

Comparative external validation of the PRECISE-DAPT and PARIS risk scores in 4424 acute coronary syndrome patients treated with prasugrel or ticagrelor

Original

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Comparative external validation of the PRECISE-DAPT and PARIS risk scores in 4,424 acute coronary syndrome patients treated with prasugrel or ticagrelor.

Matteo Bianco¹ MD; Fabrizio D'ascenzo^{*2} MD; Sergio Raposeiras Roubin^{*3} MD, PhD; Tim Kinnaird⁴ MD; Mattia Peyracchia² MD; Albert Ariza-Solé⁵ MD, PhD; Enrico Cerrato⁶ MD; Sergio Manzano-Fernández⁷ MD; Carol Gravinese¹ MD; Christian Templin⁸ MD, PhD; Paola Destefanis¹ MD, Lazar Velicki⁹ MD; Alessia Luciano¹ MD; Ioanna Xanthopoulou¹⁰ MD, PhD; Mauro Rinaldi¹¹ MD, Prof; Andrea Rognoni¹² MD; Ferdinando Varbella⁶ MD; Giacomo Boccuzzi¹³ MD; Pierluigi Omedè² MD; Andrea Montabone¹³ MD; Alessandro Bernardi² MD; Salma Taha¹⁴ MD; Roberta Rossini¹⁵ MD, PhD; Alessandro Durante¹⁶ MD; Sebastiano Gili⁸ MD; Giulia Magnani⁸ MD, PhD; Michele Autelli² MD; Alberto Grosso² MD; Pedro Flores Blanco⁵ MD; Carla Giustetto² MD, Prof; Alberto Garay⁷ MD; Giorgio Quadri⁶ MD; , Berenice Caneiro Queija³ MD; Ilija Srdanovic⁹ MD; Rafael Cobas Paz³ MD; María Cespón Fernández³ MD; Isabel Muñoz Pousa³ MD; Diego Gallo¹⁷ Eng, PhD; Umberto Morbiducci¹⁷ Eng, Prof; Alberto Dominguez-Rodriguez¹⁸ MD, Prof; Ángel Lopez-Cuenca⁷ MD; Angel Cequier⁵ MD; Dimitrios Alexopoulos¹⁰ MD, Prof; Andres Iñiguez-Romo³ MD; Roberto Pozzi¹ MD; Emad Abu Assi^{**3} MD, PhD; Marco Valgimigli^{**19} MD, Prof.

1) Division of Cardiology, San Luigi Gonzaga University Hospital, Orbassano, Italy, 2) University of Turin, 'Città della Salute e della Scienza di Torino', Division of Cardiology, Turin, Italy, 3) Department of Cardiology, Hospital Álvaro Cunqueiro, Vigo, Pontevedra, Spain, 4) Cardiology Department, University Hospital of Wales, Cardiff, United Kingdom, 5) Department of Cardiology, University Hospital de Bellvitge, Barcelona, Spain, 6) Interventional Cardiology Unit, San Luigi Gonzaga University Hospital, Orbassano and Infermi Hospital, Rivoli, Turin, Italy, 7) Department of Cardiology, University Hospital Virgen Arrixaca, Murcia, Spain, 8) Department of Cardiology, University Heart Center, University Hospital Zurich, Switzerland, 9) Medical faculty, University of Novi Sad, Novi Sad, Serbia and Institute of cardiovascular Diseases Vojvodina, Sremska Kamenica, Serbia, 10) University Patras Hospital, Athens, Greece, 11) University of Turin, 'Città della Salute e della Scienza di Torino', Division of Cardiac Surgery, Turin, Italy, 12) Catheterization Laboratory, Maggiore della Carità Hospital, Novara, Italy, 13) Department of Cardiology, S.G. Bosco Hospital, Torino, Italy, 14) Department of Cardiology, Faculty of Medicine, Assiut University, 15) Division of Cardiology, A.O Santa Croce e Carle, Cuneo, Italy, 16) U.O. Cardiologia, Ospedale Valduce, Como, Italy, 17) PolitoBIOMed Lab, Department of Mechanical and Aerospace Engineering, Politecnico di Torino, 18) Department of Cardiology, University Hospital from Canarias, Tenerife, Spain, 19) Swiss Cardiovascular Center Bern, Bern University Hospital, Switzerland

*joint second authorship

** joint last authorship

Correspondence to: Dr. Matteo Bianco, MD, Division of Cardiology, San Luigi Gonzaga University Hospital, Orbassano, Italy. E-mail: matteo.bianco87@gmail.com; www.cardiogroup.org.

