Prospective validation of the Bleeding Academic Research Consortium classification in the all-comer PRODIGY trial

Pascal Vranckx1,2,3, Sergio Leonardi4, Matteo Tebaldi5, Simone Biscaglia5, Giovanni Parrinello6, Sunil V. Rao7, Roxana Mehran8, and Marco Valgimigli3*

1Department of Cardiology and Critical Care Medicine, Hartcentrum Hasselt, Jessa Ziekenhuis, Hasselt, Belgium; 2Department of Cardiology, Thoraxcentre, Erasmus Medical Center, Rotterdam, The Netherlands; 3Thoraxcentre, Erasmus Medical Center, Rotterdam, The Netherlands; 4I.R.C.C.S. Policlinico San Matteo, Pavia, Italy; 5Department of Cardiology, University of Ferrara, Ferrara, Italy; 6Medical Statistics Unit, University of Brescia, Brescia, Italy; 7The Duke Clinical Research Institute, Durham, NC, USA; and 8Mount Sinai School of Medicine, New York, NY, USA

Received 24 August 2013; revised 11 February 2014; accepted 19 March 2014; online publish-ahead-of-print 21 April 2014

See page 2507 for the editorial comment on this article (doi:10.1093/eurheartj/ehu172)

Aims
The Bleeding Academic Research Consortium (BARC) classification has been proposed by consensus to standardize bleeding endpoint definition and reporting in cardiovascular clinical trials. There are no prospective studies on its prognostic impact.

Methods and results
We explored the association of BARC-defined bleeding with mortality and compared its prognostic value against two validated bleeding scales: the Thrombolysis in Myocardial Infarction (TIMI) and the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) scales. Non-coronary artery bypass graft (CABG)-related bleedings within the PRODIGY trial were prospectively adjudicated by a blinded Clinical Event Committee and analysed according to multiple statistical modelling. At 2 years, bleeding occurred in 143 patients (7.1%) according to BARC Type 2, 3, or 5; in 50 patients (2.5%) according to TIMI minor or major; and in 61 patients (3.1%) according to GUSTO moderate or severe. One hundred sixty-six patients died (8.1%). After multivariable modelling, BARC Type 2, 3, or 5 bleeding was associated with increased 2-year mortality [hazard ratio (HR): 3.77; 95% confidence interval (CI): 2.37–5.98]. Bleeding Academic Research Consortium Type 3 or 5 was associated with an increased mortality rate at 2 years (adjusted HR: 7.72; 95% CI: 4.75–12.54) similar to that provided by TIMI (HR: 7.64, 95% CI: 4.53–12.87) or GUSTO (HR: 7.36, 95% CI: 4.38–12.34) criteria.

Conclusions
In a contemporary, all-comer percutaneous coronary intervention trial actionable BARC bleedings were associated with increased risk of mortality with BARC Type 3 or 5 bleedings providing a similar mortality risk to that posed by TIMI or GUSTO scales.

Keywords
Bleeding • Bleeding Academic Research Consortium • Mortality • Dual anti-platelet therapy • Aspirin • Clopidogrel • Percutaneous coronary intervention

Introduction
Advances in anti-thrombotic therapy in patients with acute coronary syndromes (ACS), along with an early invasive strategy in high-risk patients, have reduced the incidence of recurrent ischaemic events but also increased bleeding complications. Extensive evidence demonstrates that patients following percutaneous coronary intervention (PCI) who bleed are at increased risk for adverse events compared with patients who do not bleed.1–3 While this association does not necessarily imply causality, multiple studies showed that pharmacological and vascular access ‘bleeding avoidance strategies’ did translate into a mortality benefit (HORIZONS-AMI, OASIS 5, WOEST).4–6 A challenge with the paradigm of the bleeding-outcome relationship is that many definitions of bleeding...
exist, and different definitions are used across clinical trials and registries. The lack of a common definition hampers comparison across studies and meta-analyses; while such comparisons may be inappropriate statistically, they play a central role at the bedside when making therapeutic decisions. Moreover, the prognostic impact of bleeding may vary across definitions implemented.9

To address these inconsistencies, the Bleeding Academic Research Consortium (BARC) has proposed standardized bleeding definitions in patients receiving anti-thrombotic therapy implementing a hierarchical approach.7 In a retrospective analysis, this consensus classification has shown to be independently associated with 1-year mortality.9 However, a prospective validation of this scale is still lacking.

