and ≈77 million disability-adjusted life years lost in 2019 alone. Presently, the global age-standardized incidence rate of intracerebral and subarachnoid bleeding was estimated to be ≈55 cases per 100,000 person years. The lifetime risk of hemorrhagic stroke for

adults worldwide is estimated to be 8.2% (13). Therefore, on average, 1 of 12 adults in the world will be at risk for developing an intracerebral or subarachnoid bleed. Despite diagnostic and therapeutic improvements in ICH management over time, no appreciable change in this risk has been observed over the past 3 decades.

Patients treated with antiplatelet agents are more likely to experience ICH with severe clinical presentations. Data from Western Europe and North America showed that up to 30% of all patients with ICH were treated with antiplatelet agents (Central Illustration) (14). In a nationwide analysis from Norway, the sex- and age-adjusted incidence rate of ICH was ≈30% higher among patients treated with ASA than those not treated with antiplatelet agents (15). Antiplatelet use was associated with larger baseline hemorrhagic volumes and a higher risk of hemorrhagic growth (odds ratio: 1.85; 95% confidence interval [CI]: 1.37–2.50) (16). This could partly explain why use of antiplatelet therapy was associated with poorer prognosis among patients with ICH. The Get With the Guidelines-Stroke registry showed that DAPT was prescribed in ≈13% of antiplatelet-treated patients who presented with intracerebral hemorrhage (17). Patients with intracerebral hemorrhage who were treated with DAPT had increased mortality compared with those treated with SAPT.

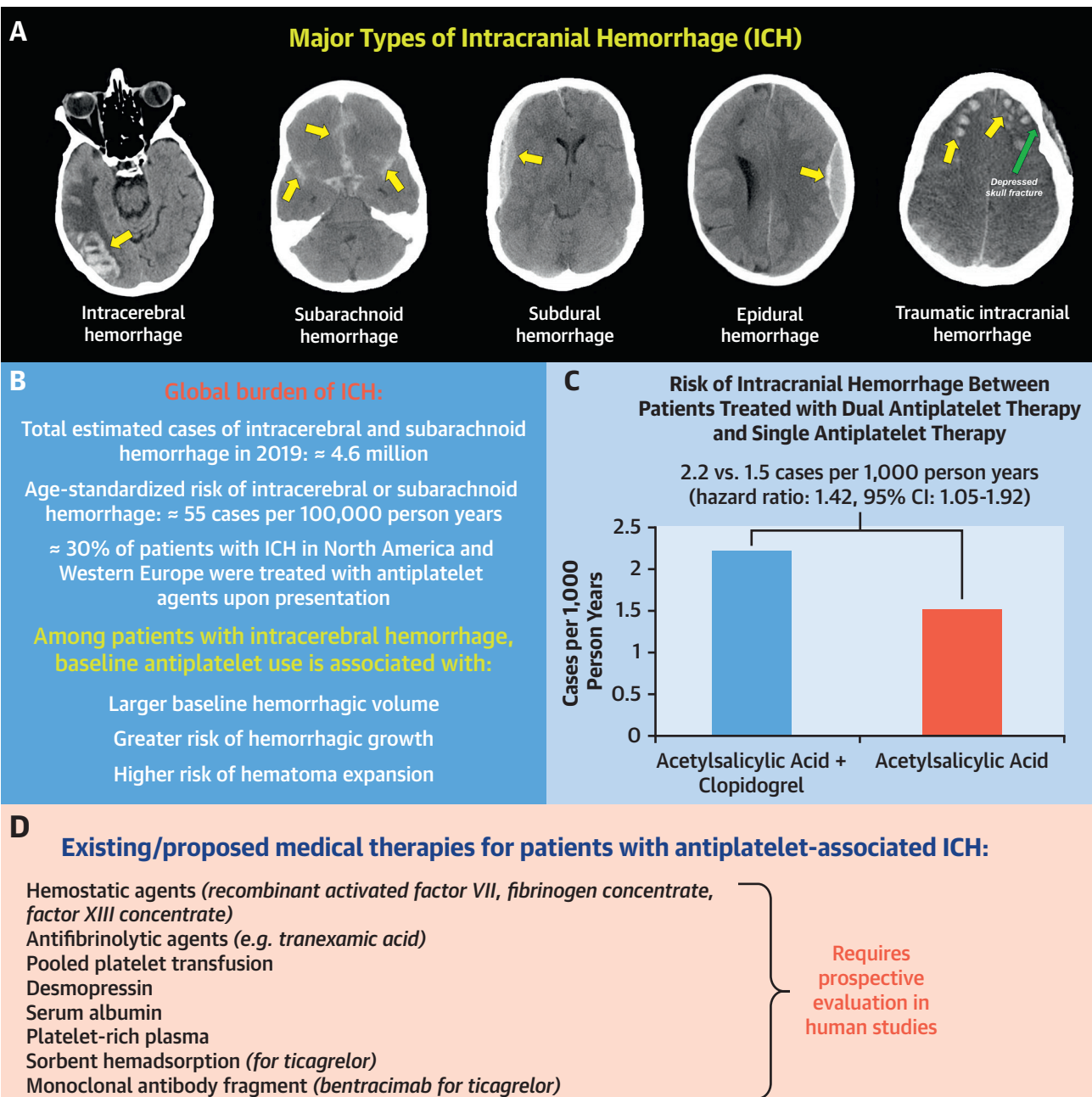
Trauma is an underrecognized but important mechanism of antiplatelet-associated ICH. Given the exponential growth of the aging population, DAPT will be increasingly prescribed for patients who are frail, older, or at risk for falls. In 2012, an estimated 82,000 deaths and 2.1 million hospitalizations due to traumatic brain injury (TBI) occurred in Europe (18,19). At least 50% of patients admitted due to TBI experienced ICH (19). About 11% of patients admitted due to TBI were treated with antiplatelet agents. Based on these estimates, the yearly volume of hospitalized TBI patients treated with antiplatelet agents and presenting with ICH would equate to 200,000 and 100,000 in Europe alone (18,19).

