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ORIGINAL RESEARCH

Predictors, Type, and Impact of Bleeding on the Net Clinical Benefit of Long-Term Ticagrelor in Stable Patients With Prior Myocardial Infarction

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BACKGROUND: Ticagrelor reduces ischemic risk but increases bleeding in patients with prior myocardial infarction. Identification of patients at lower bleeding risk is important in selecting patients who are likely to derive more favorable outcomes versus risk from this strategy.

METHODS AND RESULTS: 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) randomized 21,162 patients with prior myocardial infarction in a 1:1:1 fashion to ticagrelor 60 mg or 90 mg twice daily or placebo, with ticagrelor 60 mg approved for long-term use. TIMI major or minor bleeding was the primary end point for this analysis. Causes of bleeding were categorized by site and etiology, and independent predictors were identified. At 3 years, ticagrelor 60 mg increased the rate of TIMI major or minor bleeding by 2.0% versus placebo (1.4% placebo versus 3.4% ticagrelor). The bleeding excess was driven primarily by spontaneous gastrointestinal bleeds. A history of spontaneous bleeding requiring hospitalization and the presence of anemia were independent predictors of bleeding but not ischemic risk. Patients with at least 1 risk predictor had 3-fold higher rates of bleeding with ticagrelor 60 mg versus those who had neither (absolute risk increase, 4.4% versus 1.5%; P=0.01). Patients with neither predictor had a more favorable benefit profile with ticagrelor 60 mg versus placebo including lower mortality (hazard ratio, 0.79; 95% CI, 0.65–0.96; P interaction=0.03).

CONCLUSIONS: In patients with prior myocardial infarction, bleeding with ticagrelor 60 mg twice daily is predominantly spontaneous gastrointestinal. A history of spontaneous bleeding requiring hospitalization or the presence of anemia identifies patients at higher risk of bleeding, and the absence of either identifies patients likely to have a more favorable net benefit with ticagrelor.

REGISTRATION: URL https://www.clinicaltrials.gov/. Unique identifier: NCT01225562.

Key Words: benefit-risk ratio ■ bleeding ■ long-term ticagrelor ■ myocardial infarction

See Editorial by Cao et al.
CLINICAL PERSPECTIVE

What Is New?

- In stable patients with prior myocardial infarction on aspirin, TIMI (Thrombolysis in Myocardial Infarction) major or minor bleeding is primarily spontaneous of gastrointestinal origin and related to an underlying disease.

- Ticagrelor 60 mg increases spontaneous TIMI major or minor bleeding, including gastrointestinal bleeding, but does not increase fatal bleeding, bleeding that contributed to death, or spontaneous intracranial hemorrhage.

- Anemia at baseline and history of previous bleeding requiring hospitalization were independent predictors of bleeding and were not associated with ischemic risk or the benefit of ticagrelor. Patients without anemia at baseline or history of previous bleeding requiring hospitalization derived greater benefit from prolonged ticagrelor therapy.

What Are the Clinical Implications?

- In a stable post–myocardial infarction population, prior bleeding and anemia may be sufficient for bleeding risk prediction and may enable clinicians to consider bleeding and ischemic risk independently.

- This may be particularly helpful in groups such as the elderly in whom assessment of risks and benefits may be particularly challenging.

Nonstandard Abbreviations and Acronyms

COGENT Clopidogrel and the Optimization of Gastrointestinal Events
ICH Intracranial hemorrhage
PEGASUS Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin
TIMI Thrombolysis in Myocardial Infarction
MI Myocardial infarction
PPI Proton pump inhibitor

Long-term therapy with ticagrelor 60 mg twice daily added to aspirin in patients with a previous myocardial infarction (MI) reduced major adverse cardiovascular events 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. Based on this finding, ticagrelor 60 mg twice daily has been approved in Europe and the United States for long-term use for secondary prevention after MI. However, ticagrelor also increased the risk of TIMI major and minor bleeding, although it did not increase intracranial hemorrhage (ICH) or fatal bleeding.

Serious bleeding is an important outcome and has been associated with several adverse events including hospitalizations, procedures, cessation of medications, and mortality. Therefore, understanding the sites, etiologies, and outcomes after bleeding may be helpful in weighing the benefits and risks of antithrombotic therapies. In addition, identifying patients at greater risk of bleeding may enable personalization of therapy to those at lower bleeding risk who are more likely to derive greater benefit. A challenge to bleeding risk prediction, however, is that several characteristics are associated with both bleeding and ischemic risk.