The aim of the present analysis is two-fold: (i) to examine the association of BARC-defined actionable bleedings (BARC Class 1 excluded) with 2-year mortality after PCI and (ii) to compare the BARC definition over existing bleeding definitions in predicting clinical outcome in the all-comer PRODIGY trial.9–11

**Methods**

**Study design**

The design of the PRODIGY (PROlonging Dual anti-platelet treatment after Grading stent-induced Intimal hyperplasia study) trial has been previously described.12,13 In brief, PRODIGY was a 4 × 2 randomized, multicenter, and open-label clinical trial designed to test the efficacy and safety of 6 vs. 24 months of dual anti-platelet therapy (DAPT) involving clopidogrel or aspirin. The administration of either unfractionated heparin or bivalirudin.12 The administration of glycoprotein IIb/IIIa antagonists was allowed per current practice guidelines.

**Study patients and anti-thrombotic medications**

Patients were recruited between December 2006 and December 2008. Patient selection criteria were set broad, reflecting routine PCI practice. There was no limit for the number of treated lesions, vessels, or lesion length. Patients were not excluded based on comorbid disorders or age, apart from the following criteria: known allergy to acetyl salicylic acid or clopidogrel; planned surgery within 24 months of PCI unless patients received aspirin (160–325 mg orally or 500 mg i.v. as a loading dose and then 80–160 mg orally indefinitely) and clopidogrel (300 or 600 mg orally as a loading dose) and then 75 mg/day for the treatment duration according to the randomization scheme 6 or 24 months. Anti-coagulation during coronary intervention was accomplished according to practice guidelines through administration of either unfractionated heparin or bivalirudin.12 The administration of glycoprotein IIb/IIIa antagonists was allowed per current practice guidelines.

**Endpoint definition and follow-up**

The main outcome measure for this analysis is all-cause mortality at 2 years. All actionable bleeding events in the PRODIGY trial were triggered by the site investigator or by central review of relevant data in the case report form and prospectively assessed and adjudicated according to the Thrombolysis in Myocardial Infarction (TIMI) classification, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) classification, and the BARC classification. Thrombolysis in Myocardial Infarction and GUSTO scales were the primary bleeding scales in the original protocol.12,13 Upon publication of the BARC consensus document7 and before database lock, a protocol amendment was issued to include the BARC classification (Supplementary material online, Table S1). Supplementary material online, Table S2 relates the different grades of bleeding used for this analysis. All outcome measures in the PRODIGY trial, including death and bleeding as defined by all three bleeding scales (TIMI, GUSTO, and BARC), were adjudicated by an independent clinical endpoints committee (CEC) blinded to treatment assignment before locking the database.

The protocol required that all patients enrolled, returned for study visits at 30 days, and then every 6 months up to 2 years after randomization. During follow-up visits, patients underwent a complete clinical evaluation. Information on vital status was obtained from hospital records, death certificates or telephone contact with the patient relatives or treating physician. During the trial, all actionable bleeding events were queried (e.g. completeness, and detail in individual patient accounts, including protocol-driven laboratory examinations).

**Statistical analysis**

Patients were grouped according to bleeding events during follow-up as defined by the TIMI, GUSTO, and BARC definitions. Descriptive statistics are presented as absolute and relative frequencies or median and inter-quartile range (IQR). This pre-specified analysis included both procedural and spontaneous bleeding events that occurred after randomization. For this analysis, we only considered bleeding events not related to coronary artery bypass graft (CABG) and specifically: TIMI minor and moderate bleeding; GUSTO severe and moderate bleeding; and BARC Types 2, 3, and 5 bleedings.7,12 BARC Type 1 events were not captured consistently across the study and therefore were not included in this analysis. Because the primary outcome of this analysis was mortality, bleeding events potentially belonging to Class 5 of the BARC classification (fatal bleeding) were not analysed as a separate class but were distributed to other classes according to initial assessment by the CEC.

