NEJM Evidence

Published December 1, 2021

DOI: 10.1056/EVIDoa2100047

ORIGINAL ARTICLE

Bentracimab for Ticagrelor Reversal in Patients Undergoing Urgent Surgery

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*The REVERSE-IT investigators are listed in Supplementary Appendix S1.

Abstract

BACKGROUND Ticagrelor is a reversible oral $P2Y_{12}$ platelet inhibitor used to treat patients with acute coronary syndromes, prior myocardial infarction, high-risk coronary artery disease, transient ischemic attack, or ischemic stroke. A healthy volunteer study showed that the intravenous monoclonal antibody bentracimab rapidly reverses ticagrelor, but the effect in patients was unknown.

METHODS In a prespecified interim analysis of a single-arm, prospective study, bentracimab was evaluated in ticagrelor-treated patients who required urgent surgery or had major hemorrhage. The extent of reversal was determined using the VerifyNow $P2Y_{12}$ assay. Clinical hemostasis was assessed by central adjudication using validated criteria. Treatment-emergent safety events were evaluated. The trial is ongoing and will enroll approximately 200 patients with evaluable data.

RESULTS Of 150 enrolled patients, 142 required urgent surgery and 8 had major hemorrhage. For the end-point analysis, 129 patients had analyzable platelet data; 122 had data on adjudicated hemostasis. Bentracimab provided a rapid reversal of ticagrelor's antiplatelet effects within 5 to 10 minutes. The reversal was sustained for more than 24 hours, as measured with the VerifyNow $P2Y_{12}$ and vasodilator-stimulated phosphoprotein phosphorylation assays ($P<0.001$, with both assays and in all subgroups). Adjudicated hemostasis was achieved for more than 90% of patients ($P<0.001$); approximately 5% of patients had thrombotic events. No allergic or infusion-related reactions were reported.

CONCLUSIONS Bentracimab provided immediate and sustained reversal of the antiplatelet effects of ticagrelor in patients undergoing surgical procedures. (Funded by PhaseBio Pharmaceuticals, Inc.; ClinicalTrials.gov number, NCT04286438.)

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**The REVERSE-IT investigators are listed in Supplementary Appendix S1.*

Introduction

Ticagrelor is a potent oral antiplatelet medication that is a $P2Y_{12}$ receptor antagonist.[1] Randomized clinical trials have demonstrated its efficacy in reducing ischemic events in patients with acute coronary syndromes, prior myocardial infarction, high-risk coronary artery disease, transient ischemic attack, and stroke, based on multiple randomized clinical trials.[2–6] Several regulatory agencies worldwide, including the Food and Drug Administration (FDA), have approved ticagrelor for use in such patients.[7]

A major limitation of antithrombotic therapy is the risk for bleeding during urgent surgical or invasive procedures and the risk of spontaneous hemorrhage.[8,9] Unlike irreversible antiplatelet agents such as aspirin, clopidogrel, and prasugrel whose effects persist for the lifetime of the platelet, ticagrelor and its major metabolite bind reversibly to the $P2Y_{12}$ receptor.[10] Consequently, ticagrelor and its metabolite can bind to $P2Y_{12}$ receptors on transfused platelets, rendering platelet transfusion of limited value in ticagrelor-treated patients requiring urgent surgery or with serious bleeding.

Bentracimab (also known as PB2452) is a neutralizing recombinant human immunoglobulin G1 monoclonal antibody antigen-binding fragment that binds ticagrelor and its major active circulating metabolite with high affinity and specificity.[11] In healthy volunteers, bentracimab appeared to be safe and effective for the reversal of ticagrelor's antiplatelet effects[12] and was granted a Breakthrough Therapy designation by the FDA in 2019.[13] We aimed to study bentracimab in patients in need of ticagrelor reversal to determine its effects on platelet inhibition and hemostasis.

Methods

TRIAL DESIGN AND OVERSIGHT

REVERSE-IT (Rapid and Sustained Reversal of Ticagrelor – Intervention Trial) is an ongoing multicenter, single-arm, open-label trial to evaluate the efficacy and safety of bentracimab in ticagrelor-treated patients requiring urgent surgery or other invasive procedures or who have major bleeding. Patients were eligible for enrollment if they reported the use of ticagrelor within the prior 3 days and were judged by the treating physician to require urgent ticagrelor reversal. Bentracimab was administered as an intravenous bolus of 6 g over 10 minutes, followed immediately by a 6-g intravenous loading infusion over 4 hours and then a 6-g intravenous maintenance infusion over 12 hours. Patients with recent concomitant use of moderate or strong CYP3A inhibitors received 36 g of bentracimab. Infusions could either be extended with additional study drug or stopped early as needed. Approximately 200 patients are planned to be recruited from North America, Europe, and mainland China. In consultation with the FDA, an interim analysis was prespecified to occur when approximately 100 of the target number of patients with analyzable platelet data were enrolled.

An academic steering committee and the study sponsor (PhaseBio Pharmaceuticals, Inc.) developed the protocol (Supplementary Appendix S2) and assume final responsibility for the conduct and oversight of the trial as well as interpretation of the data. PhaseBio in North America and LabCorp in the rest of world were responsible for collecting and handling the data. The study protocol was approved by the FDA and institutional review boards of the participating sites. All data analyses in this interim report were performed by Inference, Inc. The first author wrote the first draft of the manuscript, and all of the authors participated in revisions of subsequent drafts. No one who is not an author contributed to writing this manuscript. All authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol. An independent data and safety monitoring board reviewed all safety data. An independent clinical end points committee adjudicated eligibility, achievement of hemostasis, and potential postreversal thrombotic events.