In this context, a post hoc analysis of bleeding in PEGASUS-TIMI 54 was performed, including characterization of the sites and causes of bleeding. In addition, baseline characteristics independently associated with bleeding risk, but not ischemic risk, were identified. Finally, a post hoc analysis evaluating the efficacy and safety of long-term ticagrelor stratified by baseline bleeding risk was performed.

METHODS

Study Population

The data for the analyses are held at the TIMI Study Group, and the senior author may be contacted for requests with regard to the sharing of data, methods, and materials specific to this analysis. The study protocol was approved by the relevant ethics committee at each participating site. Written informed consent was obtained from all the patients. The PEGASUS-TIMI 54 trial, described previously,1,4 randomized 21,162 patients with prior spontaneous MI occurring 1–3 years before enrollment, who had at least 1 additional atherothrombotic risk factor (age ≥65 years, diabetes mellitus requiring medication, a second prior spontaneous MI, chronic renal dysfunction, or multivessel coronary artery disease) to ticagrelor 60 mg twice daily, ticagrelor 90 mg twice daily, or placebo in a 1:1:1 fashion, all on a background of low-dose (75 mg–150 mg) aspirin. The 60-mg dose was approved for long-term secondary prevention, and therefore the primary group for analysis includes patients randomized to 60 mg (N=6958) or placebo (N=6996) with additional analyses for the 90-mg dose (N=6988) versus placebo included in the online supplement. Exclusion criteria included planned use of a P2Y12 receptor antagonist or anticoagulant therapy, a known bleeding disorder, history of stroke, a central nervous system tumor, gastrointestinal bleeding within the previous 6 months, or major surgery within the previous 30 days. Enrolling sites were requested to indicate if there...
was any history of bleeding leading to hospitalization. All patients had central laboratory testing for hemoglobin at baseline. Anemia was defined as a hemoglobin ≤13.5 g/dL for men and ≤12.0 g/dL for women.

**End Points**

The primary efficacy end point was major adverse cardiovascular events, consisting of the composite of cardiovascular death, MI, or stroke (3-point major adverse cardiac event). The primary safety end point was TIMI major bleeding. Secondary safety end points were combined TIMI major and minor bleeding, as well as ICH and fatal bleeding. TIMI major bleeding was defined as any ICH, or clinically overt signs of hemorrhage associated with a reduction in hemoglobin ≥5 g/dL (or, when hemoglobin was not available, a fall in hematocrit ≥15%), or fatal bleeding (a bleeding event that directly led to death within 7 days). TIMI minor bleeding was defined as any clinically overt hemorrhage (including that detected by imaging) that was associated with a fall in hemoglobin of 3 to <5 g/dL (or, when hemoglobin was not available, a fall in hematocrit of 9 to <15%). Hemoglobin measurements were adjusted for any packed red blood cells or whole blood given between baseline and posttransfusion measurement; transfusion of 1 unit of blood was assumed to result in an increase of 1 g/dL of hemoglobin. Bleeding events leading directly to mortality were classified as fatal bleeding events. Bleeding that was not directly fatal but was in the causal pathway leading to death (eg, death attributable to a nonbleeding complication of hospitalization prompted by bleeding) were classified as “bleeding contributing to death.” All bleeding events, as well as their relationship to mortality, were adjudicated by a clinical events committee blinded to treatment allocation. A net clinical benefit analysis was defined as cardiovascular death, MI, stroke, ICH, or fatal bleeding.

**Statistical Analysis**

Baseline characteristics, including demographics, medical history, and clinical findings at randomization were summarized using medians and quartiles (interquartile range) for continuous variables and frequencies and percentages for categorical variables. Differences were tested with the Wilcoxon rank-sum test for continuous variables and with the Pearson $\chi^2$ test for categorical data. The primary efficacy analysis and net clinical outcome were conducted on an intention-to-treat basis, whereas safety analyses included all patients who underwent randomization and received at least 1 dose of study drug. Event rates for ticagrelor and placebo were estimated by Kaplan–Meier methods from baseline to 3 years and compared with the log-rank test. In addition, the instantaneous hazard function for TIMI major or minor bleeding was also estimated by the kernel-based method. This was examined separately by treatment arm over time.