In patients treated with antiplatelet agents, even seemingly “minor” head injury is associated with an elevated risk of ICH. In THEMIS (The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study), which randomized patients with diabetes and stable coronary artery disease to receive ASA + ticagrelor versus ASA alone, a substantial proportion of ICH was related to head trauma, most of them resulting in subdural

ABBREVIATIONS AND ACRONYMS

ACS	= acute coronary syndrome
ASA	= acetylsalicylic acid
CI	= confidence interval
DAPT	= dual antiplatelet therapy
FDA	= U.S. Food and Drug Administration
HR	= hazard ratio
ICH	= intracranial hemorrhage
PCI	= percutaneous coronary intervention
RR	= risk ratio
SAPT	= single antiplatelet therapy
TBI	= traumatic brain injury
TIA	= transient ischemic attack

CENTRAL ILLUSTRATION Epidemiology, Clinical Sequelae, and Potential Therapies of Antiplatelet-Associated Intracranial Hemorrhage



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(A) The major types of intracranial hemorrhage (ICH) are shown. (Green arrow indicates depressed skull fracture.) (B) Globally, ≈ 4.6 million cases of intracerebral and subarachnoid hemorrhage occurred in 2019. Among patients with intracerebral hemorrhage, those treated with antiplatelet agents had larger hemorrhagic volume and greater hemorrhagic growth compared with those not treated with antiplatelet agents. (C) Patients treated with dual antiplatelet therapy had a greater risk of intracranial hemorrhage compared with those treated with single antiplatelet therapy. (D) There are a number of potential therapies that can attenuate the effect of antiplatelet agents, but further studies in humans are needed to establish their safety and efficacy. ICH = intracranial hemorrhage.

hematomas (5,20). In a meta-analysis of 20,247 patients with mild TBI (defined as a Glasgow Coma Scale score of 13-15), pre-injury antiplatelet use was associated with an increased risk of ICH (odds ratio: 2.72; 95% CI: 1.92-3.85) (21). Limitations of this analysis included the following: most studies were retrospective; patients were primarily treated with clopidogrel monotherapy whereas the risk of other P2Y₁₂ agents was not reported; and the risk of ICH associated with DAPT among patients with mild TBI was not addressed. If SAPT was associated with an increased risk of ICH among patients with mild TBI, DAPT would at least confer similar, if not incrementally higher, ICH risk as well.

RISK OF ICH FROM ANTIPLATELET THERAPY

ASA blocks formation of thromboxane A₂ by irreversible inhibition of cyclooxygenase-1, resulting in permanent platelet inhibition (22). When used as primary prevention therapy for coronary artery disease, the risk of ICH among patients treated with ASA monotherapy was ≈0.07% per year in randomized trials (23). This translated to a 32% relative increase in ICH risk with ASA compared with placebo and a number-needed-to-harm of 1,000. Among patients treated with ASA for secondary prevention of coronary artery disease, their annual risk of ICH is higher, in the range of 0.12%-0.21% in randomized trials (24).

Clopidogrel and prasugrel prevent platelet activation by antagonizing P2Y₁₂ receptors, which in turn inhibit binding with adenosine diphosphate. Because these agents irreversibly bind to P2Y₁₂ receptors, inhibition is maintained over the platelet's life span. Accordingly, the combined antiplatelet effect of ASA + P2Y₁₂ inhibitors is substantial and completely irreversible in the case of clopidogrel and prasugrel. Unlike clopidogrel and prasugrel, ticagrelor binds to platelet P2Y₁₂ receptors in a reversible fashion. Hence, previously inhibited platelets can be reactivated by adenosine diphosphate upon ticagrelor disengagement from P2Y₁₂ receptors (22).

The risk of ICH is increased among patients treated with DAPT compared with ASA monotherapy. In a patient-level meta-analysis of 6 randomized trials comparing extended ASA + clopidogrel versus ASA + placebo, DAPT increased patients' risk of ICH by 42% (2.2 vs 1.5 cases per 1,000 person years; hazard ratio [HR]: 1.42; 95% CI: 1.05-1.92) (Central Illustration) (8). Three large randomized controlled trials have compared ASA + ticagrelor versus ASA + placebo among patients with a spectrum of cardiovascular disease (4,5,7). In the PEGASUS-TIMI 54 (Prevention of

Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54) trial, which enrolled patients with a subacute history of myocardial infarction (1-3 years), the risk of ICH was numerically higher among patients treated with extended DAPT relative to ASA monotherapy over a median of 33 months (0.56% for ticagrelor 90 mg + ASA; 0.61% for ticagrelor 60 mg + ASA, and 0.47% for ASA only; HR of 1.44 [95% CI: 0.83-2.49] for ticagrelor 90 mg vs placebo and HR of 1.33 [95% CI: 0.77-2.31] for ticagrelor 60 mg vs placebo) (4). In THEMIS, extended DAPT (median of 39.9 months) increased patients' risk of ICH compared with ASA monotherapy (0.7% vs 0.5% or 3.0 vs 1.8 cases per 1,000 person years; HR: 1.71; 95% CI: 1.18-2.48) (5). In the THALES (Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and ASA for Prevention of Stroke and Death) trial, which randomized patients with a recent history of stroke/TIA to receive ASA + ticagrelor or ASA + placebo for 30 days, the risk of ICH was higher among patients treated with DAPT (0.4% vs 0.1%; HR: 3.33; 95% CI: 1.34-8.28) (7). Collectively, the risk of ICH was higher among patients treated with ASA + ticagrelor relative to ASA monotherapy (147 of 29,031 [0.51%] vs 75 of 22,020 [0.34%]; risk ratio [RR]: 1.59; 95% CI: 1.06-2.39; *P* = 0.02) (Supplemental Figure 1) (5-7). The results of THEMIS and THALES have each led to label expansions for ticagrelor by the U.S. Food and Drug Administration (FDA), and thus use for these indications will likely grow (25).