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62 **ABSTRACT**
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65 **Background.** The PRECISE-DAPT and PARIS risk scores (RSs) were recently developed to help
66 clinicians at individualizing the optimal dual antiplatelet therapy duration (DAPT) after
67 percutaneous coronary intervention (PCI). Nevertheless, external validation of these RSs it has not
68 yet been performed in ACS (acute coronary syndrome) patients treated with prasugrel or ticagrelor
69 in a real- world scenario.
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75 **Methods:** 4,424 ACS patients who underwent PCI and survived to hospital discharge, from
76 January 2012 to December 2016 at 12 European centers, were included. PRECISE-DAPT and
77 PARIS bleeding RS, as well as PARIS ischemic RS, were computed, and their performance at
78 predicting major bleeding (MB; BARC type 3 or 5) and ischemic events (MI and stent thrombosis)
79 during follow up was compared.
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85 **Results:** After a median follow-up of 14 (interquartile range 12-20.9) months, 83 (1.88%) patients
86 developed MB and 133 (3.0%) suffered an ischemic episode. PRECISE-DAPT performed better
87 than PARIS bleeding RS (c-statistic= 0.653 vs. 0.593; p= 0.01 for comparison) in predicting MB.
88 The RSs performance for MB prediction remained consistent in STEMI patients (c-statistic= 0.632
89 vs 0.575) or in those treated with prasugrel (c-statistic = 0.623 vs 0.586).
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95 PARIS ischemic RS exhibited modest but superior discrimination in predicting ischemic
96 complications as compared to PRECISE-DAPT (c-statistic= 0.604 vs 0.568 p= 0.05 for
97 comparison).
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101 **Conclusion:** Our data provide support to the use of PRECISE-DAPT in MB risk stratification for
102 patients receiving DAPT in form of aspirin and prasugrel or ticagrelor whereas the PARIS ischemic
103 RS has potential to complement the risk prediction with respect to ischemic events.
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113 **Keywords:** DAPT, prasugrel, ticagrelor, bleeding; PRECISE DAPT; PARIS risk score
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121 **INTRODUCTION**
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124 Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor (P2Y12i) is the
125 standard of care in patients treated with percutaneous coronary intervention (PCI) and stent
126 implantation. Yet, the most appropriate DAPT duration, especially in patients at high bleeding risk
127 with prior acute coronary syndrome (ACS) remains a subject of intense controversy.
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132 The originally proposed “one-fits-all” strategy based on an at least twelve months regimen
133 of DAPT has been questioned and a tailored treatment duration informed by the individual
134 ischemic and bleeding risks has been more recently advocated ¹⁻⁴.
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138 The PRECISE-DAPT and PARIS risk scores (RSs) have been recently developed to help
139 physicians in stratifying post-discharge bleeding and ischemic risk in patients treated with DAPT
140 after PCI^{5,6}. Although both scores demonstrated a moderate predictive ability, the European
141 Society of Cardiology (ESC) DAPT focused update exclusively endorsed, with a class IIb
142 recommendation, the use of PRECISE-DAPT score, in view of a gap in knowledge whether PARIS
143 RS improves the decision making on DAPT duration.
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147 However, the recommendation of the ESC regarding the use of PRECISE-DAPT is based
148 on a single study where patients were largely treated with aspirin and clopidogrel⁵. Therefore,
149 further investigating the predictive capability and reliability of PRECISE-DAPT seems necessary
150 before generalizing its use to other populations with different clinical features, health systems and
151 more contemporary medications. In addition, PRECISE-DAPT was derived from clinical trial
152 patients, at variance with the PARIS RSs, which was developed from registry patients.
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156 We sought to evaluate and compare the external validity of PRECISE-DAPT and PARIS