To assess the relationship between different definitions of bleeding (according to different duration of DAPT exposure and relevant cut-offs) and mortality, a proportional hazard Cox model for time-varying covariates was applied, both crude and adjusted for a pre-specified set of confounders. Baseline demographic and angiographic characteristics (Supplementary material online, Tables S3 and S4), plus stent type, and treatment allocation were entered into the model. The proportional hazards assumption was tested and fulfilled in all cases. In order to evaluate the robustness of the primary analyses, a multi-state (bleeding-death model) adjusted model was also fitted. Further exploratory analyses evaluated the influence of treatment arm and timing of bleeding on overall mortality. Differences between short (up to 6 months) and long (up to 24 months) dual anti-platelet therapy were tested by the χ² and Wilcoxon tests, when appropriate.

The discriminatory power of multivariable models with bleeding events according to BARC, TIMI, or GUSTO definitions was assessed by performing Harrell’s concordance index and by calculating the integrated discrimination improvement (IDI) according to Pencina et al.15,16 Bootstrapping (500 samples) was used to calculate confidence intervals.
of Harrell’s concordance c-index and to enable comparison of the IDI of the models with bleeding events according to BARC, TIMI, or GUSTO criteria. All analyses, carried out based on the intention to treat principle, were performed using STATA, version 11.1 (Stata Corp, College Station, TX, USA) or R 2.14.0 statistical package (http://www.R-project.org). A two-sided P-value of 0.05 was considered to indicate statistical significance.

**Results**

The PRODIGY trial enrolled 2013 patients. Ten patients withdrew informed consent and were excluded from this analysis, thus 2003 patients were analysed. The baseline characteristics of the analysis population are shown in Supplementary material online, Table S3. Three-quarters of patients (75%) suffered from an ACS (with or without persistent ST elevation) at the time of the index PCI. The proportion of women was 23.5% (473 patients).

**Bleeding events**

The incidence of bleeding events up to 2 years is shown in Table 1. The cumulative 2-year incidence of bleeding was 7.1% (143 patients) according to BARC criteria (Type 2, 3, or 5) (Figure 1), 5.5% (50 patients) according to TIMI criteria (major or minor), or 3.1% (61 patients) according to the GUSTO scale (severe or moderate). The median follow-up duration after the first BARC 2, 3 (or 5) bleeding event was 420 days (IQR: 155–674), whereas the cumulative incidence of any BARC-defined recurrent bleeding or myocardial infarction concomitantly to or after the first BARC bleeding event was 12.6% or 7%, respectively.

**Comparison of predictive value of bleeding definitions**

**Bleeding events and mortality**

In the 2003 patients analysed, there were 163 deaths (8.1%) within 2 years, with 33 (1.6%) deaths occurring within the first 30 days after randomization. The unadjusted hazard ratios (HRs) for death of all causes at 2 years for the three bleeding scales (TIMI major or minor, GUSTO severe or moderate, and BARC Class 2, 3, or 5) are shown in Table 1. The 2-year crude mortality rate was comparable for all three bleeding scales, regardless of whether bleeding occurred early (i.e. within 180 days) or late (i.e. beyond 180 days) during the course of follow-up (Supplementary material online, Table S4); and regardless of whether patients were on single (aspirin only) or on dual (aspirin/clopidogrel) anti-platelet therapy (Supplementary material online, Table S5).

**Predictors of mortality**

The adjusted, time-updated, HRs for the 2-year mortality rate according to BARC-, TIMI-, and GUSTO-defined bleedings are shown in Table 1. A multi-state model for survival data was also generated as sensitivity analysis, as shown in Table 2. Univariate HRs for the risk of 2-year death for all covariates included in the multivariable

