Clinical trials report mean differences between treatment groups, which can mask substantial heterogeneity of treatment effect for both risks and benefits. Although subgroup analyses are often used to explore variations in treatment response, these analyses stratify patients by only 1 characteristic at a time and fail to consider how the totality of a patient’s characteristics might be associated with treatment outcomes. In contrast, deploying multivariable risk prediction models at the time of medical decision making could support individualized risk predictions that better support evidence-based, individualized treatment to optimize safety, outcomes, and cost-effectiveness. Moreover, explicitly estimating individuals’ risks and benefits may better engage patients in shared decision making and could improve their subsequent adherence to therapy.

Methods and Results—Using 12,579 patients from Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), we fit risk models for ischemic events (cardiovascular death, spontaneous myocardial infarction, stroke) and bleeding (TIMI major/minor) over a 14.8-month follow-up and then calculated each patient’s predicted risk for major ischemia and bleeding with both prasugrel and clopidogrel. We found substantial heterogeneity of the treatment effect of prasugrel (mean absolute reduction in the ischemia risk with prasugrel=1.5±3.0%, ranging from an 8.4% increased risk to a 31.2% reduction in risk for ischemia compared with clopidogrel). The mean absolute increase in the bleeding risk with prasugrel versus clopidogrel was 1.3±1.4% and ranged from a 7.9% lower risk to an 11.2% higher risk with prasugrel. The ratio of the difference in predicted ischemia risk/difference in predicted bleeding risk between prasugrel and clopidogrel was calculated for each patient to identify the proportion likely to benefit from prasugrel. Considering both ischemia and bleeding risk, a large proportion of TRITON participants (42%) were predicted to experience net benefit with prasugrel, a rate that increased if patients more strongly preferred avoiding ischemic events than bleeding.

Conclusions—The expected benefits and risks of prasugrel versus clopidogrel depend highly on patient characteristics. The use of risk models could support individualized thienopyridine selection to maximize the benefits and safety of these drugs.

Key Words: acute coronary syndromes • antiplatelet therapy • individualized medicine • percutaneous coronary intervention • prediction

Editorial see p 7

Individualized prediction of patients’ benefits and risks with competing treatments is particularly important when a new treatment improves outcomes and is associated with risk. For example, in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) study, prasugrel, a more potent thienopyridine than clopidogrel, not only reduced ischemic events in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI) but also increased serious bleeding.

To better support the optimal use of prasugrel, an improved method is needed to balance these competing benefits and...
WHAT IS KNOWN

- On average, prasugrel reduces ischemic complications after acute coronary syndromes in comparison with clopidogrel, but these benefits are offset by increased bleeding risk.
- Optimizing prevention of recurrent ischemic events while minimizing bleeding and costs requires careful balancing of the anticipated benefits and risks of prasugrel for each individual.

WHAT THIS ARTICLE ADDS

- We built multivariable models using the TRITON-TIMI 38 data to generate individualized predictions of patients’ predicted risk of ischemic complications (cardiovascular death, myocardial infarction, or stroke) and serious bleeding (TIMI major or minor) with prasugrel versus clopidogrel to better inform clinical decision making.
- We used risk predictions from these models to demonstrate how personalized data on the risks and benefits of competing antiplatelet agents might influence treatment selection among a population of patients with acute myocardial infarction.

For the present analyses of the TRITON-TIMI 38 data, we excluded 518 patients with a history of prior stroke or transient ischemic attack because prasugrel is contraindicated in these patients, 183 patients who did not undergo PCI after randomization, and 328 patients who were missing data on ≥1 predictor variable, yielding a final analytic cohort of 12,579 patients.

Outcomes

We defined major ischemia as the composite of cardiovascular death, spontaneous acute myocardial infarction (MI), and stroke. As a sensitivity analysis, we also included periprocedural MI in the ischemia outcome because it has been shown to be associated with poor long-term outcomes.19 Bleeding was defined as TIMI major or minor bleeding, including procedurally related bleeding or bleeding from other sites.2 An independent clinical events committee, unaware of treatment assignment, adjudicated each component of these end points.