A multivariable Cox proportional hazards model was developed by first examining univariate associations between baseline characteristics and the risk of TIMI major or minor bleeding in the overall population. Clinically meaningful covariates that met $P$ value thresholds of 0.1 in univariable association were further retained for the pool of candidate variables. These included age, weight, systolic blood pressure, estimated glomerular filtration rate, history of spontaneous bleeding, history of diabetes mellitus, history of congestive heart failure, history of malignancy, white blood cell count, baseline anemia, and smoking status. The backward elimination method was then used to yield the final model with the reduced number of risk factors based on a $P$ value cutoff < 0.01.

Multivariable models evaluating the association between baseline characteristics and the risk of the primary efficacy end point were evaluated. The proportional hazards assumption was examined and tested by scaled Schoenfeld residuals. The linearity assumption for continuous variables was examined by restricted cubic spline plots. Characteristics that independently predicted bleeding but were not independently associated with the risk of the primary efficacy end point were identified as those most useful for patient selection. The results of these models were described using the hazard ratio (HR) with the associated 95% CI. The discrimination index was assessed using the Harrell’s C statistic. In addition, the absolute risk differences between treatment and placebo groups were compared across high- and low-bleeding-risk groups using the Gail–Simon 2-sided heterogeneity test. A sensitivity analysis of efficacy and safety was then performed, stratified by baseline bleeding risk with patients with a history of bleeding or anemia at baseline considered to be at “high bleeding risk” and those with no predictors of bleeding considered at “low bleeding risk.”

**RESULTS**

A total of 20,942 patients received at least 1 dose of the study drug (safety population). Baseline characteristics in the overall safety population, according to the occurrence of TIMI major or minor bleeding during follow-up (median, 33 months), are summarized in Table 1. Patients who experienced a TIMI major or minor bleed (n=432) were older and more likely to have hypertension, renal insufficiency, a history of malignancy, a history of a previous spontaneous bleed requiring hospitalization, and a hemoglobin value indicating anemia.

**Type, Location, and Cause of Bleeding in All Treatment Arms**

The majority of TIMI major or minor bleeding events were spontaneous (N=306; 71% of all bleeds) followed by procedural bleeding (N=65; 15%) and traumatic
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Predictors of Bleeding in All Treatment Arms

The following variables were identified as independently associated with TIMI major or minor bleeding in the total population: age, history of hypertension, current smoking, history of spontaneous (nontraumatic, nonprocedural) bleeding (N=61; 14%) (Figure 1A). Spontaneous TIMI major or minor bleeds were primarily of gastrointestinal origin (75%), followed by intracranial (12%) and genitourinary (6%, Figure 1B). The sites and causes of bleeding were similar in patients randomized to ticagrelor 60 mg twice daily or placebo (Figure S1). Of the spontaneous gastrointestinal bleeds, the most common was upper gastrointestinal ulcer or inflammation (49%), followed by diverticular bleeding or hemorrhoids (20%) and previously undiagnosed neoplasm (17%) (Figure S2).

Table 1. Baseline Characteristics by TIMI Major or Minor Bleeding During Follow-Up

|                          | TIMI Major or Minor Bleeding (N=432) | No TIMI Major or Minor Bleeding (N=20510) | P Value |
|--------------------------|------------------------------------|------------------------------------------|---------|
| Age, y, median (IQR)     | 68.0 (61.0–74.0)                   | 65.0 (59.0–71.0)                          | <0.0001 |
| Female, n (%)            | 100/432 (23.1)                     | 4903/20510 (23.9)                        | 0.71    |
| Weight, kg, median (IQR) | 79.0 (68.0–90.4)                   | 81.0 (70.0–92.0)                          | 0.04    |
| History of hypertension, n (%) | 359/432 (83.1)                  | 15879/20510 (77.4)                     | 0.005   |
| SBP, mm Hg, median (IQR) | 132.0 (120.0–145.0)               | 130.0 (120.0–142.0)                      | 0.052   |
| History of diabetes mellitus, n (%) | 139/432 (32.2)               | 6596/20510 (32.2)                         | 0.99    |
| Current smoker, n (%)    | 85/432 (19.7)                      | 3419/20505 (16.7)                        | 0.10    |
| Renal dysfunction, eGFR <60 (MDRD, mL/min/1.73 m²), n (%) | 130/426 (30.5)                 | 4658/20296 (23.0)                         | 0.0002  |
| History of CHF, n (%)    | 80/432 (18.5)                      | 4123/20510 (20.1)                        | 0.42    |
| History of malignancy, n (%) | 25/432 (5.8)                   | 1256/20510 (6.1)                         | 0.09    |
| History of spontaneous bleeding requiring hospitalization, n (%) | 19/432 (4.4)                   | 245/20510 (1.2)                          | <0.0001 |
| Anemia,* n (%)           | 126/418 (30.1)                    | 3723/20682 (18.5)                        | <0.0001 |
| WBC (10×9/L, median (IQR) | 6.7 (5.6–8.1)                    | 6.9 (5.8–8.1)                            | 0.10    |
| Proton pump inhibitor use, n (%) | 111/432 (25.7)                  | 5378/20510 (26.2)                        | 0.81    |