### Table 1

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Bleeding rates N (%)</th>
<th>Unadjusted HRs for death at 2 years</th>
<th>Adjusted** HRs for death at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of deaths</td>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td><strong>BARC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>76 (3.8)</td>
<td>3</td>
<td>1.028 (0.326–3.237)</td>
</tr>
<tr>
<td>Type 3 (or 5)</td>
<td>67 (3.3)*</td>
<td>23</td>
<td>12.69 (8.010–19.890)</td>
</tr>
<tr>
<td>Type 3</td>
<td>39 (1.9)*</td>
<td>9</td>
<td>7.597 (3.850–14.99)</td>
</tr>
<tr>
<td>Type 3B</td>
<td>14 (0.7)*</td>
<td>5</td>
<td>11.665 (7.46–28.586)</td>
</tr>
<tr>
<td>Type 3C</td>
<td>14 (0.7)*</td>
<td>9</td>
<td>45.35 (22.958–89.582)</td>
</tr>
<tr>
<td>Type 2, 3 (or 5)</td>
<td>143 (7.1)*</td>
<td>26</td>
<td>5.502 (3.588–8.437)</td>
</tr>
<tr>
<td><strong>TIMI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>26 (1.3)</td>
<td>5</td>
<td>6.316 (2.575–15.490)</td>
</tr>
<tr>
<td>Major</td>
<td>24 (1.2)</td>
<td>14</td>
<td>27.796 (15.924–48.520)</td>
</tr>
<tr>
<td>Minor or major</td>
<td>50 (2.5)</td>
<td>19</td>
<td>14.4 (8.867–23.4)</td>
</tr>
<tr>
<td><strong>GUSTO</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>34 (1.7)</td>
<td>6</td>
<td>5.507 (2.421–12.53)</td>
</tr>
<tr>
<td>Severe</td>
<td>27 (1.4)</td>
<td>14</td>
<td>23.732 (13.604–41.40)</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>61 (3.1)</td>
<td>20</td>
<td>11.92 (7.404–19.19)</td>
</tr>
</tbody>
</table>

BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; TIMI, Thrombolysis in Myocardial Infarction.

*The covariates entered in the multivariable model were: gender, age, body mass index, stent arm as per randomization scheme, short- vs. long-term clopidogrel therapy as per randomization scheme, diabetes, risk factors (number), left ventricular ejection fraction, creatinine clearance, number of diseased (defined as at least 50% diameter stenosis at visual estimation) coronary vessel(s), peripheral arterial disease, ACS presentation, and number of B2/C type lesion(s).

**Table S3** Comparison of predictive value of bleeding definitions

**Table S4** A multi-state model for survival data was also generated as sensitivity analysis, as shown in Table 2. Univariate HRs for the risk of 2-year death for all covariates included in the multivariable

**Table S5**
There was an increased risk of overall mortality across all three bleeding definition criteria with a risk of fatal events of nearly four-fold in patients with BARC Type 2, 3 (or 5) and of almost eight-fold in those with BARC Type 3 (or 5) or TIMI- (major and minor) or GUSTO-defined (moderate to severe) bleeding compared with patients who did not bleed. BARC Type 2 bleeding events alone were not independently associated with 2-year mortality.

Comparison of predictive value of bleeding definitions

The discriminatory power of the multivariable models of bleeding by TIMI-, GUSTO-, or BARC-criteria in regard to 2-year mortality was assessed with the use of Harrell’s C statistic as presented in Table 3. The inclusion of bleeding defined by all three bleeding scales significantly improved the prediction of 2-year mortality.

There were no significant change in the estimated prediction probabilities of the models with BARC Type 3 (or 5), TIMI (minor or major), or GUSTO (moderate or severe) bleeding with respect to 2-year mortality as assessed by comparison of the absolute IDI of the respective models (Table 3).

Discussion

In this first, prospective analysis of the hierarchically graded, BARC classification of bleeding in unselected patients with stable and unstable CAD undergoing PCI we observed that:

(i) Bleeding Academic Research Consortium Type 3 bleedings, but not Type 2, are independently associated with 2-year mortality.

(ii) There is a graded increase in the risk of death at 2-year after PCI, with increasing severity within BARC Type 3 (A, B, C) with Class 3C (intracranial bleeding) carrying the highest mortality risk.

(iii) BARC Type 3 bleedings have a similar association with mortality than that provided by the TIMI major or minor bleeding and GUSTO moderate or severe bleeding definitions.