Statistical Analyses

Baseline characteristics were reported as median (interquartile range [IQR]) for continuous variables, and categorical variables were reported as frequencies.

Model Construction

Using the TRITON-TIMI 38 data set, we developed separate risk models to estimate patients’ risks of major ischemic and bleeding events. Models were fit with the goal of providing risk predictions using the most parsimonious collection of variables possible to simplify their use in clinical practice. Because TRITON randomized patients before PCI, only variables that would be known before the procedure were considered. All candidate variables considered for one of the risk prediction models (ischemia or bleeding) that were also thought to have a clinically plausible relationship with the second model were considered for inclusion in both models. Candidate and retained variables for each model and their ranked contribution to the predictive capacity of the full model are included in the online-only Data Supplement Tables I and II.

For each model, we identified variables for inclusion a priori on the basis of published literature and clinical experience. We then fit multivariable logistic regression models to predict the occurrence of major ischemic and bleeding events using the Harrell backward selection strategy.16 To identify differential treatment effects between prasugrel and clopidogrel on the basis of baseline characteristics, interactions between each candidate variable and treatment assignment were also included in the full multivariable models. To develop more parsimonious models while preserving optimal discrimination, we began with full models that included all prespecified predictor variables and interactions. All variables were then ranked by their contribution to the predictive capacity of the model, and variables explaining the least variance in the model were sequentially removed until removing another variable would reduce the predictive capacity of the reduced model by >5% relative to the full model. With this approach, the reduced model accounts for >95% of the prediction capacity of the full model. The assumption of linearity was assessed for each continuous variable with the use of restricted cubic splines to identify any nonlinear association with outcomes. Discrimination (c statistic) and calibration (Hosmer-Lemeshow) were then calculated for each model.17

Identifying Heterogeneity of Treatment Effect

To understand the degree of variability in TRITON-TIMI 38 patients’ risks for major ischemia and bleeding when estimated for treatment with either prasugrel or clopidogrel, we calculated each participant’s predicted probability of both outcomes twice, first assuming treatment with prasugrel and second assuming treatment with clopidogrel. To understand the variation in risk for each outcome at the population level, we identified the mean (SD) and range of the risk for ischemia and bleeding with each thienopyridine across the TRITON-TIMI 38 population to describe the heterogeneity of outcomes. Next, to better

Patient Population

Details of the TRITON-TIMI 38 study (http://www.clinicaltrials.gov; number NCT00097591) have been described previously.3,8 Briefly, this multicenter, randomized, controlled trial compared prasugrel with clopidogrel in 13,608 moderate- to high-risk ACS patients undergoing PCI. Patients were randomized to either a prasugrel loading dose of 60 mg followed by 10 mg daily or a clopidogrel loading dose of 300 mg followed by 75 mg daily for 6 to 15 months. Important exclusion criteria included cardiogenic shock, chronic oral anticoagulation, other antiplatelet agents that could not be discontinued, severe anemia, thrombocytopenia, intracranial pathology, or thienopyridine use within 5 days before enrollment. The research protocol was approved by the institutional review board of each participating hospital, and all patients provided written informed consent.8

Methodology
appreciate the spectrum of difference in risk for ischemia and bleeding complications between prasugrel and clopidogrel at the level of the individual, we identified the difference in the absolute risk for each outcome between treatment with prasugrel and clopidogrel for every TRITON-TIMI 38 patient. These differences were calculated by subtracting each patient’s predicted probability of ischemia when treated with prasugrel from the predicted probability of ischemia when treated with clopidogrel. For the bleeding outcome, the risk difference was calculated by subtracting the risk of bleeding if treated with clopidogrel from that patient’s risk of bleeding if treated with prasugrel. The distribution of the absolute predicted risk for each outcome between prasugrel and clopidogrel treatment across the TRITON-TIMI 38 population is presented graphically with density plots.