ELIGIBILITY

Eligible patients were men and women older than 18 years of age who had taken ticagrelor in the prior 3 days and required urgent surgery or invasive procedures or who had major bleeding defined by hemodynamic compromise, critical location of hemorrhage, low hemoglobin, or need for transfusion. Exclusion criteria included recent use of antiplatelet agents other than ticagrelor and aspirin and recent use of systemic anticoagulants other than heparin. Written or witnessed oral informed consent was obtained from all patients or their legal representatives.

OUTCOMES

There were two primary efficacy outcomes: achievement of ticagrelor reversal using the VerifyNow $P2Y_{12}$ platelet

function assay (Accriva/Instrumentation Laboratory, San Diego, CA) to determine the minimum percent inhibition of $P2Y_{12}$ reactivity units (PRU) within 4 hours of study drug initiation, and achievement of effective hemostasis in the overall study population as assessed by the independent clinical end points committee, using prespecified hemostatic efficacy criteria adapted from the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) bleeding scale (mild, not meeting moderate or severe criteria; moderate, blood transfusion but no hemodynamic compromise; or severe, fatal bleeding, intracranial hemorrhage, or bleeding with hemodynamic compromise that requires pharmacologic or surgical intervention) and a clinical trial of andexanet alfa for surgical patients and patients with bleeding, respectively.[14,15] Key secondary outcomes included the minimum percent inhibition of the platelet reactivity index as measured with the vasodilator-stimulated phosphoprotein phosphorylation (VASP) immunoassay (modified CY-QUANT VASP $P2Y_{12}$ assay; BioCytex, Marseille, France) and maximum reversal of PRU and the platelet reactivity index. See Supplementary Appendix S1 for a description of the VerifyNow P2Y12 and VASP assays and details of the hemostatic criteria.

Other prespecified end points included type and timing of blood products transfused and proportion of patients restarting ticagrelor. Safety outcomes included the frequency and severity of treatment-emergent adverse events (AEs), post-reversal thrombotic events, and immunogenicity. To assess whether bentracimab induced potentially prothrombotic alteration of platelet activity, biomarkers of platelet activation, circulating P-selectin and mean platelet volume, were measured predose and at multiple time points postreversal.

STATISTICAL ANALYSIS

To assess the primary reversal end point, the difference in percent inhibition of PRU before and within 4 hours after the initiation of bentracimab infusion was assessed. The minimum percent inhibition of PRU within the 4-hour window compared with predose inhibition was tested with a two-sided alpha of 0.0365 for this interim analysis. A mixed model was used to estimate the difference in percent inhibition pretreatment compared with post-treatment with population, time, and population-by-time interaction as fixed factors and patient as a random factor, such that the least-squares means difference between pre- and post-treatment would be adjusted for the interim analysis and tested at the two-sided alpha of 0.0365. To assess the primary hemostasis end point, a pooled analysis of evaluable patients was used to determine the proportion of patients adjudicated as achieving effective hemostasis within 24 hours from the initiation of bentracimab compared with a 50% rate of hemostasis expected in the absence of reversal using an exact two-sided test with an alpha of 0.00916. Categorical variables were summarized by frequency and percentage. Continuous variables are presented as the mean (±SD) and median (minimum and maximum). Descriptive statistics are presented for secondary, safety, and other prespecified end points. All analyses were performed with SAS software (version 9.4; SAS Institute). The details of the statistical analyses are described in the study protocol and statistical analysis plan (both available in Supplementary Appendix S2).

Results

STUDY POPULATION

A total of 150 patients from 23 sites in North America and Europe were enrolled and treated with bentracimab between March 2020 and September 2021. Of these patients, 142 required urgent surgery or invasive procedures and 8 had major bleeding (Figure S1 in Supplementary Appendix S1). Coronary artery bypass graft (CABG) surgery was the most common procedure, and intracranial hemorrhage was the most common bleeding event (Table S1 in Supplementary Appendix S1). All patients were taking ticagrelor, and 97.3% were taking aspirin. Enrollment and study drug administration occurred in the hospital setting, and baseline characteristics of the study population were comparable to a real-world cardiac intensive care unit multicenter registry population as shown in Tables 1 and S2 in Supplementary Appendix S1.[16] The safety population included all treated patients. Four patients reported concomitant CYP3A inhibitor use, two of whom received 36 g of study drug. Six other patients received between 24 and 36 g of bentracimab owing to a clinical need for extended reversal. Twenty-one patients were not included for reversal assessments: 19 had pretreatment PRU in the normal range (>180) and 2 did not have predose PRU recorded. Adjudication identified seven surgical patients not meeting enrollment criteria and four who were miscategorized as surgical or bleeding. The final reversal analysis population included 129 patients, and the final hemostasis analysis population included 122 patients. One patient was dosed with bentracimab twice as a result of the unexpected cancelation and rescheduling of a surgical procedure.