In randomized trials of DAPT that compared P2Y₁₂ inhibitors, patients' risk of ICH was numerically higher when they were treated with prasugrel or ticagrelor instead of clopidogrel. On a per-trial basis, this difference was not statistically significant (Table 1) (26-34). In the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis In Myocardial Infarction 38) and TRIL-OGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trials, which randomized patients with ACS to receive ASA + prasugrel vs ASA + clopidogrel, comparable ICH rates were observed (26,28). However, patients with a history of stroke/TIA in the TRITON-TIMI 38 trial experienced a significantly higher risk of ICH when randomized to receive prasugrel compared with clopidogrel (2.3% vs 0%; *P* = 0.02) (26). In the PLATO trial, which randomized 18,624 hospitalized patients with ACS to receive ASA + ticagrelor vs ASA + clopidogrel over 12 months, the rate of ICH was numerically higher among

TABLE 1 Rates of ICH and Fatal or BARC Type 5 Bleeding From Randomized Controlled Trials That Directly Compared P2Y₁₂ Inhibitors

Trial Name (Ref. #)	Patient Population	Antiplatelet Regimen	Follow-Up Duration	ICH Rate	Fatal or BARC Type 5 Bleeding Rate
Ticagrelor vs clopidogrel					
PLATO (27)	18,624 patients hospitalized due to ACS, with or without ST-segment elevation	ASA + ticagrelor vs ASA + clopidogrel	12 mo	ASA + ticagrelor: 26/9,235 (0.28%) ASA + clopidogrel: 14/9,186 (0.15%) HR: 1.87 (95% CI: 0.98-3.58)	ASA + ticagrelor: 20/9,235 (0.22%) ASA + clopidogrel: 23/9,186 (0.25%) HR: 0.87 (95% CI: 0.48-1.59)
TREAT (31)	3,799 patients (age <75 y) with STEMI treated with fibrinolytic therapy	ASA + ticagrelor vs ASA + clopidogrel	12 mo	ASA + ticagrelor: 10/1,913 (0.52%) ASA + clopidogrel: 9/1,886 (0.48%) HR: 1.10 (95% CI: 0.44-2.69)	BARC type 5 bleeding ASA + ticagrelor: 8/1,913 (0.42%) ASA + clopidogrel: 5/1,886 (0.27%) HR: 1.58 (95% CI: 0.52-4.82)
POPular AGE (34)	1,002 patients (age ≥70 y) with NSTEMI-ACS	ASA + ticagrelor or prasugrel vs ASA + clopidogrel	12 mo	ASA + clopidogrel: 2/500 (0.40%) ASA + ticagrelor ^a : 5/502 (1.00%) HR: 0.41 (95% CI: 0.08-2.09)	BARC type 5 bleeding ASA + clopidogrel: 0/500 (0%) ASA + ticagrelor ^a : 5/502 (1.00%) HR: 0.02 (95% CI: 0-20.79)
TICAKOREA (32)	800 ACS patients with or without ST-segment elevation in whom an invasive treatment was planned	ASA + ticagrelor vs ASA + clopidogrel	12 mo	ASA + ticagrelor: 4/400 (1.00%) ASA + clopidogrel: 1/400 (0.25%)	ASA + ticagrelor ^b : 4/400 (1.00%) ASA + clopidogrel: 0/400 (0%)
EUCLID (29)	13,885 patients with symptomatic peripheral artery disease	Ticagrelor monotherapy vs clopidogrel monotherapy	30 mo (median)	Ticagrelor monotherapy: 34/6,910 (0.49%) Clopidogrel monotherapy: 34/6,932 (0.49%) HR: 1.06 (95% CI: 0.66-1.70)	Ticagrelor monotherapy: 10/6,910 (0.14%) Clopidogrel monotherapy: 20/6,932 (0.29%) HR: 0.53 (95% CI: 0.25-1.13)
Prasugrel vs clopidogrel					
TRITON-TIMI 38 (26)	13,608 patients with ACS with scheduled PCI	ASA + prasugrel vs ASA + clopidogrel	14.5 mo (median)	ASA + prasugrel: 19/6,741 (0.28%) ASA + clopidogrel: 17/6,716 (0.25%) HR: 1.12 (95% CI: 0.58-2.15)	ASA + prasugrel: 21/6,741 (0.31%) ASA + clopidogrel: 5/6,716 (0.07%) HR: 4.19 (95% CI: 1.58-11.11)
TRILOGY ACS (28)	7,243 patients (<75 y) with NSTEMI-ACS who did not undergo revascularization	ASA + prasugrel vs ASA + clopidogrel	17 mo (median)	ASA + prasugrel: 8/3,590 (0.22%) ASA + clopidogrel: 12/3,590 (0.33%) HR: 0.67 (95% CI: 0.28-1.65)	ASA + prasugrel: 4/3,590 (0.11%) ASA + clopidogrel: 4/3,590 (0.11%) HR: 1.01 (95% CI: 0.25-4.05)
Prasugrel vs ticagrelor					
ISAR-REACT 5 (33)	4,018 patients with ACS in whom an invasive strategy was planned	ASA + ticagrelor vs ASA + prasugrel	12 mo	BARC type 3c bleeding ASA + ticagrelor: 4/2,012 (0.20%) ASA + prasugrel: 2/2,006 (0.10%)	BARC type 5 bleeding ASA + ticagrelor: 4/2,012 (0.20%) ASA + prasugrel: 4/2,006 (0.20%)
BARC (Bleeding Academic Research Consortium) type 3c bleeding consists of intracranial hemorrhage (ICH) or intraocular hemorrhage resulting in visual impairment; BARC type 5 bleeding consists of probable or definite death due to bleeding. ^aIn the POPular AGE trial, 95% of patients randomized to receive acetylsalicylic acid (ASA) + ticagrelor or prasugrel were treated with ASA + ticagrelor. The investigators grouped the results into a single cohort (ASA + ticagrelor). ^bOne patient died of intracranial bleeding. ACS = acute coronary syndrome; CI = confidence interval; DAPT = dual antiplatelet therapy; EUCLID = Examining Use of Ticagrelor in Peripheral Artery Disease; HR = hazard ratio; ISAR-REACT 5 = The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5; NSTEMI-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PLATO = Study of Platelet Inhibition and Patient Outcomes; POPular AGE = Ticagrelor or Prasugrel Versus Clopidogrel in Elderly Patients With an Acute Coronary Syndrome and a High Bleeding Risk: Optimization of Antiplatelet Treatment in High-risk Elderly; STEMI = ST-segment elevation myocardial infarction; TICAKOREA = Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management; TREAT = Ticagrelor in patients with ST-elevation Myocardial Infarction Treated with Pharmacological Thrombolysis; TRILOGY ACS = Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes; TRITON-TIMI 38 = Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction 38.					

patients treated with ASA + ticagrelor, but this finding did not reach statistical significance (0.28% vs 0.15%; HR: 1.87; 95% CI: 0.98-3.58; $P = 0.06$) (27). Patients randomized to receive ASA + ticagrelor were more likely to experience fatal ICH than those randomized to receive ASA + clopidogrel (0.12% vs 0.01%; $P = 0.02$). The pooled rate of ICH was higher among patients treated with ASA + ticagrelor than those treated with ASA + clopidogrel (45 of 12,050

[0.37%] vs 26 of 11,972 [0.22%]; RR: 1.69; 95% CI: 1.04-2.75; $P = 0.04$) (Supplemental Figure 2) (27,31,32,34).