157 RSs in contemporary real-world ACS patients treated with aspirin and prasugrel or ticagrelor.
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180 **METHODS**
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183 **Study Population**
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185 The design and patient population of RENAMI (**RE**gistry of **N**ew **A**ntiplatelet therapy in
186 **M**ycardial **I**nfarction) was comprehensively described elsewhere⁷. Briefly, in RENAMI dataset,
187 consecutive ACS patients recruited at 12 European centers from January 2012 to December 2016
188 were included (**supplementary appendix**). The RENAMI registry included all comer patients with
189 a final diagnosis of ACS: unstable angina (UA), non ST-segment elevation myocardial infarction
190 (NSTEMI), or ST-segment elevation myocardial infarction (STEMI), aged at least 18 years, who
191 consented for participation in the study. All patients underwent in-hospital coronary angiography
192 and PCI with stent implantation followed by aspirin and either ticagrelor or prasugrel, at discretion
193 of the treating physician. All patients were discharged with DAPT (aspirin plus ticagrelor or aspirin
194 plus prasugrel). Excluded patients from the present analysis were those who experienced any
195 adverse event defined as major bleeding (MB), new MI, stent thrombosis (ST), cardiovascular
196 death or death for any causes during the index hospitalization. The institutional review board of
197 each center approved the study protocol.
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211 **Objectives**
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214 We sought to evaluate and compare the performance of PRECISE-DAPT and PARIS RSs
215 at predicting post-discharge MB and ischemic events (MI and ST), in the overall cohort and in
216 subgroups of interest, including STEMI vs. NSTEMI, ticagrelor vs. prasugrel,
217 and according to different DAPT durations (< 12 months, 12 months, and > 12 months).
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222 **Follow-up and definitions**
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225 The follow-up was conducted at each single center with at least two in contact visits within
226 the first year after inclusion in order to assess the occurrence of any relevant clinical events and
227 assess drug-adherence. Data on vital status (alive or dead) and events during follow-up were
228 obtained from hospital clinical data records, as well as from administrative records (vital statistics
229 registers, hospital discharge data and emergency department data), and telephone contact was
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239 made with patients or their relatives and primary care physicians in particular cases for which
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241 information was not available.
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244 Follow-up time was ended by DAPT duration; therefore, the events recorded (MB or MI/ST
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246 or cardiovascular death) occurred while patients were on DAPT. We only considered the first MB
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248 or MI/ST episodes occurred during follow-up. Therefore, in patients who had developed more than
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250 one complication, the follow-up time was ended at the time of the first of the prior complications.
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253 Major bleeding was defined as those fulfilling type 3 or type 5 BARC criteria⁸. Ischemic
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255 events were defined as a composite of new MI or stent thrombosis or cardiovascular death. A new
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257 MI was defined according to the third definition of myocardial infraction⁹. ST was defined according
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259 to Academic Research Consortium criteria¹⁰. Cardiovascular death includes deaths that result from
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261 an MI, sudden cardiac death, death due to heart failure, death due to stroke, death due to
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263 cardiovascular procedures.
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265 **Risk scores calculation**