CHF indicates congestive heart failure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; TIMI, Thrombolysis in Myocardial Infarction; and WBC, white blood cell count.

*Anemia was defined as hemoglobin ≤13.5 g/dL for men and ≤12.0 g/dL for women.

Predictors of Bleeding in All Treatment Arms

The following variables were identified as independently associated with TIMI major or minor bleeding in the total population: age, history of hypertension, current smoking, history of spontaneous (nontraumatic, nonprocedural) bleeding. Of the 432 patients who experienced a TIMI major or minor bleed, 42 (9.7%) died of causes related to bleeding, with 28 having a directly fatal bleed and 14 in whom bleeding contributed to death. The median time from the bleeding event to death was 2.0 days (interquartile range, 0–5) for directly fatal bleed and 10 days (interquartile range, 2–61) for bleeding that contributed to death. Of the patients who survived their bleeding, an additional 38 died later during the study (median, 207.5 days after bleeding; interquartile range, 78–404) for causes unrelated to bleeding, including cardiovascular causes (45%), sepsis or organ failure (18%), and malignancy (37%) (Figure 2).
bleeding requiring hospitalization, and anemia at baseline (Table 2). Supplemental Figure S3 shows cubic splines for hemoglobin and risk of TIMI major or minor bleeding in women (a) and men (b). Age, history of hypertension, and current smoking were also independent predictors of ischemic risk. However, anemia and a history of spontaneous bleeding requiring hospitalization were not.

**Bleeding With Ticagrelor 60 mg Versus Placebo**

Compared with placebo, ticagrelor 60 mg twice daily increased the risk of TIMI major or minor bleeding (HR, 2.54; 95% CI, 1.93–3.35; \( P < 0.001 \)). The instantaneous hazard function for TIMI major or minor bleeding is shown in Figure S4. At 3 years, ticagrelor 60 mg twice daily increased TIMI major or minor bleeding by 2.0% (3.4% with ticagrelor compared with 1.4% with placebo). This excess was primarily in spontaneous bleeds (1.5%), traumatic (0.3%) or procedural (0.2%) (Figure 3a). The excess in spontaneous bleeds was primarily attributable to gastrointestinal bleeding (absolute risk increase, 1.1%; Figure 3b). The rate of gastrointestinal bleeding was less frequent in patients on ticagrelor 60 mg twice daily and a proton pump inhibitor (PPI), compared with patients not taking a PPI (0.4% versus 0.8%; HR, 0.47; 95% CI, 0.27–0.82; \( P = 0.009 \)).

There was no significant increase in ICH with ticagrelor 60 mg compared with placebo (HR, 1.18; 95% CI, 0.55–2.50; \( P = 0.67 \); Figure 3b). In addition, there was no significant increase in fatal bleeding or bleeding contributing to death with ticagrelor 60 mg relative to placebo (Figure 4). Results for ticagrelor 90 mg twice daily compared with placebo were similar and are reported in Figure S5a and S5b and Figure S6.

**Efficacy and Safety of Ticagrelor 60 mg in Patients at High and Low Bleeding Risk**

Based on the models of ischemic and bleeding risk, high bleeding risk was defined as either a history of spontaneous bleeding requiring hospitalization, anemia at baseline, or both (N=2714; 19% of the population), whereas low bleeding risk was defined as the absence of either characteristic (N=11 240; 81% of the population). Table S1 shows baseline characteristics stratified by high versus low bleeding risk in the overall population. When comparing the safety of ticagrelor 60 mg twice daily versus

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**Figure 2.** Incidence and cause of mortality among patients who experienced a TIMI major or minor bleeding (overall safety cohort). TIMI indicates Thrombolysis in Myocardial Infarction.