Table 1. Characteristics at Baseline.*			
Characteristic	**Surgical Patients (n = 142)**	**Patients with Bleeding (n = 8)**	**All Patients (N = 150)**
Age — yr	64.8 ± 10.42	67.0 ± 12.53	65.0 ± 10.56
Sex			
Male	112 (78.9)	4 (50.0)	116 (77.3)
Female	30 (21.1)	4 (50.0)	34 (22.7)
Weight — kg	85.19 ± 19.26	76.91 ± 27.51	84.79 ± 19.80
Height — cm	170.9 ± 8.59	168.7 ± 10.82	170.8 ± 8.72
BMI — kg/m^2†	29.13 ± 6.18	27.79 ± 10.61	29.06 ± 6.47
Ethnicity			
Hispanic or Latino	1 (0.7)	2 (25.0)	3 (2.0)
Not Hispanic or Latino	141 (99.3)	6 (75.0)	147 (98.0)
Race			
White	118 (83.1)	7 (87.5)	125 (83.3)
Black or African American	5 (3.5)	1 (12.5)	6 (4.0)
Asian	16 (11.3)	0 (0)	16 (10.7)
American Indian or Alaskan	1 (0.7)	0 (0)	1 (0.7)
Other	2 (1.4)	0 (0)	2 (1.3)
Hypertension	114 (80.3)	6 (75.0)	120 (80.0)
Diabetes	57 (40.1)	2 (25.0)	59 (39.3)
Myocardial infarction	118 (83.1)	4 (50.0)	122 (81.3)
Baseline eGFR < 60 (MDRD)	28 (19.7)	4 (50.0)	32 (21.3)
Time from last ticagrelor — d			
0 to 1	109 (76.8)	8 (100)	117 (78.0)
2	23 (16.2)	0 (0)	23 (15.3)
3	10 (7.0)	0 (0)	10 (6.7)

* Data are presented as the number of patients (%) or means (±SD). In general, the baseline value is defined as the last nonmissing measurement obtained prior to the randomization. There was no significant baseline difference between surgical and bleeding groups for any variable recorded. Race was reported by the investigator. BMI denotes body-mass index, eGFR estimated glomerular filtration rate, and MDRD Modification of Diet in Renal Disease.

† BMI is the weight in kilograms divided by the square of the height in meters.

‡ eGRF is measured in milliliters per min per 1.73 m^2.

TICAGRELOR REVERSAL

Reversal of the antiplatelet effects of ticagrelor was assessed by PRU measurement before and after bentracimab infusion. For the primary end point, the peak post-treatment PRU within 4 hours of study drug initiation was used to calculate the minimum percentage inhibition of PRU, which was compared with the pretreatment PRU inhibition. A highly significant 135% reduction in inhibition was observed with bentracimab, indicating achievement of the primary reversal end point ($P < 0.001$; Fig. 1A). The PRU at multiple time points after study drug initiation increased significantly from a mean of 65 PRU pretreatment to 230 PRU within 5 to 10 minutes of initiation of infusion and remained between 230 and 300 PRU through 24 hours before declining modestly by 72 hours after the drug infusion ($P < 0.001$ across all time points Fig. 1B). All prespecified subgroups, including the subgroup with bleeding, exhibited a similar reduction in PRU inhibition (Fig. 2A). Despite the lower number of patients with bleeding relative to those requiring urgent surgery, the recovery of PRU was similar in both groups (Fig. S2-A in Supplementary Appendix S1).

The VASP immunoassay was used to compare the pre- and post-treatment platelet reactivity index, which measures $P2Y_{12}$ receptor activity. A significant reduction in platelet reactivity index inhibition was observed ($P < 0.001$; Fig. 1C). The mean pretreatment platelet reactivity index of 30% recovered to approximately 90% within 5 to 10 minutes of bentracimab initiation and was sustained above 90% through 12 hours before declining modestly between 24 and 72 hours ($P < 0.001$ across all time points; Fig. 1D). As observed with PRU, ticagrelor reversal measured with the VASP platelet reactivity index was similar in patients undergoing surgery and in those with bleeding (Fig. S2 B in Supplementary Appendix S1).