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267 PRECISE-DAPT and PARIS were calculated in each patient on the basis of the original
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269 definitions used in their development cohorts (**Supplementary Table 1-2, Supplementary Figure**
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271 **1**)^{5,6}. PRECISE-DAPT assigns patients into four risk strata (very low: ≤ 10 , low: 11-17, moderate:
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273 18-24, and high: ≥ 25 points), whereas PARIS bleeding risk score categorizes patients into three
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275 risk groups (low: < 3 , moderate: 3-7, and high: ≥ 8 points). PARIS ischemic risk score also
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277 categorized patients into three strata but with different cut points: low: < 2 ; intermediate: 3-4; and
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279 high: ≥ 5 points.
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282 To enable comparisons between the PRECISE-DAPT and PARIS risk classification
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284 systems we categorized all patients into three risk strata by considering the very low and low risk
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286 categories in PRECISE-DAPT as a unique category.
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298 **Data presentation and statistical analysis**
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301 Baseline and clinical characteristics of the RENAMI external validation population, and the
302 derivation cohorts of the PRECISE- DAPT and PARIS scores are presented as mean \pm standard
303 deviation (SD) and medians (interquartile ranges [IQR]) for continuous variables, and as
304 proportions for categorical variables.
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309 The total RSs, as continuous variables, were entered into separate Cox regression models
310 to test their association with ischemic and MB events. The ability to separate high-risk from lower
311 risk patients was visually appraised by generation of Kaplan-Meier curves for events of interest and
312 compared using the log-rank test. The magnitude of the association between each of the three
313 predefined risk categories from the RSs was calculated and expressed as hazard ratios (HR) with
314 their 95% confidence intervals (95% CI); the low risk category was considered as a reference
315 category.
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323 The predictive capacity of the RSs was tested by means of indices of discrimination and
324 calibration. To assess discrimination, using the total RS as a global prognostic indicator, we
325 calculated and compared the Harrell c-statistic for censored time-to-event data, for both scores¹¹.
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329 Calibration was computed using the Grønnesby and Borgan χ^2 test, and plotted observed vs.
330 predicted outcomes.
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333 The time-frame of 12 months was used to assess the ability of both scores to predict outcomes
334 over the first year, in order to decide to stop or to prolong DAPT. The Kaplan-Meier curves end at
335 18 months in order to show the whole study follow-up.
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339 We further assessed the net reclassification improvement index (NRI)¹². For the NRI calculation,
340 individuals were compared based on their bleeding and ischemic risk using the three categories of
341 the two RSs. Since the probability of MB and MI/ST was set at different thresholds in the
342 respective risk categories of PRECISE-DAPT and PARIS, we further analyzed possible
343 improvement in the discrimination ability of one score vs. the other by means of the “categoryless”
344 NRI. Although there are no established benchmarks for category-free NRI (cfNRI), Pencina et al.
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357 suggest cfNRI greater than 0.6 indicates a strong contribution and NRI(>0) between 0.2 and 0.6
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359 implies moderate improvement^{13,14}.
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362 Decision curve analyses (DCA) were also used to quantify the net benefit of the prediction
363 scores; the higher the net benefit, the better the RS, in terms of clinical usefulness. The theoretical
364 range of net benefit is from negative infinity to the incidence of disease.
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368 Finally, we considered the average daily difference between ischemic and bleeding events
369 according to the risk categories of PRECISE-DAPT and PARIS risk scores limiting the analysis to
370 the first event occurring (MB, MI, death, ending of DAPT). The average daily rate for a given
371 interval was defined as the total number of events in that interval divided by the total number of
372 patient-days of follow-up (number of patients multiplied by how many days each patient was at risk
373 in that given period).
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381 A two-sided $p < 0.05$ was considered statistically significant. All statistical analysis was
382 performed using SPSS 24 and the statistical package for R 3.2.1 (R Foundation for Statistical
383 Computing, Vienna, Austria).
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389 RESULTS