(iv) Crude mortality hazards following bleeding are comparable regardless their timing after PCI (i.e. within or after 6-month landmark analysis) and/or platelet anti-platelet regimen (i.e. single vs. dual).

The strengths of our analysis rely on the extended follow-up (2 years), the all-comers population reflecting routine clinical practice, the prospective collection and blinded adjudication of bleeding events, and the opportunity to study patients with two different anti-platelet regimens. In this analysis, we have analysed all bleeding events from PCI to 2-year, at variance with previous manuscripts from the PRODIGY trial, in which only events occurring after 30 days were
Three-quarters of patients in our study underwent PCI for ACS (vs. 27.5% in a recent retrospective validation study by Ndrepepa et al.), reflecting current day PCI practice.8

In the present study, the BARC definition was compared with the TIMI and the GUSTO bleeding definitions. We chose these two bleeding definitions as comparators because they are widely used in pharmaco-intervention trials and because they have been shown robust association with mortality. The TIMI definition integrates mainly laboratory-based data, whereas the GUSTO is largely clinically based. The BARC definition offers a balanced combination of laboratory-based and clinically based metrics in bleeding definitions.7

In fact, non-CABG actionable bleeding events can be reclassified according to the BARC bleeding scale (Classes 2, 3, and 5) using data collected for the TIMI and GUSTO scales (Supplementary material online, Table S2).

In PRODIGY, across a wide spectrum of patients with obstructive CAD undergoing PCI, only BARC Class 3 criteria offered prognostic information with respect to overall mortality, at a similar magnitude compared with TIMI (major or minor) and GUSTO (moderate or severe) bleeding criteria. Bleeding Academic Research Consortium Class 3C (intracranial bleeding) bleeding events were associated with the worst prognosis. While BARC Class 2 bleeding events were, per se, not associated with increased mortality, their relevance to contemporary practice should not be dismissed. Bleeding Academic Research Consortium 2 events, being actionable by definition, are likely associated with increased morbidity, worse quality of life, and are conceivably associated with increased healthcare expenditure.17 Interestingly, even Type 1 BARC events (i.e. non-actionable bleedings) following myocardial infarction were recently shown to be associated with decreased short, and long-term quality of life.18

In PRODIGY, therapy with clopidogrel plus aspirin, when compared with aspirin alone, was associated with a 38% increase in the odds of actionable bleeding events.10 In our analysis, associated case fatality was similar for bleeding events occurring early (within 6 months) or late (beyond 6 months and up to 2 years) after the index PCI. The fact that bleeding occurring both early and late after index PCI carries similar prognostic implications suggests the detrimental nature of bleeding per se. Our findings complement the results from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) which suggested that the impact of bleeding on mortality was restricted to serious bleeding events.19 Analyses focusing on the time dependency of this relationship showed that this association existed only for the first week after a instrumented or traumatic serious bleeding event. Spontaneous serious bleeding events tended to have a longer impact on mortality, with a significantly elevated hazard for ~1 month. However, there did not appear to be a prolonged hazard beyond these time periods. As shown in our analysis, the prognostic impact of bleeding on mortality appeared mostly similar over time irrespective of the timing of bleeding (i.e. early vs. late after PCI). On the other side, the decline in HR for mortality late after a single serious bleeding event, is biologically plausible, and may explain the slight attenuation in HR beyond 6 months in our analysis. This finding reinforces the concept that bleeding, irrespective of its mechanism (i.e. instrumented or spontaneous), concomitant medication(s) (i.e. single vs. double anti-platelet agent(s)) or timing (early or late after index PCI) is detrimental and emphasizes the importance of minimizing any bleeding events (i.e. both early and late after PCI, as well as both instrumented and spontaneous ones) in order to optimize both short- and long-term outcomes after intervention.