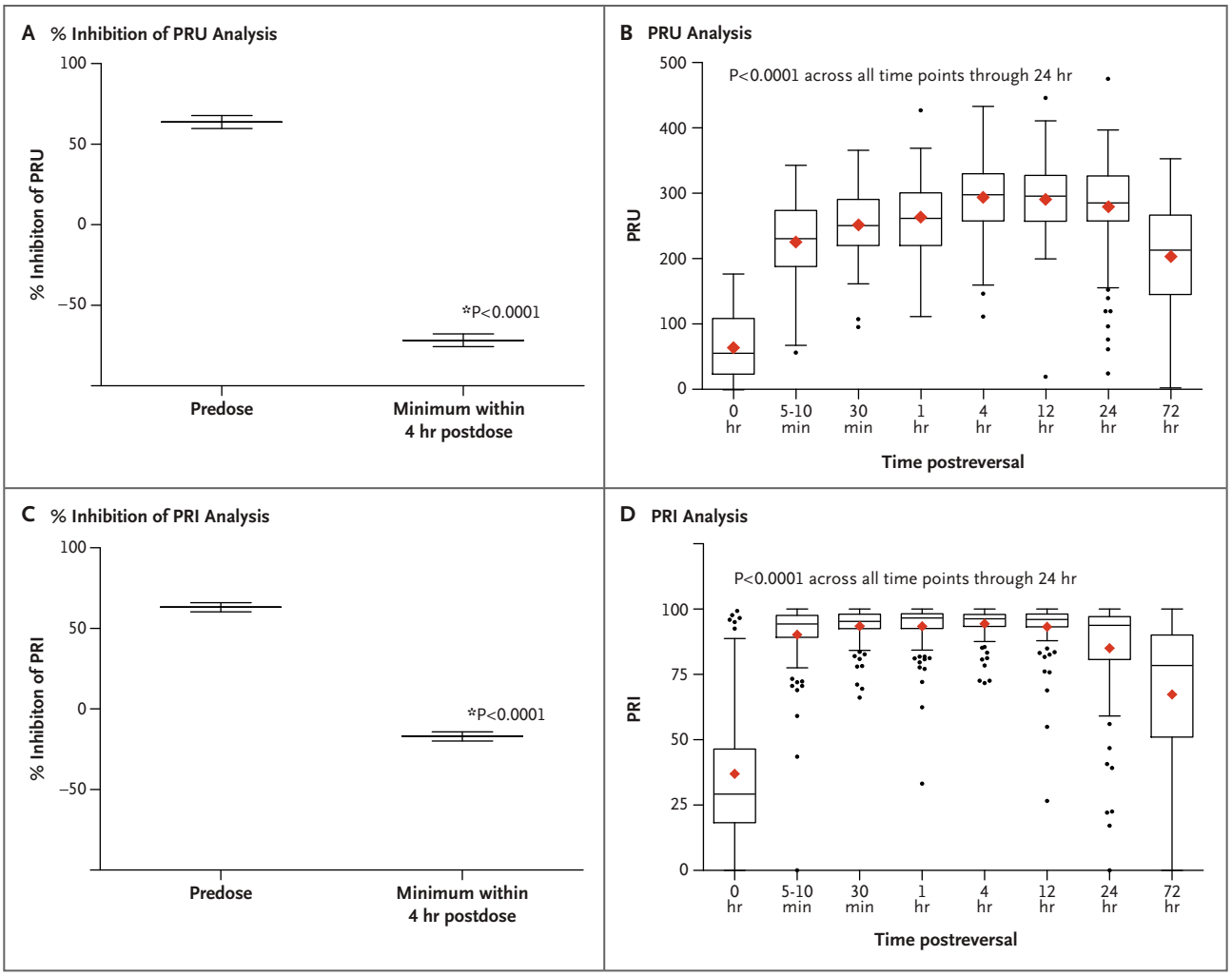

Figure 1. Ticagrelor Reversal with VerifyNow PRU and VASP Platelet Reactivity Index.

Ticagrelor reversal is shown as a reduction in percent inhibition of $P2Y_{12}$ reactivity units (PRU) or the platelet reactivity index (PRI) and as an increase in PRU or PRI at multiple time points post-treatment. A) Shown is the comparison of percent inhibition of PRU pretreatment and the minimum percent inhibition of PRU within 4 hours of initiation of bentracimab infusion. B) Onset and duration of ticagrelor reversal in bentracimab-treated patients observed as an increase in PRU with Bonferroni-adjusted P values at each time point. C) Comparison of the percent inhibition of PRI pretreatment and the minimum percent inhibition of PRI within 4 hours of initiation of bentracimab infusion. D) The onset and duration of ticagrelor reversal in bentracimab-treated patients observed as an increase in PRI with Bonferroni-adjusted P values at each time point. Red diamonds indicate the mean, and horizontal lines are the median. The top and bottom of the boxes indicate the 25th and 75th percentiles (interquartile range), respectively. I-bars indicate the largest value within 1.5 times the interquartile range. Dots indicate values outside the I-bar range. *P<0.0001.

HEMOSTASIS

The clinical end points committee adjudicated all 150 patients in the safety population. Seven surgical patients did not meet eligibility criteria; three patients enrolled as surgical patients were adjudicated to be more appropriately categorized as patients with bleeding (two aortic dissections and one ruptured aneurysm); and one patient with bleeding was recategorized as a surgical patient. Achievement of effective hemostasis was adjudicated using standardized hemostatic criteria in all treated patients who met the eligibility criteria and had evidence of ticagrelor-mediated antiplatelet effects, which included 113 surgical patients and 9 patients with bleeding (Tables S3 and S4 in Supplementary Appendix S1). Surgical hemostasis data are shown in Table 2 and Figure 2B. The data for hemostasis for patients with bleeding are shown in Table S5 in