390 Baseline characteristics

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392 The baseline characteristics of the RENAMI population are summarized in **table 1**. Patients
393 in RENAMI were younger and less frequently females, as compared with those used to generate
394 the the PRECISE-DAPT and PARIS RSs.
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400
401 Most of patients in this study had STEMI and largely received drug eluting stent implantation. All
402 patients received DAPT in form of either prasugrel or ticagrelor. A total of 22.3%, 50.1% and
403 27.6% of the patients in the RENAMI study received DAPT for less then 12 months, 12 months or
404 more than 12 months, respectively.
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416 The PRECISE-DAPT varied from 0 to 75 points (17±10 points), and 20.4% of patients were
417 categorized as having high risk of bleeding. (**Figure 1**). In contrast, the PARIS bleeding RS values
418 ranged from 0 to 10 points (3±2 points), with only 3.9% of patients fulfilling the high-risk category
419 (**Figure 1**).

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424 The PARIS ischemic score ranged from 1 to 13 points (4±2 points) with 23.1% of the patients
425 being categorized at high ischemic risk.
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428 429 430 431 432 433 **Bleeding and ischemic risk assessment based on the RSs classification systems** 434

435
436 After a median follow-up of 14 (IQR: 12-20.9) months, 83 (1.88%) patients developed MB
437 and 133 (3.0%) suffered an ischemic episode. Median time for first MB was 5.0 (IQR 1.6-9.4)
438 months, and for ischemic events 9.6 (IQR 2.6-16.9) months. The Kaplan-Meier curves based on
439 risk categories assigned by each score for the occurrence of MB are shown in **Supplementary**
440 **Figure 2**. Both PRECISE-DAPT and PARIS bleeding RSs showed significant predictive capability
441 (log-rank test, $p < 0.01$). The observed bleeding rates for the two scores increased monotonically
442 from low- to high-risk categories. However, Kaplan-Meier curves diverged in a more pronounced
443 way with PRECISE-DAPT (χ^2 values were 23 [$p < 0.001$] for PRECISE-DAPT vs. 10 [$p = 0.002$] for
444 PARIS). After an adjustment for potential clinically relevant confounders (age, sex, hypertension,
445 diabetes mellitus, history of malignancies, prior-MI, prior-bleeding, anemia, creatinine clearance,
446 ACS or non-ACS clinical presentation, DES or BMS, enrolling center), with Cox regression models
447 both PRECISE DAPT and PARIS bleeding RSs confirmed their independent ability to predict MBs
448 on the basis of their risk categories (PRECISE DAPT moderate risk HR: 2.56 CI: 1.52 – 4.31 $p <$
449 0.0001; PRECISE DAPT high risk HR: 4.01 CI: 2.57 – 6.28 $p < 0.0001$ and PARIS bleeding
450 moderate risk HR: 2.11 CI: 1.39 – 3.21 $p < 0.0001$; PARIS bleeding high risk HR: 5.78 CI: 3.16 –
451 10.55 $p < 0.0001$). Similar results were observed for the prediction of ischemic events (PRECISE
452 DAPT moderate risk HR: 2.33 CI: 1.34 – 4.08 $p = 0.003$; PRECISE DAPT high risk HR: 3.07 CI:
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475 1.88 – 5.04 $p < 0.0001$ and PARIS ischemic moderate risk HR: 2.00 CI: 1.31 – 3.07 $p = 0.001$;
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477 PARIS ischemic high risk 2.60 CI: 1.68 – 4.02 $p < 0.0001$).

479 Consistent findings were noted for the predictive value of both RSs in predicting MI/ST or
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481 cardiovascular death (**supplementary materials Figure 3-4**)

486 487 **Discrimination**

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489 Both PRECISE-DAPT and PARIS bleeding scores, as continuous variables, were better
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491 than the chance for predicting MB. However, the PRECISE-DAPT performed better than the
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493 PARIS bleeding RS at c-statistics (c-statistic= 0.653, [95%CI: 0.59-0.71]; c-statistic: 0.593, [95%CI:
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495 0.528-0.658]; $p=0.01$ for correlated c-statistic values comparison).

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498 In contrast, the discriminative capacity of PARIS ischemic RS, as compared to PRECISE-DAPT,
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500 was slightly higher (c-statistic = 0.604, [95%CI: 0.550-0.657] and 0.568 [95%CI: 0.509-0.626];
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502 $p=0.05$ for correlated c-statistics values comparison).

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504 The c-statistic values for different DAPT duration, clinical presentation, P2Y12 inhibitors,
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506 age and serum creatinine level are summarized in **table 2**. Briefly, the PRECISE-DAPT score was
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508 able to predict MB reasonably well and better than the PARIS bleeding RS in almost all analyzed
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510 sub-categories but its discriminative capacity for MB was found to be slightly reduced in patients
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512 treated with prasugrel, patients > 75 years and in patients with STEMI at presentation compared to
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514 those treated with ticagrelor, patients < 75 years and those with NSTEMI at presentation. Finally,
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516 PARIS ischemic RS was better than PRECISE DAPT in predicting ischemic events in all subgroup
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518 analyses with the exception of patients treated with ticagrelor in which the discrimination
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520 performance of the scores is almost the same.

522 523 **Calibration**

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525 Calibration of observed against predicted MB was good for both RSs, although PRECISE
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527 DAPT slightly tended to underestimate the predicted probability of MB compared to PARIS

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534 bleeding RS. The calibration of PRECISE DAPT for observed against predicted ischemic events
535 was suboptimal if compared with PARIS ischemic risk score as shown in **Supplementary figure 5**.
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537 In the figure, for each bin, the y-value is the proportion of true outcomes, and x-value is the mean
538 predicted probability. Therefore, a well-calibrated model has a calibration curve that hugs the
539 predicted probability. Therefore, a well-calibrated model has a calibration curve that hugs the
540 straight line $y=x$ (blue line). The red points identify the observed probability of events based on the
541 estimate of the score, so that if they are above the blue line they indicate that the score
542 underestimates, and if they are below the blue line it indicates that the score overestimate.
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548 **Average daily rate events**