**Table 2.** Independent Predictors of TIMI Major or Minor Bleeding in the Overall Population

| Predictors                                      | HR (95% CI)       | P Value | \( \chi^2 \) |
|-------------------------------------------------|-------------------|---------|--------------|
| Age (continuous, per 10-y increase)             | 1.47 (1.31–1.66)  | <0.0001 | 40.2         |
| History of spontaneous bleeding requiring hospitalization | 3.56 (2.24–5.64)  | <0.0001 | 29.1         |
| Anemia at baseline                              | 1.72 (1.39–2.13)  | <0.0001 | 24.6         |
| Current smoker                                  | 1.59 (1.24–2.03)  | 0.0002  | 13.4         |
| History of hypertension                         | 1.43 (1.10–1.84)  | 0.007   | 7.3          |

c-index for variables listed 0.65 (95% CI, 0.62–0.68); HR, hazard ratio; and TIMI, Thrombolysis in Myocardial Infarction.
placebo, the HR for TIMI major or minor bleeding was 2.93 (95% CI, 1.80–4.78) in patients at high bleeding risk, and 2.37 (95% CI, 1.70–3.32) in patients at low bleeding risk. There was a greater absolute increase in the rate of TIMI major or minor bleeding with ticagrelor in the high-bleeding-risk group (increase of 4.4% at 3 years; 95% CI, 2.3%–6.4%) compared with the increase with ticagrelor in patients in the low-bleeding-risk group (increase of 1.5% at 3 years; 95% CI, 0.8%–2.1%) with a significant interaction based on absolute differences (P value for absolute risk difference = 0.01; Figure 5). Table S2 shows the primary end point and TIMI major bleeding rates stratified by high versus low bleeding and ischemic risk.

In an exploratory analysis to evaluate the efficacy of ticagrelor 60 mg twice daily compared with placebo on the basis of bleeding risk, ticagrelor 60 mg reduced the risk of cardiovascular death, MI, or stroke by 20% in patients with low bleeding risk (HR, 0.80; 95% CI, 0.70–0.92; P = 0.0015; Figure 6). However, there was no apparent benefit of ticagrelor
in patients at high bleeding risk (HR, 0.98; 95% CI, 0.77–1.26; \( P = 0.88 \), \( P \) interaction = 0.15). Results for the net clinical benefit showed a consistent pattern with ticagrelor 60 mg twice daily associated with favorable effects in the low-bleeding-risk patients (HR, 0.82; 95% CI, 0.71–0.94; \( P = 0.004 \)) but no apparent benefit in high bleeding risk (HR, 1.03; 95% CI, 0.81–1.31). Finally, there was significant heterogeneity for mortality with ticagrelor based on low versus high bleeding risk with a reduction in low bleeding risk (HR, 0.79; 95% CI, 0.65–0.96) and no benefit in high bleeding risk (HR, 1.14; 95% CI, 0.86–1.50; \( P \) interaction = 0.03; Figure 6, Table S3).

**DISCUSSION**

The current analysis provides three novel observations with regard to bleeding risk with ticagrelor in patients with prior MI. First, bleeding caused by ticagrelor in this population is most frequently spontaneous gastrointestinal bleeding in patients with occult sources, such as ulcer or malignancy. Second, there were 2 independent predictors of TIMI major or minor bleeding that were not independent predictors of ischemic risk, namely, prior hospitalization for bleeding and anemia. Finally, in an analysis of the efficacy of ticagrelor 60 mg twice daily stratified by bleeding risk, those at low risk appeared to have greater benefit, including lower rates of mortality, while patients at high risk appeared to have no benefit.

The observation that more potent antithrombotic therapy increases spontaneous gastrointestinal bleeding supports other recent trials evaluating bleeding risk in stable secondary prevention populations. Observations regarding gastrointestinal bleeding may be helpful in considering the risks and benefits of...
Magnani et al Predictors of Bleeding With Long-Term Ticagrelor therapy. In addition, they support strategies to reduce gastrointestinal bleeding such as PPI inhibitors, which have been shown to attenuate this risk.8,9 Finally, this analysis supports the identification of anemia as a key risk marker for future bleeding. This finding suggests that hemoglobin may be a simple and widely available biomarker that may identify patients at heightened risk of gastrointestinal bleeding with more intensive anti-thrombotic therapy.