RISK FACTORS FOR ANTIPLATELET-ASSOCIATED ICH

Having the ability to identify antiplatelet-treated patients with the highest risk of ICH may allow physicians to individualize the risk/benefit ratio of the

TABLE 2 Published Risk Prediction Scores for ICH Among Patients With a History of Stroke or TIA

	S₂TOP-BLEED (38,40)	Intracranial-B₂LEED₂S (42)	Ariesen et al (41)
Year of publication	2017	2017	2006
Patient population of development data set	Patient-level data from 6 randomized trials evaluating antiplatelet therapy for patients with a history of stroke or TIA (CAPRIE, ESPS-2, MATCH, CHARISMA [stroke/TIA patient subset], ESPRIT, PROFESS) (n = 43,112)	Patient-level data from the PERFORM trial, which enrolled patients with non-cardioembolic stroke or TIA (n = 19,100)	Patient-level data from the Cerebrovascular Cohort Studies Collaboration, which included 8 trials of patients with a history of cerebral ischemia (n = 12,648 patients; 53,761 person years)
Bleeding outcome examined	ICH Major or life-threatening bleeding (fatal, symptomatic intracranial, significantly disabling, require hospital admission, transfusion, or surgery)	ICH	ICH
Components of risk score	Sex (male = 2 points; female = 0 point) Smoking (current = 1 point; no = 0 point) Type of antiplatelet agent (clopidogrel = 0 point; ASA ± dipyridamole = 1 point; ASA + clopidogrel = 5 points) Outcome on mRS (0-2 = 0 point; 3-5 = 2 points) Prior stroke (Yes = 1 point; No = 0 point) Blood pressure (hypertension) (Yes = 1 point; No = 0 point) Low BMI (<20 kg/m ² = 2 points, 20-25 = 1 point; >25 kg/m ² = 0 point) Elderly (≥85 y = 12 points; 75-84 y = 9 points; 65-74 y = 6 points; 55-64 y = 4 points; 45-54 y = 2 points) Ethnicity (Asian = 1 point; non-Asian = 0 point) Diabetes (Yes = 1 point; No = 0 point)	BMI (<25 kg/m ² = 1 point; ≥25 kg/m ² = 0 point) Blood pressure (high) (Yes = 2 points; No = 0 point) Lacune/small vessel disease (Yes = 1 point; No = 0 point) Elderly (≥75 y = 1 point; <75 y = 0 point) Ethnicity (Asian = 2 point; non-Asian = 0 point) Cardiovascular Disease (Yes = 2 points; No = point) Cerebrovascular Disease (Yes = 2 points; No = point) DAPT or anticoagulant (Yes = 1 point; No = point) Sex (Male = 1 point; Female = 0 point)	Age (≥60 y = 6 points; <60 y = 0 point) Blood glucose (≥7 mmol/L = -10 points; <7 mmol/L = 0 point) Systolic blood pressure (≥140 mm Hg = 7 points; <140 mm Hg = 0 point) Antihypertensive drug use (Yes = 4 points; No = 0 point)
Development discrimination for ICH risk	AUC: 0.61 (95% CI: 0.58-0.64)	AUC: 0.64 (95% CI: 0.61-0.68)	AUC: 0.65 (95% CI: 0.59-0.74)
Validation discrimination for ICH risk	AUC: 0.65 (95% CI: 0.58-0.72)	AUC: 0.58 (95% CI: 0.55-0.62) (validation cohort #1) AUC: 0.60 (95% CI: 0.51-0.70) (validation cohort #2) (40)	AUC: 0.53 (95% CI: 0.49-0.57) ^a
Predicted ICH risk in relation to risk score (development data set)	3-year risk of ICH: 45-54 y: ≥14 points (2.7%) 55-64 y: ≥13 points (3.2%) 65-74 y: ≥11 point (3.2%) 75-85 y: ≥8 points (3.2%)	2-year risk of ICH: 6 points: 2.4% 7 points: 3.0% 8 points: 3.8% ≥9 points: 5.2%	5-year risk of ICH: <6 points: 0.4% 6-10 points: 0.6% 11-13 points: 1.3% >13 points: 2.0%

^aValidated for major bleeding.

AUC = area under the curve (also known as the C-statistic); BMI = body mass index; Intracranial-B₂LEED₂S = low body mass index, blood pressure, lacune, elderly, Asian ethnicity, coronary artery or cerebrovascular disease history, dual antithrombotic agent or oral anticoagulant, gender; mRS = modified Rankin score; S₂TOP-BLEED = male sex, smoking, type of antiplatelet agents (aspirin-clopidogrel), outcome on modified Rankin Scale ≥3, prior stroke, high blood pressure, lower body mass index, elderly, Asian ethnicity, and diabetes; TIA = transient ischemic attack; other abbreviations as in Table 1.

intensity and duration of antiplatelet therapy. In a meta-analysis of studies of patients without symptomatic cardiovascular disease who were treated with ASA versus placebo, East Asian race (RR: 1.84; 95% CI: 1.04-3.27) and low body mass index of <25 kg/m² (RR: 1.84; 95% CI: 1.04-3.27) were associated with an increased risk of ICH (35). Among studies of patients treated with DAPT (ASA + P2Y₁₂ inhibitor), a history of stroke (ischemic or hemorrhagic) or TIA was an important risk factor for antiplatelet-associated ICH (36,37). In fact, ICH is a common bleeding manifestation among antiplatelet-treated patients with a history of stroke/TIA. In a pooled analysis of 6 randomized trials that evaluated the use of antiplatelet agents for patients with a history of stroke/TIA, ICH accounted for 26% of all major bleeding events (392 of 1,530 events) (38). In this patient population, DAPT incrementally elevated the risk of major bleeding by

70% compared with ASA monotherapy. Due to the increased risk of ICH observed in the TRITON-TIMI 38 trial, the FDA issued a “black box warning” against the use of prasugrel for patients with a history of stroke/TIA (39). Very careful consideration must be given when physicians prescribe antiplatelet therapy (particularly DAPT) for patients with a history of stroke/TIA.