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551 PRECISE DAPT was able to predict the average daily difference between bleeding and ischemic
552 events better than PARIS risk scores in all the three risk categories in the first year as shown in
553 **supplementary materials Figure 6**. In particular, the average daily difference of events followed
554 the risk categories stratification for PRECISE DAPT whereas wide overlap between risk categories
555 and observed average daily rate events was noted for the two PARIS risk scores.
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561 **Decision curves analyses for MB**

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564 **Figure 2** compares the decision curves from classifying individuals using the PRECISE
565 DAPT and PARIS bleeding RSs, assuming all patients will bleed (all positive or all are at high risk
566 of bleeding), and assuming all patients as if none will bleed (all negative or all are at low risk of
567 bleeding; horizontal line at 0). The DCA showed that the use of PRECISE DAPT is superior to
568 PARIS bleeding RS at a risk threshold of $\geq 2\%$. PARIS bleeding RS did not prove to be
569 advantageous, as compared to no use of the score, at a risk threshold of $\geq 3\%$, whereas PRECISE-
570 DAPT RS continued to stratify the bleeding risk until a threshold of 10% MB risk. The net benefit
571 analysis for MB is summarized in **Supplementary Table 3**. The PRECISE DAPT showed superior
572 predictive capability for MB events as opposed to the PARIS bleeding RS with a moderate
573 improvement on risk prediction even when using a category-free NRI = 0.41 (95% CI: 0.20-0.65)
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584 **.DISCUSSION**

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586 The main findings of this study are:
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593 1) The PRECISE DAPT and PARIS bleeding RS perform moderately well in predicting MB
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595 in patients treated with ticagrelor or prasugrel in the first fourteen months after discharge. 2)
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597 PRECISE DAPT is significantly superior to PARIS bleeding RS for predicting MB. 3) The
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599 performance of both the RSs is consistent in all the subgroups included in the analysis. 4) PARIS
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601 ischemic RS is slightly better than PRECISE DAPT in predicting ischemic events.
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603
604 There is an emerging need to focus on the trade off between ischemic and bleeding risks
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606 when treating contemporary patients with prolonged potent anti-thrombotic medications. in order to
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608 maximize the benefit and avoid the risks. The ischemic risk is progressively decreasing in the last
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610 years thanks to a great technological improvement of the stents and of PCI techniques¹⁵. At the
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612 same time, the use of more potent anti-platelets therapies in ACS patients and to the ageing of
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614 patients undergoing routine treatment, the bleeding events have become prevalent and they are
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616 able to dramatically affect the prognosis of our patients¹⁶⁻¹⁹.
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619 Costa et al. and Baber et al. generated new models to better predict the incidence of MB
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621 and ischemic events in the first 12 or 24 months of treatment respectively, overcoming the
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623 limitations of previous studies, which mainly focused on in hospital events. The PRECISE DAPT
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625 modeled exclusively the bleeding risk and found that a score ≥ 25 points may be used in the
626
627 decision-making of shortening DAPT duration to avoid bleeding. It was validated in patients
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629 enrolled in the PLATO study and in the Bern PCI registry (both ACS and stable angina) and
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631 showed superiority in the discrimination and reclassification performance respect to the PARIS
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633 bleeding RS.