Predicting bleeding risk remains a challenge in clinical practice. One issue is the recognition that many factors that predict bleeding, such as advanced age and renal dysfunction, also predict ischemic events and potential benefit of risk reduction therapies.10

The Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy score was derived to predict bleeding risk and in its validation showed a c-index of 0.66.11 Findings from the current analysis both support and add novel information. First, prior bleeding and anemia in the current analysis demonstrates the predictive importance of these 2 factors. In contrast, white blood cell count was not predictive of bleeding in PEGASUS-TIMI 54, and the mechanism by which it would predict bleeding is unclear. Finally, in the current analysis, both age and renal dysfunction were associated with bleeding risk but also ischemic risk, and in the case of renal dysfunction, it has been shown previously to be associated with greater absolute benefit of ticagrelor.11 Importantly, the current analysis shows that in a stable post-MI population, the absence of the 2 identified bleeding risk predictors did not reduce the ability to identify high bleeding risk, and in fact, their inclusion identified only 1 additional patient as high risk for bleeding (Table S4). Therefore, in a stable post-MI population, prior bleeding and anemia may be sufficient for bleeding risk prediction and may enable clinicians to consider bleeding and ischemic risk independently. This may be particularly helpful in groups such as the elderly in whom assessment of risk and benefit may be particularly challenging.

Although the findings of this analysis are exploratory, the greater efficacy of ticagrelor and formal interaction for all-cause mortality in low- versus high-bleeding-risk patients helps to underscore the importance of assessment of bleeding risk. Although there was no difference in fatal bleeding or the novel outcome of bleeding contributing to death with ticagrelor, bleeding may lead to downstream consequences such as procedures and discontinuation of antithrombotic therapies, which may increase the risk of mortality. In PEGASUS-TIMI 54, premature drug discontinuation was higher with ticagrelor than placebo and largely driven by bleeding and dyspnea.12 In this context, the lower observed mortality in the low-bleeding-risk group suggests that the ischemic benefits outweigh the risks and downstream consequences of bleeding.

There are several limitations to the current analysis. The eligibility criteria for PEGASUS TIMI 54 led to a selected population that excluded some features associated with the risk of bleeding, such as low platelet

Figure 6. Efficacy and safety of ticagrelor 60 mg vs placebo stratified by high (N=2714) or low (N=11 240) bleeding risk at baseline.

A sensitivity analysis of efficacy and safety was performed based on baseline bleeding risk, defined as the presence or absence of either a history of spontaneous bleeding requiring hospitalization before the randomization or anemia (defined as hemoglobin ≤13.5 g/dL for men and ≤12.0 g/dL for women); ARR indicates absolute risk increase; ARD, absolute risk difference; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction, ICH, intracranial hemorrhage; and TIMI, Thrombolysis in Myocardial Infarction.
count, known bleeding diathesis, active malignancy, and prior stroke. In addition, use of PPI therapy was not randomized, and therefore we cannot conclude that PPI use would have mitigated gastrointestinal bleeding caused by ticagrelor; however, the COGENT (Clopidogrel and the Optimization of Gastrointestinal Events) trial did show significantly lower gastrointestinal bleeding with PPI in patients receiving dual antiplatelet therapy. It should also be noted that although apparent differences in outcomes between groups were observed, there was no formal heterogeneity by interaction testing for many outcomes, and this should be considered in interpreting the results. Finally, evaluations of efficacy and safety of ticagrelor by baseline bleeding risk were exploratory and should be viewed in this context.

CONCLUSIONS

In conclusion, in stable patients with prior MI treated with ticagrelor in addition to aspirin, TIMI major or minor bleeding is primarily spontaneous of gastrointestinal origin and related to an underlying gastrointestinal disease. Ticagrelor 60 mg twice daily did not increase fatal bleeding or ICH. Anemia and prior hospitalization for bleeding independently predict bleeding risk but not ischemic risk in this population. In patients with neither of these bleeding predictors, the balance of efficacy and safety of long-term secondary prevention of MI with ticagrelor 60 mg twice daily appears to be favorable.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S4
Figures S1–S6

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**Table S1.** Baseline characteristics in the overall population stratified by high and low bleeding risk.