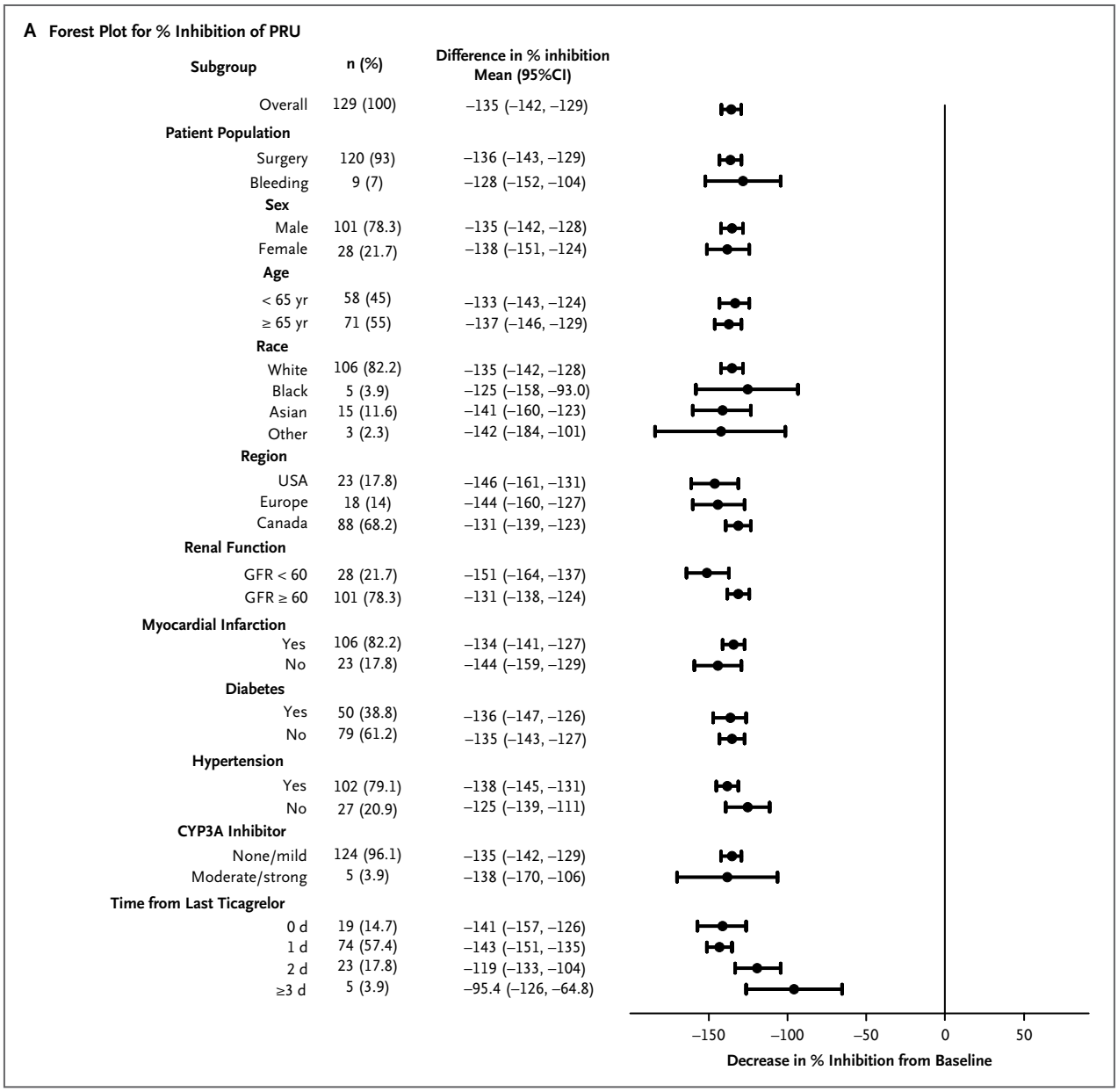

Figure 2. Prespecified Subgroup Analyses of Primary Reversal and Hemostasis End Points.

The primary reversal end point was the minimum percent inhibition of $P2Y_{12}$ reactivity units (PRU) within 4 hours of study drug initiation compared to pretreatment percent inhibition of PRU. A) Shown is a forest plot of the pretreatment percent inhibition of PRU compared to the minimum percent inhibition within 4 hours of study drug in prespecified subgroups. The primary hemostasis end point was the proportion of patients adjudicated to have achieved effective hemostasis compared to 50% expected by the null hypothesis. B) Shown is a forest plot of the proportion of patients with effective hemostasis within 24 hours of initiation of bentracimab infusion in prespecified subgroups. n denotes the number of subjects successfully achieving hemostasis and N the total number of subjects in the category. Confidence intervals are bounded at 100%.