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635 In our study we tested the performance of PRECISE DAPT and PARIS RSs in a real-world
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637 registry with characteristics different from the derivation cohorts. First, all our patients were ACS
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639 with more than fifty percent of those presenting STEMI and were treated with prasugrel or
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641 ticagrelor. Yet, both bleeding RSs demonstrated a reasonable discriminative capacity to predict
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643 MB, hence confirming the results of previous studies, which were largely undertaken in patients
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645 treated with clopidogrel^{5,6}.
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652 We found that PRECISE DAPT was superior to PARIS bleeding RS in predicting MB.
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654 Despite similar results in the risk stratification of our population, the discrimination power, the
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656 average daily difference between bleeding and ischemic events and net benefit of PRECISE DAPT
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658 was superior particularly in the first year of follow-up. These results are consistent with the study of
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660 Costa et al⁵.
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663 A recent study of Abu-Assi et al provided opposite results in terms of performance of the
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665 two bleeding RSs considered²⁰. This could be due to some differences in the baseline
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667 characteristics between the prior study and this cohort. Patients included in the RENAMI study
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669 were treated with prasugrel or ticagrelor, while in the study by Abu-Assi et al the majority of
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671 patients received clopidogrel; moreover, twenty percent of the patients of Abu-Assi et al were
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673 treated with a bare metal stent and data on the DAPT duration was not taken into account²⁰. Taken
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675 all together, the prior study seems less generalizable to a population treated with the current
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677 standard of care and this could explain the different performance of bleeding RSs observed.
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680 Of note, in our study, the use of both bleeding RSs was superior to the strategies of not
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682 using the RSs for bleeding risk classification, as observed in the DCA. This means that the use of
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684 PRECISE-DAPT and PARIS bleeding RS is of clinical value to drive clinical decisions in bleeding
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686 risk stratification. Moreover, our work confirms the previous results from Raposeiras Roubin et al.
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688 on the utility of the PARIS RSs but shows that the PRECISE DAPT score is even better. In fact,
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690 over a risk score threshold of the 3% the PARIS bleeding RS failed to demonstrate a benefit over
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692 the strategy of not using a RS. For this reason, our observations strengthen the recommendation
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694 of the recent ESC position paper on anti-platelet therapy who recommend to use PRECISE DAPT
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696 score in bleeding risk stratification¹.
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699 Due to the great difference in baseline characteristics between RENAMI cohort and the
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701 derivation cohorts of the PRECISE DAPT and PARIS RSs, we appraised the accuracy in predicting
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703 bleeding and ischemic events in different patient subgroups. We found a modest reduction in the
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705 accuracy of predicting MB events of PRECISE DAPT and PARIS bleeding RS in particular among
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707 patients treated with prasugrel, in those presenting with STEMI and in those > 75 years. In this
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711 three cohorts, the accuracy of both the scores was slightly reduced compared to the general
712 population but overall, as showed in **Table 2**, the discrimination capacity is consistent in all the
713 subgroups included in the analysis. The reduction in the discrimination ability of PRECISE DAPT
714 score in patients treated with prasugrel was already shown by Costa et al. and is probably related
715 to the average low bleeding profile of patients treated with prasugrel (< 75 years, > 60 kg and
716 without previous intracranial bleedings)⁵. Finally, our analysis confirmed that the accuracy of
717 bleeding risk scores decrease in elderly population as already shown in a previous study²².
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725 The ischemic events prediction of PRECISE DAPT score is largely insufficient which is a
726 consistent observation with the fact that this model was purely generated for bleeding prediction
727 purposes.
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732 The current results endorse the implementation of PRECISE DAPT score in the clinical
733 practice as novel tool, particularly within the first year after intervention, to balance the bleeding
734 and ischemic risks as shown by our average daily difference events analysis. The PRECISE-DAPT
735 score allows selecting patients who derive benefit from a short DAPT (3 or 6 months) as well as
736 those who should be treated with DAPT as long as possible, which is in keeping with current
737 European guidelines¹. On the other hand, the use of the PARIS risk scores does not seem to
738 provide clinicians with clear risk stratification information due to some degree of overlap among
739 different risk strata for bleeding and ischemic events.
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750 **LIMITATIONS**

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752 This study has several limitations. This was a retrospective observational study, so we cannot rule
753 out the presence of selection bias and unmeasured confounding factors. Moreover, we used
754 treatment at discharge as a principle of intention-to-treat analysis, as we did have data on DAPT
755 duration during follow-up. However, this principle was also applied in the PLATO and Bern PCI
756 external validation cohorts used in the development of the PRECISE-DAPT score, and in the
757 PARIS development cohorts^{5,6}. Finally, BARC criteria were used to define bleeding in our study
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770 and in PARIS, in contrast to PRECISE-DAPT where bleeding definitions were based on TIMI
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772 criteria. This point could have affected the comparability of the scores. However, BARC bleeding
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774 criteria were also used as an alternative bleeding definition in the external validation cohorts of
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776 PRECISE-DAPT. Additionally, BARC bleeding criteria are currently considered the standard
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778 bleeding definition. Finally, Costa et al. showed a lower discrimination of PRECISE-DAPT score in
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780 patients treated with proton pump inhibitors (PPI); these medications are very important to reduce
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782 gastro intestinal bleedings in patients treated with DAPT, unfortunately we did not collect
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784 systematically the PPI treatment in our database and we are not able to provide any analysis on
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786 the influence of PPI in the performance of the RSs included in the analysis.
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791 **CONCLUSION**