Several prediction rules predict the risk of ICH among antiplatelet-treated patients with a history of stroke/TIA (Table 2) (38,40-42). The S₂TOP-BLEED score was derived from 6 trials that enrolled patients with a history of stroke/TIA and who were treated with antiplatelet agents (38). This score was developed to predict major bleeding or ICH, with older age and use of DAPT (ASA + clopidogrel) being the strongest determinants of increased risk. The annual ICH risk was estimated at >1.0% for patients aged 55-

TABLE 3 Published Risk Prediction Scores for Bleeding for Patients Treated With DAPT				
	DAPT (45)	PARIS (44)	PRECISE-DAPT (46)	BleeMACS (47)
Year of publication	2016	2016	2017	2018
Patient population of development data set	Patients without major bleeding or ischemic events at 12 mo after PCI from the DAPT trial (n = 11,648)	PCI patients in the PARIS registry (n = 4,190)	Pooled analysis of 8 PCI RCTs (n = 14,963)	PCI patients in the BleeMACS registry (n = 15,401)
Bleeding outcome examined by the model	GUSTO moderate or severe bleeding	BARC type 3 or 5 bleeding	TIMI major TIMI major or minor	Serious spontaneous bleeding: defined as any ICH or any other bleeding leading to hospitalization and/or red blood cell transfusion (≥1 U), occurring within the first year after hospital discharge
Was ICH separately examined as an outcome?	No	No	No	No
Components of risk score	MI at presentation (1 point) Prior MI or PCI (1 point) Diabetes (1 point) Stent diameter <3 mm (1 point) Cigarette smoking (1 point) Paclitaxel-eluting stent (1 point) CHF/EF <30% (2 points) Vein graft stent (2 points) Age (<65 y = 0 point; 65-74 y = -1 point; ≥75 y = -2 points)	Age (<50 y = 0 point; 50-59 y = 1 point; 60-69 y = 2 points; 70-79 y = 3 points; ≥80 y = 4 points) BMI (<25 kg/m ² or ≥35 kg/m ² = 2 points; 25-34.9 = 0 point) Current smoking (Yes = 2 points; No = 0 point) Anemia (Yes = 3 points; No = 0 point) CrCl <60 mL/min (Yes = 2 points; No = 0 point) ASA + P2Y ₁₂ + OAC on discharge (Yes = 2 points; No = 0 point)	Age (per 10-year increase): HR: 1.34 (95% CI: 1.11-1.48) Previous bleeding: HR: 4.14 (95% CI: 1.22-14.02) Hemoglobin (per 1 g/dL increase): HR: 0.67 (95% CI: 0.53-0.84) WBC (for each 10 ³ cell per μL increase): HR: 1.06 (95% CI: 0.99-1.13) CrCl (per 10 mL/min increase); HR: 0.90 (95% CI: 0.82-0.99)	Age (<67 y = 0 point; 67-74.9 y = 7 points; ≥75 y = 9 points) Hypertension (7 points) Vascular disease (6 points) History of bleeding (19 points) Creatinine (<1 mg/dL = 0 point; 1-1.5 mg/dL = 3 points; ≥1.5 mg/dL = 12 points) Hemoglobin (<11 g/dL = 18 points; 11-13.9 g/dL = 9 points; ≥14 g/dL = 0 point) Malignancy (8 points)
Development discrimination for bleeding risk	AUC: 0.68 (95% CI: 0.65-0.72)	AUC: 0.72	AUC: 0.71 (95% CI: 0.57-0.85) (TIMI major bleeding)	AUC: 0.71 (95% CI: 0.68-0.74)
Validation discrimination for bleeding risk	AUC: 0.64 (95% CI: 0.55-0.73)	AUC: 0.64	AUC: 0.68 (95% CI: 0.63-0.74) (TIMI major bleeding; PLATO cohort) AUC: 0.65 (95% CI: 0.58-0.71) (TIMI major bleeding; BernPCI cohort)	AUC: 0.65 (95% CI: 0.64-0.66)
Bleeding risk in relation to risk score (development data set)	Observed bleeding risk for the highest risk subgroup -2 to 0 point: 3.7% over 18 mo (ASA + P2Y ₁₂) -2 to 0 point: 1.7% over 18 mo (ASA only)	Observed bleeding risk for the highest risk subgroup ≥8 points: ≥9.5% over 2 y	Observed bleeding risk for the highest risk subgroup ≥25 points: ≥0.99% over 1 y (TIMI major bleeding)	Observed bleeding risk for the highest risk subgroup ≥26 points: ≥8% within 1 y after hospital discharge
BleeMACS = Bleeding complications in a Multicenter registry of patients discharged after an Acute Coronary Syndrome; CHF = congestive heart failure; CrCl = creatinine clearance; DAPT = Dual Antiplatelet Therapy; EF = ejection fraction; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; OAC = oral anticoagulation; PARIS = Patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients; PRECISE-DAPT = Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy; RCT = randomized controlled trials; TIMI = Thrombolysis In Myocardial Infarction; WBC = white blood cell; other abbreviations as in Tables 1 and 2.				

65 years, 65-75 years, and 75-85 years if their S₂TOP-BLEED score was ≥13, ≥11, and ≥8, respectively. Given that an annualized ICH risk of ≥1.0% had been proposed as a threshold above which the benefit of antithrombotic therapy might be nullified (10), the S₂TOP-BLEED prediction rule could assist clinicians when balancing the risks and benefits of antiplatelet therapy for patients with previous stroke/TIA. The Intracranial-B₂LEED₃ score was developed to predict the risk of ICH among patients with ischemic stroke who were treated with antiplatelet agents (42). A score of ≥5 predicted a ≥1% annual risk of ICH. It should be noted that the discriminative capacity of

these scores was modest (C-statistic: 0.53-0.65) (38,40-42). Also, these scores have not been specifically validated for patients with acute ischemic stroke/TIA (ie, within 30 days). This is an important consideration because the benefit of DAPT in reducing the risk of recurrent stroke is greatest within the first 30 days after ischemic stroke/TIA (absolute risk reduction by ≈2%) (43). As such, a high bleeding risk score should not be used to justify withholding DAPT for patients with acute ischemic stroke/TIA.