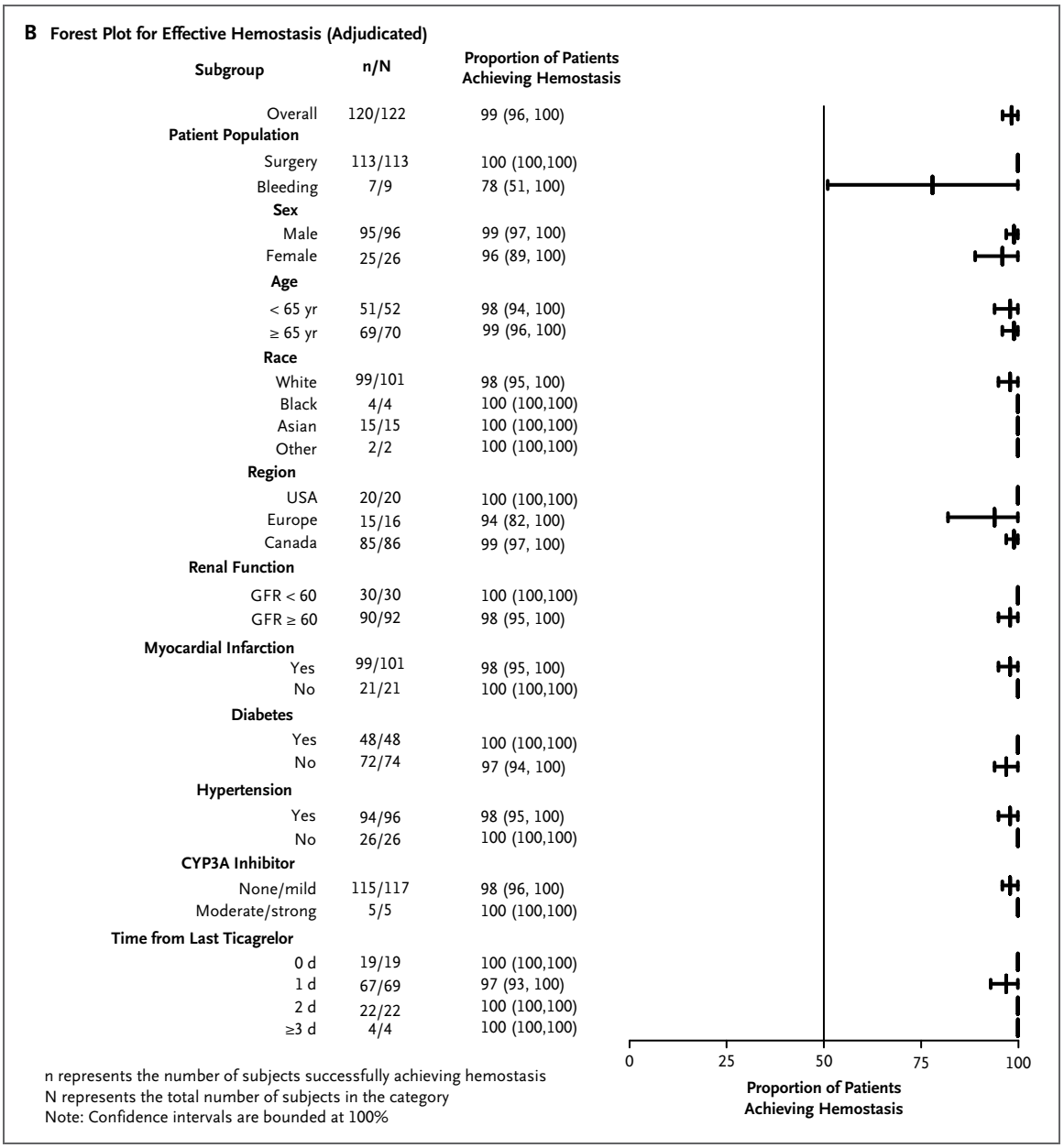

Figure 2. Continued.

Supplementary Appendix S1. For the primary hemostasis end-point analysis, the combined proportion of patients achieving hemostasis (98.4%) was significantly higher than the 50% rate of hemostasis expected in a similar population not treated with a ticagrelor reversal agent ($P < 0.001$). Among surgical patients, 66.4% had mild GUSTO bleeding, and 33.6% had moderate GUSTO bleeding perioperatively. In a post hoc analysis, there was no difference in the extent of reversal in the patients with GUSTO moderate compared with GUSTO mild bleeding (Fig. S3 in Supplementary Appendix S1).

Investigator-reported hemostasis was similar to adjudicated hemostasis results for surgical patients and patients with bleeding (Tables 2 and S5 in Supplementary Appendix S1). Allogeneic blood product transfusions (red blood cells, whole blood, or platelets) for management of perioperative bleeding occurred for less than 10% of surgical

Table 2. Adjudicated and Investigator-Reported Surgical Outcomes.*

Hemostasis in Surgical Patients	No. of Patients (%)
Adjudicated achieved hemostasis (n=113)	113 (100.0)
GUSTO†	
Mild	75 (66.4)
Moderate	38 (33.6)
Severe	0 (0)
Investigator-reported achieved hemostasis (n=142)	135 (95.1)
Bleeding	
Normal or mildly abnormal	110 (77.5)
Moderately abnormal	25 (17.6)
Severely abnormal (4) or not reported (3)	7 (4.93)
Blood product transfusions	
Total blood transfusions (pRBCs or whole blood)	56 (39.04)
Blood transfusions for bleeding event	10 (7.04)
Total platelet transfusions	19 (13.4)
Platelet transfusions for bleeding event	6 (4.22)
Other surgical outcomes	
Restarted $P2Y_{12}$ inhibition	111 (74)
Time to restart — d‡	2 (0, 22)
Total mortality	4 (2.8)

* Investigators were required to specify in case report forms whether allogeneic blood and platelet products were transfused for bleeding events or other routine perioperative use. Total transfusions and transfusions for bleeding events are shown in the table. GUSTO denotes Global Use of Strategies to Open Occluded Coronary and pRBC packed red blood cell.

† GUSTO bleeding scale categories are as follows: mild indicates does not meet criteria for moderate or severe; moderate requires blood transfusion but does not result in hemodynamic compromise; and severe indicates fatal bleeding, intracranial hemorrhage, or bleeding that causes hemodynamic compromise that requires pharmacologic or surgical intervention.

‡ Values are presented as the median (minimum, maximum).

patients (Table 2). Reinitiation of $P2Y_{12}$ inhibitors postreversal occurred for 74% of patients during the 35-day follow-up period. Among these, the median time to restarting $P2Y_{12}$ inhibition was 2 days for surgical patients, whereas the median time to restart was 5 days for patients with bleeding (Tables 2 and S5 in Supplementary Appendix S1).