**Calculating Individual Patients’ Net Clinical Benefit**

To estimate patient’s net clinical benefit, we identified the absolute difference in each patient’s risk of ischemia (predicted probability of ischemia treated with clopidogrel minus predicted probability treated with prasugrel) and the absolute difference in each patient’s risk of bleeding between the 2 medications (predicted probability treated with prasugrel minus predicted probability treated with clopidogrel). We then identified the ratio of the difference in risk of ischemia/difference in the risk of bleeding for each patient. Patients with a ratio of benefit (absolute reduction in risk for ischemia with prasugrel) over risk (absolute increase in risk for bleeding with prasugrel) >1 were identified as experiencing net benefit with prasugrel (ie, the ischemic benefits were equal to or greater than the excess bleeding risks).

**Sensitivity Analyses**

Because the patients and clinicians might value the benefit of reducing ischemic events and preventing bleeding differently, we modeled alternative benefit-to-risk ratios in sensitivity analyses. These hypothetical thresholds are similar to weights used when calculating net clinical benefit. If a provider or patient valued reduction in the risk of major ischemia as being 2 times more important than preventing bleeding, a benefit-to-risk ratio of 0.5 would define net benefit with prasugrel (ie, the ischemic benefits were equal to or greater than the excess bleeding risks).

**Results**

**Patient Characteristics and Outcomes**

Characteristics of TRITON-TIMI 38 patients are presented in the Table. Over a median follow-up of 14.8 months, 11.5% of the analytic cohort randomized to clopidogrel and 9.1% randomized to prasugrel experienced an ischemic end point (cardiovascular death, MI, and stroke), whereas 3.7% of patients receiving clopidogrel and 5.0% of those assigned to prasugrel experienced TIMI major or minor bleeding.

### Table. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
</tr>
<tr>
<td>Age (median, IQR), y</td>
<td>60 (52, 69)</td>
</tr>
<tr>
<td>Age &gt;75 y, %</td>
<td>12.9</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>25.6</td>
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<tr>
<td>White race, %</td>
<td>92.2</td>
</tr>
<tr>
<td>Type of acute coronary syndrome</td>
<td></td>
</tr>
<tr>
<td>Unstable angina, %</td>
<td>18.6</td>
</tr>
<tr>
<td>NSTEMI, %</td>
<td>55.6</td>
</tr>
<tr>
<td>STEMI ≤12 h after onset, %</td>
<td>17.6</td>
</tr>
<tr>
<td>STEMI &gt;12 h after onset, %</td>
<td>8.1</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
</tr>
<tr>
<td>Body weight, median (IQR), kg</td>
<td>82 (72–93)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>63.4</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>55.5</td>
</tr>
<tr>
<td>History of diabetes mellitus, %</td>
<td>22.5</td>
</tr>
<tr>
<td>Current or prior tobacco use, %</td>
<td>38.7</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>17.3</td>
</tr>
<tr>
<td>Prior unstable angina, %</td>
<td>14.4</td>
</tr>
<tr>
<td>Prior PCI, %</td>
<td>13.1</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>7.4</td>
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<tr>
<td>History of heart failure, %</td>
<td>3.6</td>
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<tr>
<td>History of peripheral arterial disease, %</td>
<td>4.9</td>
</tr>
<tr>
<td>History of atrial fibrillation, %</td>
<td>3.0</td>
</tr>
<tr>
<td>Index admission</td>
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</tr>
<tr>
<td>Killip class, %</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>93.7</td>
</tr>
<tr>
<td>II</td>
<td>5.3</td>
</tr>
<tr>
<td>III</td>
<td>0.7</td>
</tr>
<tr>
<td>IV</td>
<td>0.3</td>
</tr>
<tr>
<td>Systolic blood pressure, median (IQR), mm Hg</td>
<td>120 (110–132)</td>
</tr>
<tr>
<td>(n=2675)</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance, median (IQR), mL/min</td>
<td>100.2 (78.4–126.2)</td>
</tr>
<tr>
<td>Fibrinolytic therapy, %</td>
<td>3.1</td>
</tr>
<tr>
<td>Femoral access, %</td>
<td>91.7</td>
</tr>
<tr>
<td>Sheath size, %</td>
<td></td>
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<tr>
<td>5F</td>
<td>2.9</td>
</tr>
<tr>
<td>6F</td>
<td>82.1</td>
</tr>
<tr>
<td>7F</td>
<td>12.5</td>
</tr>
<tr>
<td>8F</td>
<td>2.5</td>
</tr>
<tr>
<td>Antithrombotic agents (before PCI or planned in support of PCI), %</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>84.5</td>
</tr>
<tr>
<td>LMWH</td>
<td>42.5</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>6.5</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor</td>
<td>54.6</td>
</tr>
<tr>
<td>Pharmacotherapy at admission, %</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>50.6</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>74.2</td>
</tr>
<tr>
<td>Statin use</td>
<td>78.9</td>
</tr>
<tr>
<td>Aspirin</td>
<td>33.4</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin converting enzyme; CABG, coronary artery bypass grafting; IQR, interquartile range; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment-elevation myocardial infarction. n=12 579.
Predicting Major Ischemia and Bleeding Risk in TRITON-TIMI 38