A rich source of data on DAPT-related bleeding comes from the PCI arena, with multiple published models consisting of at least 46,000 patients (Table 3)

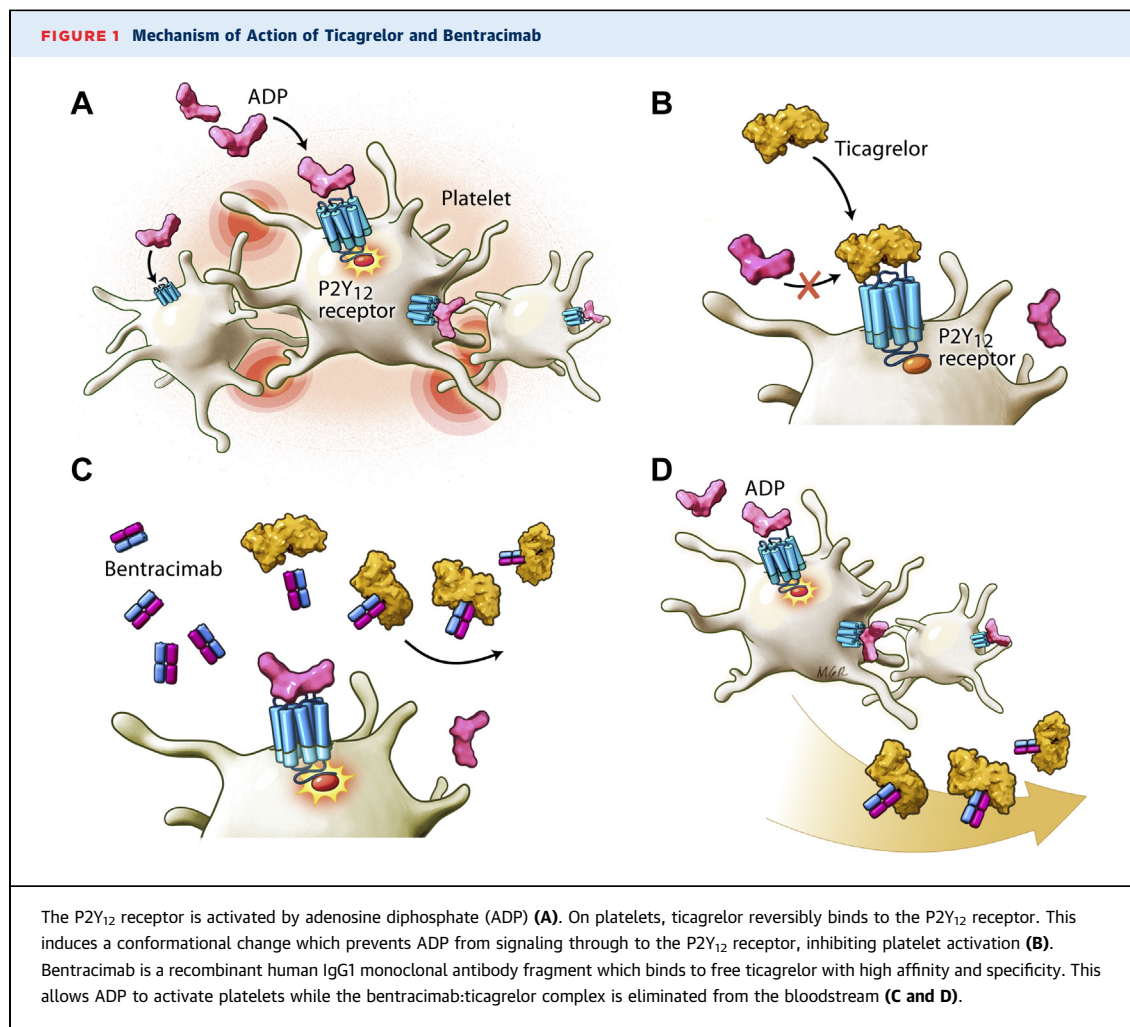
TABLE 4 Proposed Strategies to Reverse the Antiplatelet Effect of Oral P2Y₁₂ Inhibitors