SAFETY

Treatment-emergent AEs were reported by 92.7% of enrolled patients. Four patients died: two with septic shock and two with cardiogenic shock. Seventy-one serious AEs were reported for 45 of the 150 patients (Table 3). The most common AEs were complications related to procedures, such as procedural pain or incisional pain, and none were considered serious (Table S6 in Supplementary Appendix S1). Cardiac and metabolic disorders, such as atrial fibrillation, sinus tachycardia, and electrolyte abnormalities, were also common. No infusion-related, allergic, or anaphylactic reactions have been reported to date. In immunogenicity testing for antidrug antibodies, 22.6% of patients had preexisting antidrug antibodies, 24.3% of patients developed antidrug antibodies after study drug infusion, and 53% of patients had no such antibodies. Neutralizing antibody testing is ongoing. The presence of antidrug antibodies had no effect on ticagrelor reversal measured with PRU or the platelet reactivity index (Fig. S4 in Supplementary Appendix S1).

POSTREVERSAL THROMBOTIC EVENTS

Of 150 patients, 8 (5.3%) reported AEs that were serious and adjudicated to be thrombotic events (Table 3). Three of these patients had restarted $P2Y_{12}$ inhibition at the time of the event. None resulted in death. Three patients had myocardial infarction with graft occlusion 1 to 29 days postreversal. Three patients had cerebrovascular events 1 to 5 days postreversal (one transient ischemic attack and two ischemic strokes). Two patients were noted to have right lower-extremity arterial thromboembolism on the same day of study drug administration. Neither P-selectin nor mean platelet volume appeared to change after bentracimab infusion compared with predose levels (Fig. S5 in Supplementary Appendix S1).

Discussion

In this trial of an intravenous ticagrelor reversal agent, bentracimab significantly restored platelet function adequate for hemostasis as assessed by two platelet assays at several time points in patients undergoing urgent surgical procedures who had previously received ticagrelor. The assessment of clinical hemostasis by independent adjudicators demonstrated that surgical patients appeared to achieve adequate hemostasis. The use of blood products in patients undergoing surgery appeared similar to that expected for patients who had no preoperative antiplatelet agent exposure. The proportion of patients in REVERSE-IT to date undergoing urgent CABG with GUSTO severe bleeding (0%) or CABG-related bleeds leading to blood transfusion (7.04%) appeared to be lower than the overall rates observed in the PLATO (Platelet Inhibition and Patient Outcomes) study (10.6% and

Table 3. Total Treatment-Emergent Serious Adverse Events.*

Patient Enrollment Diagnosis	Serious Adverse Event(s)	Days from Study Drug	Adjudicated Thrombotic Event
Upper GI bleed	Upper GI bleed	27	
CABG	Ventricular fibrillation	1	
CABG	Nosocomial pneumonia	10	
CABG	Postoperative wound infection	15	
CABG	Myocardial infarction	7	Yes
CABG	Symptomatic bradycardia	18	
CABG	Appendicitis	30	
CABG	Incomplete revascularization	1	
CABG + AVR	Cardiogenic shock	1	
	Multiorgan dysfunction	5	
	Left lung laceration	10	
	Innominate vein laceration	10	
CABG	Post-pericardiotomy syndrome	20	
CABG	Transient ischemic attack	2	Yes
	Staphylococcus aureus bacteremia	7	
Tracheostomy	MRSA sepsis with shock	2	
	Upper GI bleed	8	
	Worsening respiratory failure	2	
CABG	Lacunar stroke	1	Yes
CABG	Syncope	18	
CABG	Pneumothorax	2	
CABG	Slow to mobilize	7	
CABG	Sternal wound infection	14	
Hemicolectomy	Acute kidney injury	6	
	Sepsis	5	
Hip + femur ORIF	Acute cholecystitis	19	
	Septic shock	20	
	Oliguric acute renal injury	19	
	Acute respiratory failure	21	
ICH + hematoma evacuation	Symptomatic left cerebellar cyst	12	
CABG	Lightheadedness	39	
CABG	Total graft occlusion	4	Yes
	Cardiac arrest	4	
	Inferior STEMI	0	
	Anterior STEMI	1	
	Worsening multiorgan failure	21	
CABG	Sepsis	20	
CABG	Complete heart block	1	
CABG	Pericardial effusion	37	
AVR	Superior vena cava tear	0	
CABG + AVR	Lower limb pain	8	
	Physical deconditioning	8	
CABG	Arrhythmia	4	
	Pleural effusion	7	
CABG + thrombectomy	Popliteal and tibial artery emboli	0	Yes
	Ischemic right leg	0	
CABG	LIMA kink repaired post-CABG	1	

(continued)

Table 3. Total Treatment-Emergent Serious Adverse Events.* (cont.)