The prediction models for major ischemia and bleeding are presented in Figures 1 and 2 and the online-only Data Supplement Figures I and II. The model for major ischemia included interactions of treatment assignment with diabetes mellitus, Killip class, intravenous heparin, and age. The bleeding risk prediction model included interactions of treatment with low-molecular-weight heparin use, glycoprotein IIb/IIIa antagonist use, and type of ACS. Both models demonstrated acceptable discrimination, with a c statistic of 0.70 for the major ischemia model and 0.68 for the bleeding model and good calibration (Hosmer-Lemeshow P=0.33 and 0.93, respectively).

### Major Ischemia Risk Model

- **c-statistic=0.70, Hosmer-Lemeshow p=0.33**
- **OR (95% CI)**
  - Age (prasugrel, per 10 years) 1.51 (1.38, 1.67)
  - Age (clopidogrel, per 10 years) 1.24 (1.13, 1.35)
  - STEMI > 12 hrs vs UA 1.94 (1.14, 2.20)
  - STEMI <= 12 hrs vs UA 1.93 (1.02, 1.77)
  - NSTEMI vs UA 1.88 (1.52, 2.31)
  - Diabetes (prasugrel) 2.60 (1.33, 3.52)
  - Diabetes (clopidogrel) 1.55 (1.06, 2.49)
  - Killip class >= 2 (prasugrel) 1.29 (1.03, 1.55)
  - Killip class >= 2 (clopidogrel) 1.20 (0.65, 2.33)
  - Prior MI 1.12 (0.98, 1.29)
  - Prior PCI 1.02 (0.77, 1.34)
  - Hypertension 1.02 (0.77, 1.34)
  - Atrial Fibrillation 0.98 (0.69, 1.39)
  - IV Heparin (prasugrel) 1.02 (0.77, 1.34)
  - IV Heparin (clopidogrel) 1.02 (0.77, 1.34)
  - Prior CABG 1.02 (0.77, 1.34)
  - Fibrinolytic therapy 1.02 (0.77, 1.34)
  - Chronic heart failure 1.02 (0.77, 1.34)
  - Peripheral arterial disease 1.02 (0.77, 1.34)