| Characteristic                  | High Bleeding Risk         | Low Bleeding Risk         | p-value |
|--------------------------------|----------------------------|---------------------------|---------|
|                                | N=4,054                    | N=16,888                  |         |
| Age ≥ 75                       | 986 (24.3)                 | 2051 (12.1)               | <0.001  |
| Female                         | 813 (20.1)                 | 4190 (24.8)               | <0.001  |
| BMI, median (IQR)              | 27.1 (24.2 – 30.4)         | 28.1 (25.4 – 31.2)        | <0.001  |
| Current Smoking                | 485 (12.0)                 | 3019 (17.9)               | <0.001  |
| COPD                           | 318 (7.9)                  | 1150 (6.8)                | 0.0203  |
| History of Hypertension        | 3218 (79.4)                | 13020 (77.1)              | 0.0018  |
| Hypercholesterolemia           | 3061 (75.5)                | 13019 (77.1)              | 0.0309  |
| eGFR < 60 ml/min               | 1422 (35.3)                | 3366 (20.2)               | <0.001  |
| Diabetes Mellitus              | 1616 (39.9)                | 5119 (30.3)               | <0.001  |
| Peripheral Artery Disease      | 295 (7.3)                  | 835 (4.9)                 | <0.001  |
| Multivessel Coronary Disease   | 2333 (57.6)                | 10090 (59.8)              | 0.0109  |
| History of PCI                 | 3295 (81.3)                | 14084 (83.4)              | 0.0012  |
| History of CABG                | 239 (5.9)                  | 723 (4.3)                 | <0.001  |
Table S2. Primary endpoint and TIMI major bleeding rates stratified by high versus low bleeding and ischemic risk.

|                  | High Bleeding Risk events (KM%) | Low Bleeding Risk events (KM%) |
|------------------|---------------------------------|-------------------------------|
|                  | N= 3511                         | N= 14106                      |
| High Bleeding Risk | 353 (11.36%)                    | 1055 (8.29%)                  |
| PEP              | 127 (5.25%)                     | 266 (2.61%)                   |
| Low Bleeding Risk | 22 (4.39%)                      | 113 (4.58%)                   |
| TMB              | 10 (2.57%)                      | 29 (1.40%)                    |

*High ischemic risk defined as age ≥ 75, hypertension and current smoking, low ischemic risk is defined as the age < 75, no hypertension and no current smoking.*

(Note: A total of 20937 subjects out of safety population were included in this analysis. There were five subjects with missing Ischemic risk status.)

(Note: 3 year KM estimates are reported)

(Note: PEP = CVD/MI/Stroke. TMB = TIMI Major or minor bleeding)
Table S3: Other outcomes of ticagrelor 60 mg vs. placebo stratified by high or low bleeding risk at baseline.

| Endpoint                                      | Ticagrelor 60 mg (n KM %) | Placebo (n KM %) | HR 95% CI            | P for interaction |
|-----------------------------------------------|---------------------------|------------------|----------------------|-------------------|
| **Myocardial infarction**                     |                           |                  |                      |                   |
| Lower bleeding risk                           | 227 (4.39)                | 264 (5.09)       | 0.85 (0.72-1.02)     | 0.71              |
| Higher bleeding risk                          | 58 (5.14)                 | 74 (5.94)        | 0.80 (0.56-1.12)     |                   |
| **Stroke**                                    |                           |                  |                      |                   |
| Lower bleeding risk                           | 67 (1.38)                 | 100 (1.96)       | 0.66 (0.49-0.91)     | 0.12              |
| Higher bleeding risk                          | 24 (1.85)                 | 22 (1.85)        | 1.12 (0.63-1.99)     |                   |
| **Coronary heart disease death**              |                           |                  |                      |                   |
| Lower bleeding risk                           | 61 (1.25)                 | 97 (1.90)        | 0.63 (0.45-0.86)     | 0.008             |
| Higher bleeding risk                          | 45 (3.70)                 | 35 (2.85)        | 1.30 (0.84-2.03)     |                   |
| **Non-CV Death**                              |                           |                  |                      |                   |
| Lower bleeding risk                           | 74 (1.44)                 | 73 (1.44)        | 1.01 (0.73-1.39)     | 0.88              |
| Higher bleeding risk                          | 39 (3.82)                 | 38 (3.09)        | 1.06 (0.68-1.66)     |                   |
| **ICH or fatal bleeding**                     |                           |                  |                      |                   |
| Lower bleeding risk                           | 22 (0.60)                 | 22 (0.54)        | 1.09 (0.60-1.97)     | 0.56              |
| Higher bleeding risk                          | 11 (1.25)                 | 8 (0.91)         | 1.51 (0.61-3.75)     |                   |
| **Myocardial infarction, Stroke, death, or TIMI major bleeding** |                           |                  |                      |                   |
| Lower bleeding risk                           | 477 (11.36)               | 531 (11.51)      | 0.97 (0.86 – 1.10)   | 0.18              |
| Higher bleeding risk                          | 181 (18.67)               | 170 (15.50)      | 1.15 (0.93 – 1.42)   |                   |
| **Myocardial infarction, Stroke, death, or TIMI major or minor bleeding** |                           |                  |                      |                   |
| Lower bleeding risk                           | 513 (9.99)                | 546 (10.51)      | 0.94 (0.83 – 1.06)   | 0.0697            |
| Higher bleeding risk                          | 201 (17.02)               | 177 (14.15)      | 1.16 (0.95 – 1.43)   |                   |