	P2Y ₁₂ Inhibitor Studied	Study Design and Key Results	Comments
Transfusion of pooled platelets (51-55)	Clopidogrel Prasugrel Ticagrelor	Most studies were in vitro in design. The APTITUDE-CABG trial was an in vivo study that enrolled patients who experienced bleeding after CABG while being treated with DAPT (ASA + P2Y ₁₂ inhibitor) (53). Platelet transfusion did not improve platelet aggregation in the blood of patients treated with ticagrelor, particularly if the last dose was taken within 24 h of platelet transfusion. The degree of platelet aggregation affected by platelet transfusion was more pronounced in the blood of patients treated with clopidogrel or prasugrel.	Results require confirmation with additional in vivo studies and clinical trials. Existing evidence does not support the use of platelet transfusion to reverse the effect of ticagrelor in acute severe bleeding. Based on expert consensus, platelet transfusion could result in partial neutralization of ticagrelor if the last drug intake was >24 h (55). Based on expert consensus, platelet transfusion at >2 times the standard dose could be considered for patients treated with clopidogrel or prasugrel who experience acute severe bleeding (55). Efficacy may be reduced if platelets were transfused <6 h after last intake of clopidogrel or prasugrel (55).
Hemostatic agents (recombinant activated factor VII, fibrinogen concentrate, tranexamic acid, factor XIII concentrate) (58)	Ticagrelor	In vitro experiments in which human blood spiked with ticagrelor was mixed with hemostatic or control agents. None of the 4 hemostatic agents affected platelet aggregation parameters. Measures of fibrin formation or fibrinolysis were variably affected by these agents.	Ticagrelor-induced platelet inhibition could not be reversed by hemostatic agents. However, some of the platelet inhibitory effects related to ticagrelor could be bypassed with use of these hemostatic agents. Results require confirmation with in vivo models before human studies can be initiated.
Desmopressin (59,60)	Clopidogrel Prasugrel Ticagrelor	Randomized, double-blind, 2-period crossover study in which 21 healthy volunteers were treated with 5 d of ticagrelor (270-mg loading dose then 180 mg twice daily) for 5 d (59). Desmopressin (0.3 µg/kg) or saline intravenous infusions were administered on day 5. Desmopressin had no effect on platelet aggregation, bleeding time, or ticagrelor pharmacokinetics variables.	In clinical practice, desmopressin is unlikely to be helpful in attenuating the antiplatelet effect of ticagrelor.
Human serum albumin (54)	Clopidogrel Prasugrel Ticagrelor	In vitro experiments in which human serum albumin was mixed with blood of patients who were treated with P2Y ₁₂ inhibitors. At a high concentration of human serum albumin (80 g/L), an increase in platelet reactivity was observed in the blood of patients treated with ticagrelor. This effect was less for those treated with clopidogrel or prasugrel.	Results require confirmation with in vivo models before human studies can be initiated. In clinical settings, the volume of human serum albumin required to reverse the antiplatelet effect of ticagrelor may render this strategy not feasible.
Platelet-rich plasma (decanted supernatant obtained from centrifugation of pooled human platelets) (54)	Clopidogrel Prasugrel Ticagrelor	In vitro experiments in which platelet-rich plasma was mixed with the blood of patients who were treated with P2Y ₁₂ inhibitors. Addition of platelet-rich plasma increased platelet reactivity in the blood of patients treated with clopidogrel or prasugrel. The magnitude of platelet reactivity increase was lowest among patients treated with ticagrelor.	Results require confirmation with in vivo models before human studies can be initiated.
Bentricimab (recombinant human IgG1 monoclonal antibody fragment) (61)	Ticagrelor	Randomized, double-blind, placebo-controlled, Phase I human study involving 64 healthy volunteers. Intravenous bentricimab (bolus dose of 6.0 g over 10 min followed by 12.0 g over 16 h) resulted in rapid (within 5 min), sustained (up to 20 h), and substantial (≈80%) reversal of ticagrelor's antiplatelet effect.	An ongoing patient trial is underway to examine the effect of bentricimab in 2 clinical scenarios: 1) ticagrelor-treated patients with acute severe bleeding; and 2) ticagrelor-treated patients who require urgent surgery or invasive procedures (NCT04286438).
Sorbent hemadsorption (56,57)	Ticagrelor	In vitro experiment involving: 1) bovine serum albumin solution; and 2) human blood mixed with ticagrelor (56). Sorbent hemadsorption with CytoSorb (CytoSorbents Corporation) was able to remove ticagrelor from human blood with >99% efficiency.	Use of CytoSorb was described in a case series of ticagrelor-treated patients undergoing urgent CABG surgery. CytoSorb was integrated within the cardiopulmonary bypass circuit (57). Prospective studies are needed to confirm the safety and efficacy of this approach.

CABG = coronary artery bypass graft; IgG1 = immunoglobulin G1; other abbreviations as in Tables 1 and 2.

(44-47). These models have reasonably good discriminative properties, with C-statistics of 0.63 to 0.70. These models suggest that the most important risk factors for bleeding include: prior bleeding, long-term use of oral anticoagulation, chronic kidney disease (estimated glomerular filtration rate <30 mL/min), chronic bleeding diathesis, cirrhosis,

anemia (hemoglobin <11 g/dL), thrombocytopenia (<100 × 10⁹/L), history of ICH, and severe ischemic stroke within 6 months (44-48). Of note, these prediction rules examined major bleeding, not ICH, as the outcome of interest. Whether these models can be applied to predict patients' risk of ICH has not been specifically examined. However, because these



models have good predictive performances for the most serious bleeding subtypes (ie, BARC [Bleeding Academic Research Consortium] types 3 or 5, TIMI major, or GUSTO [Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries] severe), it seems plausible that they can be used to predict ICH risk for patients who are treated with DAPT.

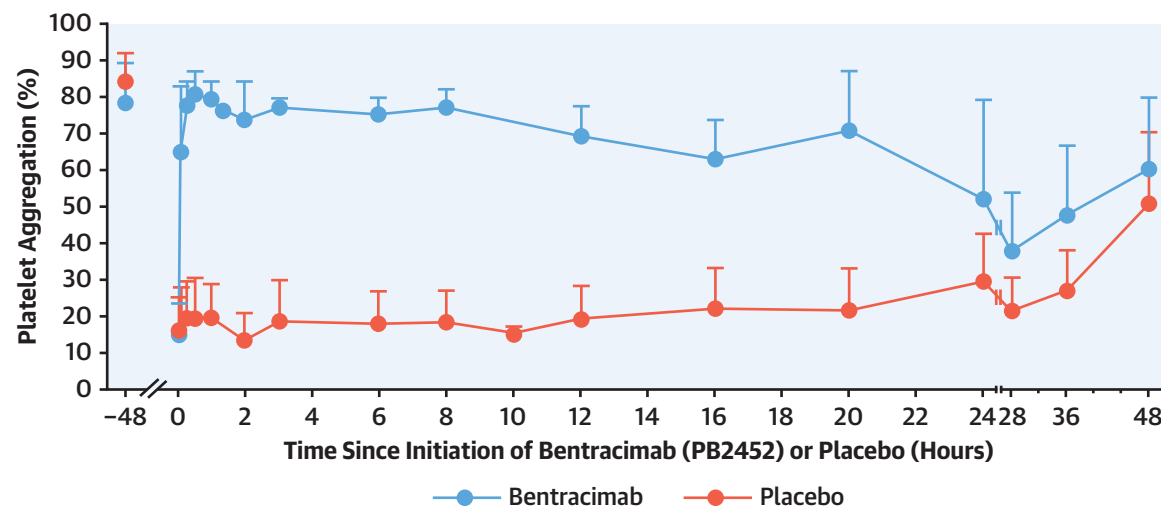
PREVENTION AND MANAGEMENT OF ICH

All cases of ICH constitute a medical emergency and require immediate attention, including blood pressure stabilization, intensive neuromonitoring, prevention and management of seizures, and reduction of cerebral edema (9). Prompt neurosurgical consultation for decompressive craniotomy can be life-saving for patients with cerebellar bleeding and brainstem compression or those with early-onset (<24 hours) supratentorial bleeding with rapidly

deteriorating neurologic status. Among antiplatelet-treated patients who experience ICH, interventions that can rapidly reverse drug activity may potentially reduce the extent of bleeding and facilitate earlier neurosurgical management if indicated.