### Bleeding Risk Model

- **c-statistic=0.68, Hosmer-Lemeshow p=0.93**
- **OR (95% CI)**
  - Age (per 10 years) 0.75 (0.53, 1.08)
  - Female vs male 1.12 (0.77, 1.63)
  - STEMI > 12 hrs vs UA (prasugrel) 1.11 (0.80, 1.51)
  - STEMI <= 12 hrs vs UA (prasugrel) 1.11 (0.80, 1.51)
  - NSTEMI vs UA (prasugrel) 1.20 (0.75, 1.69)
  - STEMI > 12 hrs vs UA (clopidogrel) 1.13 (0.74, 1.72)
  - STEMI <= 12 hrs vs UA (clopidogrel) 1.13 (0.74, 1.72)
  - NSTEMI vs UA (clopidogrel) 1.13 (0.74, 1.72)
  - Bivalirudin 1.03 (0.69, 1.50)
  - Peripheral arterial disease 1.03 (0.69, 1.50)
  - Low molecular weight heparin (prasugrel) 1.03 (0.69, 1.50)
  - Low molecular weight heparin (clopidogrel) 1.03 (0.69, 1.50)
  - Glycoprotein IIb/IIIa antagonist (prasugrel) 1.03 (0.69, 1.50)
  - Glycoprotein IIb/IIIa antagonist (clopidogrel) 1.03 (0.69, 1.50)
  - Sheath size (6F vs 5F) 1.03 (0.69, 1.50)
  - Sheath (7F vs 5F) 1.03 (0.69, 1.50)
  - Sheath size (6F vs 5F) 1.03 (0.69, 1.50)
  - Fibinolytic therapy 1.03 (0.69, 1.50)
  - Hypertension 1.03 (0.69, 1.50)
  - Weight (per 10 Kg) 1.03 (0.69, 1.50)
  - Radial access 1.03 (0.69, 1.50)
Predicted Benefits, Risks, and Heterogeneity of Treatment Effect

On average, the predicted risk of major ischemia was higher with clopidogrel (mean, 7.2±6.1%) than with prasugrel (mean, 5.7±4.7%). Importantly, there was substantial variability in patients’ predicted risks of major ischemia across the population (range with clopidogrel treatment, 1.2%–78.3%; range with prasugrel treatment, 0.5%–61.0%). The average predicted risk of bleeding was lower with clopidogrel (mean, 3.7±2.6%) than with prasugrel (mean, 5.0±3.1%) but also varied dramatically across the population (range with clopidogrel treatment, 0.3%–28.5%; range with prasugrel treatment, 0.4%–26.4%). When the absolute risk difference between the 2 thienopyridines was calculated for each outcome, there was also substantial variability in the benefit and risk of prasugrel compared with clopidogrel (Figure 3). The mean absolute reduction in the risk of ischemia with prasugrel was 1.5±3.0% (median, 0.9%; IQR, 0.2%–2.0%) and ranged from an 8.4% increase in risk to a 31.2% reduction in risk for ischemic events with prasugrel compared with clopidogrel. Similarly, the mean increase in the risk of bleeding with prasugrel was 1.3±1.4% (median, 1.1%; IQR, 0.5%–1.9%) and ranged from a 7.9% lower to an 11.2% higher bleeding risk with prasugrel. To illuminate how these models might be useful to predict individuals’ risks when choosing between these 2 thienopyridines, Figure 4 demonstrates a potentially actionable output format for these models when used at the bedside for clinical decision making.

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Figure 5. Each patient’s net predicted risk for ischemia and bleeding in Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). Dots represent each patient’s net predicted risk of major ischemia (prasugrel minus clopidogrel) plotted on the x axis against their net risk of bleeding (prasugrel minus clopidogrel) on the y axis. The further to the right on the x axis, the greater the absolute reduction in risk of ischemia with prasugrel. The further to the right on the y axis, the greater the absolute increase in risk of bleeding with prasugrel. Lines represent thresholds for identifying net benefit with prasugrel. Each patient to the right of line 1 would be expected to experience net benefit with prasugrel if ischemia and bleeding were valued equally, whereas every patient to the right of the line marked 0.5 would be expected to benefit if ischemia prevention were valued 2 times more than bleeding prevention. Patients to the right of line 2 would be identified as likely to derive net benefit from prasugrel if bleeding prevention were considered 2 times more important than preventing ischemia.

When the absolute risk difference between the 2 thienopyridines was calculated for each outcome, there was also substantial variability in the benefit and risk of prasugrel compared with clopidogrel (Figure 3). The mean absolute reduction in the risk of ischemia with prasugrel was 1.5±3.0% (median, 0.9%; IQR, 0.2%–2.0%) and ranged from an 8.4% increase in risk to a 31.2% reduction in risk for ischemic events with prasugrel compared with clopidogrel. Similarly, the mean increase in the risk of bleeding with prasugrel was 1.3±1.4% (median, 1.1%; IQR, 0.5%–1.9%) and ranged from a 7.9% lower to an 11.1% higher bleeding risk with prasugrel. To illuminate how these models might be useful to predict individuals’ risks when choosing between these 2 thienopyridines, Figure 4 demonstrates a potentially actionable output format for these models when used at the bedside for clinical decision making.