HR=Hazard Ratio, CI=Confidence Interval, CV= Cardiovascular, ICH= Intracranial Hemorrhage, KM= Kaplan Meier
Table S4. PRECISE-DAPT score versus PEGASUS low or high bleeding risk, based on anemia and history of spontaneous bleeding.

| PRECISE-DAPT Score | PEGASUS TIMI 54 Low bleeding risk* |  | PEGASUS TIMI 54 High bleeding risk* |
|---------------------|-----------------------------------|--|--|
|                     | N (%) | ARI** 3 yrs KM rate (%) | N (%) | ARI** 3 yrs KM rate (%) |
| Very low risk       | 16,337 (81.2) | 1.8 | 3,775 (18.5) | 3.6 |
| Low risk            | 6 (3.2) | 0   | 182 (96.8)  | 7.8 |
| Moderate risk       | 1 (0)  | 0   | 50 (98)     | 21.7 |
| High risk           | 0 (0)  | 0   | 14 (100)    | 24  |

* Based on anemia and history of spontaneous bleeding only
**Absolute risk increase of TIMI major or minor bleeding, ticagrelor pooled vs. placebo
N = number, ARI = absolute risk increase, KM = Kaplan Maier
Figure S1. Etiology and Sites of TIMI major or minor bleeding in the Ticagrelor 60 mg group (Safety cohort).

A. Etiology

- **Spontaneous**: 121 (72%)
- **Procedural**: 23 (14%)
- **Trauma**: 24 (14%)

B. Site

- **Gastrointestinal**: 89 (73%)
- **Genitourinary**: 14 (12%)
- **Intracranial**: 10 (8%)
- **Other**: 8 (7%)
Figure S2. Sites of spontaneous gastrointestinal TIMI major or minor Bleeding (doses pooled).

GI= Gastrointestinal.
Figure S3. Spline of hemoglobin and TIMI major or minor bleeding in women (a) and men (b), dashed lines at the cutpoint defined for anemia.
Figure S4. Instantaneous hazard for TIMI major or minor bleeding. HR=Hazard Ratio, TIMI=Thrombolysis in Myocardial Infarction.
Figure S5. Sites (a) and etiologies (b) of TIMI major or minor bleeding, Ticagrelor 90 mg vs. placebo. HR=Hazard Ratio, CI=Confidence Interval, TIMI=Thrombolysis in Myocardial Infarction, ARI=Absolute risk Increase, KM=Kaplan Maier.

ARI=0.3%
HR 2.05
95% CI (1.09 – 3.85)
P=0.026

ARI=0.3%
HR 3.08
95% CI (1.49 – 6.36)
P=0.002

ARI=1.8%
HR 3.35
95% CI (2.41 – 4.67)
P<0.001

Procedural

0.3
0.6

Traumatic

0.2
0.5

Spontaneous

0.9

2.9
TI:MI major or minor bleeding at 3 years (KM)

**Placebo**

- **ARI=1.6%**
  - HR 3.84
  - 95% CI (2.59 – 5.70)
  - P<0.0001

**Ticagrelor 90 mg**

- **ARI=0.2%**
  - HR NA

**ARR=0.1%**

- HR 0.97
- 95% CI (0.43 – 2.16)
- P=0.94
Figure S6. Bleeding and death, Ticagrelor 90 mg vs. placebo. HR=Hazard Ratio, CI=Confidence Interval, TIMI=Thrombolysis in Myocardial Infarction, KM=Kaplan Maier.

HR 0.93
95% CI (0.45 – 1.93)
p=0.84