Patient Enrollment Diagnosis	Serious Adverse Event(s)	Days from Study Drug	Adjudicated Thrombotic Event
CABG	Echodensities on LV	6	
CABG	Myasthenia gravis attack	1	Yes
	Perioperative stroke	5	
	Septicemia	10	
CABG	Hypoxic respiratory failure	18	
CABG	Superficial venous thrombus	6	
	Postoperative ileus	3	
CABG	Septic shock	2	
	Dehydration	9	
CABG	Acute coronary syndrome	29	Yes
CABG	Hypovolemic shock	1	
CABG	Presyncope	9	
CABG	Hypoglycemia	28	
CABG	Cholecystitis	28	
CABG + Bentall procedure	Ischemic RLE	0	Yes
CABG	Delirium	3	
	Agitation	3	
	Anemia	11	
Acute GI bleed	Acute chronic GI bleed	22	
	Gastric carcinoma	30	
	Hypoxic respiratory failure	0	
	Sepsis	20	
CABG + AVR	Anemia	2	
Subdural hematoma	Subdural hematoma	24	

* AVR denotes aortic valve replacement, CABG coronary artery bypass graft surgery, GI gastrointestinal, ICH intracranial hemorrhage, LIMA left internal mammary artery, LV left ventricle, MRSA methicillin-resistant *Staphylococcus aureus*, ORIF open reduction and internal fixation, RLE right lower extremity, and STEMI ST segment elevation myocardial infarction.

16.2%, respectively).[17] No allergic reactions were noted. There was no evidence of platelet hyperreactivity upon cessation of bentracimab infusion.

A prior study of bentracimab in healthy volunteers demonstrated effective restoration of platelet function by platelet function testing.[12] The current study extends these results to patients requiring urgent surgical procedures. Furthermore, the prior study had not been designed to examine bleeding; the current study provides support that bentracimab promotes adequate hemostasis in ticagrelor-treated patients undergoing urgent surgery.

Bleeding with antiplatelet agents is a major problem prompting hospitalizations and transfusions, with a small but concerning risk for fatal or intracranial bleeding as well.[18,19] Additionally, there are several still-expanding indications for long-term oral antiplatelet therapy, and it is not uncommon for patients to need urgent or emergent surgical and other invasive procedures while being treated with antiplatelet agents. These situations frequently complicate patient care, forcing patients and physicians to make difficult choices between performing procedures while taking antiplatelet therapy and accepting the higher bleeding risk or attempting to delay necessary invasive procedures with potential ischemic risk while ticagrelor is withheld. Furthermore, professional society guidelines and the labeling of antiplatelet agents generally advise against operating until several days after antiplatelet therapy cessation.[10,20–26] Because of its reversible binding to the platelet $P2Y_{12}$ receptor, ticagrelor stands apart from other commonly used oral antiplatelet agents. Our data showed that patients pretreated with bentracimab who needed urgent or emergent procedures did not suffer from procedure-limiting bleeding. However, for ethical reasons there was no control group of patients who were not bentracimab treated for comparison; further study of bentracimab is needed in patients who have spontaneous bleeding. Approved anticoagulant reversal

agents have already been shown to be useful in such clinical scenarios.[27–29]

The overall safety profile of bentracimab appeared favorable. There were no allergic or infusion-related reactions in this study. The analyses of P-selectin and mean platelet volume were consistent with the relatively low number of thrombotic events seen in this trial that included a large proportion of patients at high risk of ischemic and thromboembolic complications. The finding that slightly more than 5% of patients who had severe thrombotic events in close temporal proximity to treatment (Table 3), whether drug induced or as a result of their underlying conditions, is a reason for caution.

Limitations of this study include the lack of a control group. However, without an evidence-based alternative to bentracimab, a cohort study was utilized because it was deemed unethical to randomly assign patients with life-threatening hemorrhage to placebo, although one could argue that randomization in the context of the surgical patients might have been ethical. However, this approach of not utilizing a placebo arm was similar to prior evaluations of anticoagulant reversal agents.[15,27,28,30] Nevertheless, in the absence of a control group and because of small numbers in the bleeding group, the full extent to which bentracimab provided true clinical benefit, especially in patients with bleeding, cannot be known. The present results are from an interim analysis, although again this route was taken for prior reversal agents to accelerate potential regulatory approval for use in life-threatening situations; however, those programs had enrolled more patients with spontaneous bleeding than has REVERSE-IT to date.[15,30] The majority of surgical patients underwent cardiac surgery, with a relatively smaller proportion of patients undergoing other types of procedures, although the effects of bentracimab are unlikely to differ with other surgeries. In addition, while some surgeries such as for aortic dissection are clearly emergent, CABG categorized as urgent may depend on the particular surgeon's judgment. However, there was greater than 90% concordance between investigator judgment on the urgency of CABG procedures and adjudicator assessment of procedure urgency. The number of patients enrolled with spontaneous bleeding in this interim analysis was low. Although surgery is an excellent model of induced bleeding, and the platelet function results were similar in both cohorts, more patients with spontaneous bleeding must be studied with bentracimab, and such patients are being enrolled in this ongoing trial.

In conclusion, bentracimab rapidly and effectively reversed the antiplatelet effect of ticagrelor in patients undergoing surgical procedures or with bleeding, with no evidence of rebound platelet hyperreactivity. Bentracimab appeared to promote adequate hemostasis in the majority of ticagrelor-treated patients studied.

Supported by PhaseBio Pharmaceuticals.

We thank the patients who participated in this trial; Susan Marble-Gibson (Boston Clinical Research Institute), Michelle Fitzpatrick (Boston Clinical Research Institute), Julie Farner (PhaseBio), and Pompi Borkakoty (PhaseBio) for administrative support of adjudication; Joe Massaro, Ph.D. (Boston University), for statistical expertise; and Katie Reyes (PhaseBio) for support with references, collation of author comments, and formatting (all funded by PhaseBio Pharmaceuticals).

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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Author disclosures and other supplementary material are available with the full text of this article at evidence.nejm.org.

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