Influence of Individualized Risk Prediction and Patient Preferences on Treatment Selection

When considering patients’ risks for both ischemia and bleeding, we found dramatic variability across the patient population. Figure 5 depicts a plot of each patient’s absolute difference in the risk of ischemia (clopidogrel estimate minus prasugrel estimate) on the x axis against the absolute difference in risk of bleeding on the y axis (prasugrel estimate minus clopidogrel estimate). Most participants were predicted to have some reduced risk of ischemia with prasugrel that was offset, to some extent, by increased bleeding risk (dots in the right upper quadrant of Figure 5, 72% of all patients). If ischemia prevention and bleeding prevention were valued equally, 42.0% of TRITON-TIMI 38 patients had a benefit/risk ratio >1 (points to the right of the line labeled 1.0 on Figure 5) and would be expected to choose prasugrel.

Sensitivity Analyses

Alternative valuation of the importance of the prevention of ischemic events and bleeding influenced the proportion of patients expected to derive greater benefit from prasugrel treatment. When the ischemic events of death, MI, and stroke were considered twice as bad as nonfatal bleeding, 56.9% of patients would be expected to benefit from prasugrel (patients to the right of line 0.5 on Figure 5), whereas the proportion expected to derive net benefit from prasugrel treatment declined to 25.4% when the value of bleeding prevention was 2-fold higher than ischemia (patients to the right of line 2 on Figure 5).

To illustrate the clinical importance of treatment interactions, we stratified the population by age, because age had a significant interaction with treatment in the prediction model for ischemic events (P=0.004). Most patients (56.6%) who were ≤60 years of age were predicted to experience net benefit with prasugrel, assuming that ischemia and bleeding outcomes were valued equally. In contrast, 28.9% of patients 61 to 75 years of age and 19.5% of patients older than 75 years were predicted to experience net benefit with prasugrel versus clopidogrel.

Different definitions of the ischemia and bleeding outcomes also influenced the proportion of the population who might experience net benefit with prasugrel. If all MIs in follow-up (including periprocedural events) were considered important components of the ischemic end point (online-only Data Supplement Figure III; c statistic=0.64; Hosmer-Lemeshow P=0.33), there was greater mean reduction in ischemic risk with prasugrel compared with clopidogrel (2.4±3.2%) and a greater proportion of the population (51.7%) who derived net benefit from treatment with prasugrel. If clinicians considered only TIMI major bleeding to represent serious bleeding events (online-only Data Supplement Figure IV; c statistic=0.65; Hosmer-Lemeshow P=0.36), patients’ predicted risks of bleeding were lower (clopidogrel treatment: mean, 1.8±0.9%; range, 0.2%–12.1%; prasugrel treatment: mean, 2.5±1.3%; range, 0.3%–11.5%). When this model was paired with the ischemia risk prediction model, 58.1% of patients were predicted to have net benefit when treated with prasugrel. When the analyses were repeated after pairing both alternative outcomes (ie, defining ischemia as cardiovascular death/all MIs/stroke and bleeding as TIMI major bleeding), the differences in the risk of ischemia (mean, 2.4±3.2% lower with prasugrel) and bleeding (0.7±0.8% higher with prasugrel) between clopidogrel and prasugrel are greater, and the portion of patients who are expected to benefit from prasugrel versus clopidogrel is higher (65.7%) if both outcomes are considered equal.
**Discussion**

Thienopyridine selection at the time of PCI for an ACS highlights the complexity of individualizing treatment decisions, particularly when the potential benefits and risks of treatment vary substantially as a function of patients’ characteristics. Meeting the goals of safer, more evidence-based, patient-centered health care, as advocated by the Institute of Medicine, requires that accurate estimations of patients’ potential outcomes, as a function of their individual risk profiles, be understood at the time of medical decision making. To demonstrate this approach, we developed prediction models that could be implemented at the time of PCI for an ACS to project patients’ risk for major ischemic complications and bleeding if treated with prasugrel or clopidogrel. Because Web-based solutions can now be leveraged to deploy prediction models at the point of care, it is possible to explicitly estimate the trade off between benefit and risk with competing treatments for any individual at the time of clinical decision making to personalize care, to optimize outcomes, and to lower costs.