### Limitations

Several limitations of the current analysis warrant consideration. First, BARC Class 1 bleeding events were not considered in this analysis. While a detailed ascertainment of BARC Class 1 events might have been relevant for the research question, the need of dedicated and paced queries and the requirement of relevant resources to allow an accurate assessment of this bleeding events made an accurate capture challenging in this investigator-driven project. Second, despite the all-comers nature of PRODIGY, subjects with some features indicating increased risk of bleeding, such as active bleeding or previous stroke in the past 6 months; concomitant or foreseeable need for oral anti-coagulation therapy were not included in the present trials, possibly hampering the external validity of our analysis to a more complex and heterogeneous patient population such as that treated in everyday clinical practice.8 Third, there was some variability in the timing of clopidogrel cessation in the short DAPT arm, with 128 patients (12.7% of those randomized to short DAPT) who stopped clopidogrel at 1 month, all of whom were randomized to a BMS, and 62 patients (6.2%) who stopped clopidogrel between 1 and 6 months. Therefore the bleeding-related outcomes reported in this analysis should be interpreted against the background of this variability. As for the TRITON-TIMI 38 trial, this analysis was not powered to detect any definitive time-related effect between bleeding events and mortality.19 The distribution of bleeding events across the BARC scale (i.e. from Type 1 to 5) may depend on the potency of concomitant anti-thrombotic agents. While treating physician was left free to give either 300 or 600 mg clopidogrel loading dose at the time of index PCI to randomized patients, cumulative bleeding events at 2 years appeared not to be affected by the different clopidogrel loading regimens.

Moreover, in PRODIGY patient adherence to the assigned anti-platelet treatment regimen was >95%.10 This high adherence is harder to reach in the ‘real world’ and may have impacted our study results.20,21 However, in the PARIS registry, disruption of DAPT (i.e. non-physician recommended discontinuations) for

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>c-Index (95% CI)</th>
<th>IDI (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARC Type 2, 3 (or 5)</td>
<td>0.78 (0.74–0.81)</td>
<td>0.005 (0.000–0.024)</td>
</tr>
<tr>
<td>BARC Type 3 (or 5)</td>
<td>0.80 (0.75–0.82)</td>
<td>0.015 (0.003–0.046)</td>
</tr>
<tr>
<td>TIMI minor or major</td>
<td>0.79 (0.75–0.82)</td>
<td>0.016 (0.002–0.044)</td>
</tr>
<tr>
<td>GUSTO moderate or severe</td>
<td>0.79 (0.75–0.82)</td>
<td>0.011 (0.000–0.038)</td>
</tr>
</tbody>
</table>

BARC, Bleeding Academic Research Consortium; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; TIMI, Thrombolysis in Myocardial Infarction.
bleeding or non-compliance was associated with a low attributable risk for cardiac death or other major cardiac adverse events. 20

Finally, the open-label design may have potentially biased adjudications. However, a blinded clinical events committee adjudicated all suspected events, which limits the possibility of this bias.

Conclusions

In this prospective validation of the BARC classification of bleeding, we observed that BARC Type 3 (or 5) bleeds predicted 2-year mortality to a similar extent to that provided by TIMI and GUSTO scales. These data support the clinical validity of the BARC classification, which, by integrating elements of both GUSTO and TIMI scales, may be helpful to standardize bleeding endpoint definition in clinical investigations and may be thus be used in addition or in substitution of these two scales.

Supplementary material

Supplementary information is available at European Heart Journal online.

Funding

The present study is an investigator-driven clinical trial. The conduct of this study did not receive any direct or indirect external funding but was entirely supported by the University of Ferrara, which employed dedicated personnel for data monitoring, data management, events adjudication, and independent statistical analyses.

Conflict of interest: Dr Valgimigli has received honoraria for lectures/advisory board and research grants from Merck, Iroko, Eli Lilly, Medtronic and Terumo; honoraria for advisory board and lectures from The Medicines Company, Eli Lilly Co; Daichi Sankyo, Inc., St Jude and Abbott Vascular; lectures from Cordis, CID, and Terumo. S.L. has no conflicts of interests relevant to this manuscript.

References

tions for cardiovascular clinical trials: a consensus report from the Bleeding Acad-
15. Hochholzer W, Wiviott SD, Antman EM, Contant CF, Ggjolz, Giugliano RP, Dabiy DL, Montalescot G, Braunwald E. Predictors of bleeding and time dependence of