There is currently no approved therapy that can rapidly reverse the effect of antiplatelet agents if the clinical need arises. Platelet transfusion had been proposed as a potential strategy to overcome the antithrombotic effect of antiplatelet agents for patients with ICH. In a randomized trial of platelet transfusion for ASA-treated patients with acute intracerebral hemorrhage (<6 hours after onset), a signal of harm was observed for those treated with this intervention (49). Clinical practice guidelines neither recommend for or against platelet transfusion for ICH occurring in the setting of antiplatelet use (50). In vitro studies suggested that platelet transfusion could partially reverse the antiplatelet effect of clopidogrel or prasugrel, but in vivo data are lacking

FIGURE 2 Reversal of Ticagrelor by Bentracimab



Bentracimab was studied in a Phase I study of healthy volunteers who received 5 doses of ticagrelor (180-mg loading dose followed by 90 mg every 12 hours). Patients received a 6.0-g bolus of bentracimab over 10 minutes followed by 12.0 g over 16 hours. Compared with placebo (red), patients who received bentracimab (blue) had greater degrees of platelet aggregation (as measured by light transmission aggregometry) across all time points post-infusion. Adapted from Bhatt et al (61). Copyright 2019 Massachusetts Medical Society.

(51,52). On the other hand, platelet transfusion was ineffective in reversing ticagrelor's antiplatelet effect (53). Potential strategies to reverse the antiplatelet effect of P2Y₁₂ inhibitors are shown in Table 4 and the Central Illustration (51-61).

Because ticagrelor reversibly binds to platelets, an opportunity exists to develop agents to reverse its antiplatelet effect. Bentracimab is a monoclonal antibody fragment capable of binding to ticagrelor and its major active circulating metabolite with high affinity (Figure 1). In a randomized, double-blind, placebo-controlled, Phase I trial of healthy volunteers, intravenous administration of bentracimab resulted in rapid (within 5 minutes), sustained (up to 20 hours), and substantial ($\approx 80\%$) reversal of ticagrelor's antiplatelet effect (Figure 2) (61). Based on these results, bentracimab received designation as breakthrough therapy from the FDA in April 2019. A breakthrough designation is intended to expedite review and approval of drugs for serious or life-threatening conditions. This is contingent on preliminary data showing that the drug can substantially improve at least one clinically significant outcome over available therapies (62). A similar approach was used to expedite review and approval of andexanet alfa and idarucizumab, 2 reversal agents for direct-acting oral anticoagulants. The REVERSE-IT (Rapid and Sustained Reversal of Ticagrelor-Intervention Trial; NCT04286438) is an international multicenter study evaluating the effect of bentracimab in

ticagrelor-treated patients who require urgent surgery/invasive procedures or have uncontrolled severe bleeding. If shown to be effective, bentracimab may obviate the need to withhold ticagrelor for >5 days when patients undergo invasive interventions with high bleeding risks (1).

When should antiplatelet therapy be restarted for patients who experienced ICH, if at all? The risk of major bleeding needs to be balanced against the benefit of ischemic protection when clinicians make decisions on whether and when antiplatelet therapy should be re-initiated for patients with cardiovascular disease. Presently, the optimal timing of antiplatelet therapy resumption after ICH is not well defined. The RESTART (Restart or Stop Antithrombotics Randomised Trial) trial randomized patients who experienced intracerebral bleeding while treated with antithrombotic therapy to either resume or avoid antiplatelet agents (63). On average, patients were restarted on SAPT at a median of 2.5 months after their index intracerebral bleed. No difference in the rate of recurrent symptomatic spontaneous intracerebral hemorrhage was observed between the 2 groups. In fact, there was a trend toward lower bleeding rates for patients who resumed antiplatelet therapy. Ongoing randomized trials (RESTART-Fr [NCT02966119] and STATICH [Study of Antithrombotic Treatment After IntraCerebral Haemorrhage; NCT03186729]) will expand the evidence base on this important clinical question.

Among patients who resumed antiplatelet therapy in the RESTART trial, only 9 (3%) were treated with DAPT (ASA + clopidogrel) (63). In the absence of randomized trial data to inform clinical practice, use of DAPT for patients after ICH should be avoided unless extenuating circumstances exist. For example, DAPT may need to be restarted for patients who underwent PCI within 1 month of ICH to mitigate the risk of stent thrombosis.

Strategies to avoid head injury should be included when health care providers educate patients on the potential bleeding risks of antiplatelet therapy. Also, patients should be informed that their risk of ICH from antiplatelet agents is not trivial, and this risk is even higher when DAPT is prescribed. Measures such as helmet use during sports activities, use of seatbelts when riding in motor vehicles, and fall prevention strategies for at-risk individuals should be explicitly discussed with patients (64).

CONCLUSIONS

DAPT with ASA and a P2Y₁₂ inhibitor has well-proven ischemic protective effects for a wide spectrum of patients with cardiovascular disease. However, this is at the expense of increased risk of major bleeding events, with ICH being the most devastating bleeding complication. Although the incidence of ICH is relatively low among patients treated with antiplatelet agents (0.2%-0.3% annually), the cumulative number of antiplatelet-associated ICH cases is not inconsequential. The global burden of antiplatelet-related ICH will likely continue to rise, especially because DAPT is commonly prescribed and often for extended periods of time. The risk of ICH associated with DAPT must be carefully considered for certain high-risk patient subsets, such as those with previous stroke/TIA. Risk prediction scores may help physicians delineate this trade-off, which, in turn, can enhance shared decision-making with patients at high risk for bleeding. In current clinical practice, there are no reversal agents that can rapidly and effectively neutralize the antiplatelet effect of P2Y₁₂ inhibitors. A reversal agent for ticagrelor is under investigation.

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KEY WORDS dual antiplatelet therapy, intracranial hemorrhage, reversal agent, risk prediction

APPENDIX For supplemental figures, please see the online version of this paper.