We found significant heterogeneity of treatment effect with respect to both the benefits and risks of prasugrel and clopidogrel across the TRITON-TIMI 38 population. We also demonstrated how multivariable models could be used to deliver individualized risk estimates that may support more tailored treatment selection than broadly applying a treatment without considering patients’ underlying risk profiles. This approach can allow clinicians to consider patients’ risks for what they identify as the most clinically relevant outcomes for each treatment decision. Given that different outcome definitions could be modeled, we fit additional models using alternative definitions of the bleeding outcome and the major ischemia outcome. This method could enable providers to consider those outcomes (eg, including TIMI major but not TIMI minor bleeding or spontaneous but not periprocedural MI) that they deem most important when generating risk estimates and discussing treatment options with patients.

This approach might also improve the dialog between patients and physicians by providing transparent estimates of risks and benefits. For example, Figure 4 depicts an output format that could be used to support decision making when operationalizing these models in practice. In the case of the young diabetic man in this example, a striking 11.4% absolute risk reduction for major ischemia with prasugrel is offset by only a 0.6% increase in bleeding risk, indicating likely benefit with very acceptable risk of bleeding if prasugrel is selected. On the contrary, the 66-year-old woman with ST-elevation MI has reduced risk of ischemic events and a much higher risk of bleeding if treated with prasugrel and would likely select treatment with clopidogrel. Although the concept of sharing expected risks and benefits of treatment is exemplified in this study by the choice between alternative thienopyridines, this approach could be used to support decision making for numerous interventions in which alternative treatments offer different benefit and risk profiles. The models to estimate the heterogeneity of treatment benefit could be generated concurrently with the analyses of major randomized, clinical trials and used to accelerate the translation of evidence into clinical care.

Our findings should be considered in the context of the following potential limitations. First, these findings have not been validated in an independent sample. Future efforts should be made to confirm the accuracy of these models in other populations. Given the inclusion and exclusion criteria in the TRITON-TIMI 38 trial, these models may require recalibration for use in other populations. In fact, the exclusion of some patients from the trial such as those requiring long-term anticoagulation or with severe anemia means that the contribution of these risk factors to predicted outcomes is not represented and should be examined in future studies. However, for patients similar to the participants in TRITON-TIMI 38, these models may provide additional insight into anticipated risks and benefits of prasugrel versus clopidogrel in comparison with considering only the average pooled benefits and risks for all patients in the study. Second, we used a composite end point to represent benefit. Although patients may value preventing death differently than preventing acute MI and stroke, all of these events are clinically important adverse outcomes. We also selected a risk model that included only serious TIMI major and minor bleeds and did not model lesser bleeding or bruising. Third, our models had adequate, but modest, c statistics. However, considering multiple patient characteristics when selecting treatment is a substantial improvement over the current practice of assuming that the average benefit for the entire population applies to all patients equally or using univariate subgroup analyses to guide treatment selection. Prior reports have found such models to improve benefit to patients when the c statistics of the models are >0.60. Finally, our findings are not generalizable to patients with a history of stroke or transient ischemic attack because we excluded these patients from analyses.

**Conclusions**

In conclusion, we have developed the infrastructure with which to personalize thienopyridine selection at the time of PCI for an ACS. We developed multivariable risk prediction models that can identify individual patient’s risk of major ischemia and bleeding after PCI for an ACS, which allow the TRITON-TIMI 38 data to be used to better tailor selection of antiplatelet therapy to each individual patient’s risk profile. Further study of the impact of individualized benefit and risk prediction on clinical decision making, medication adherence, and clinical outcomes is warranted.

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References


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