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793 Our data provide support to the use of PRECISE-DAPT in MB risk stratification for patients
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795 receiving DAPT in form of aspirin and prasugrel or ticagrelor whereas the PARIS ischemic RS has
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797 potential to complement the risk prediction with respect to ischemic events.
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801 **CONFLICT OF INTERESTS**

802
803 Prof. Valgimigli has received research grants to the institution from Terumo, Medicure, Abbott,
804
805 Astrazeneca and honorarium fees from Abbott, Chiesi, Bayer, Daiichi Sankyo, Amgen, Terumo,
806
807 Astrazeneca, Alvimedica and Biosensors.
808

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SUPPLEMENTARY APPENDIX

Supplementary Methods

Leading Study Centers

Dipartimento di Scienze Mediche, Divisione di Cardiologia, Città della Salute e della Scienza, Turin, Italy

Department of Cardiology, University Hospital Álvaro Cunqueiro, Vigo, Spain.

PolitoBIOMed Lab, Department of Mechanical and Aerospace Engineering, Politecnico di Torino.

Participating Study Centers

Department of Cardiology, Department of Medical Sciences, University of Torino, Italy.

Department of Cardiology, University Hospital Álvaro Cunqueiro, Vigo, Spain.

Cardiology Department, University Hospital of Wales, Cardiff, United Kingdom.

Department of Cardiology, University Hospital de Bellvitge, Barcelona, Spain.

Department of Cardiology, University Hospital Virgen Arrixaca, Murcia, Spain.

Department of Cardiology, University Heart Center, University Hospital Zurich, Switzerland.

Institute of cardiovascular Diseases, Vojvodina, Serbia.

University Patras Hospital, Athens, Greece.

Interventional Unit, San Luigi Gonzaga University Hospital, Orbassano and Infermi Hospital, Rivoli, Italy.

Catheterization Laboratory, Maggiore della Carità Hospital, Novara, Italy.

Department of Cardiology, S.G. Bosco Hospital, Torino, Italy.

Department of Cardiology, Faculty of Medicine, Assiut University.

U.O. Cardiologia, Ospedale Valduce, Como, Italy. Department of Cardiology, University Hospital from Canarias, Tenerife, Spain.

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SUPPLEMENTARY TABLES

Supplementary table 1: variables comprising the PARIS bleeding risk score.

Variable	Assigned points
Age, years	
<50	0
50–59	1
60–69	2
70–79	3
≥80	4
Body mass index, kg/m ²	
<25	2
25–34.9	0
≥35	2
Current smoking	
Yes	2
No	0
Anaemia	
Present	3
Absent	0
Creatinine clearance <60 ml/min	
Present	2
Absent	0
Triple therapy on discharge	
Yes	2
No	0

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Supplementary table 2: variables comprising the PARIS ischemic risk score.

Variable	Assigned points
Diabetes mellitus	
None	0
Non insulin-dependent	1
Insulin-dependent	3
ACS	
No	0
Yes Tn-negative	1
Yes Tn-positive	2
Current smoking	
Yes	1
No	0
Prior PCI	
Yes	2
No	0
Prior CABG	
Yes	2
No	0
Creatinine clearance <60 ml/min	
Present	2
Absent	0

Supplementary Table 3. Net benefit of using the PRECISE-DAPT and PARIS scores compared to alternative strategies for identifying **BARC type 3 or 5** bleeding risk conditional on different risk thresholds.

Risk threshold (%)	Net benefit of assuming all as low risk	Net benefit of assuming all as high risk	Net benefit of using PRECISE-DAPT	Net benefit of using PARIS
1	0%	0,9%	0,9%	0,9%
2	0%	-0,09%	0,38%	0,25%
3	0%	-1,07%	0,08%	0%

Note: net benefit at different risk thresholds is calculated as $\{\text{true-positive classifications} - [\% \text{ risk threshold} / (100 - \% \text{ risk threshold}) \times \text{false-positive classifications}]\} / \text{total number of participants}$.

The number of additional true positives per 100 patients the risk scores can identify without additional false positives, is calculated as follows: $(\% \text{ net benefit of using the score of interest} - \% \text{ net benefit of the alternative strategy in question}) / [\% \text{ risk threshold} / 100 - \text{risk threshold}]$. This value is the equivalent to the reduction in false positive without a decrease in the number of true positives. The calculated net benefits are relative to not use any risk score.

Class of risk of patients in the RENAMI registry

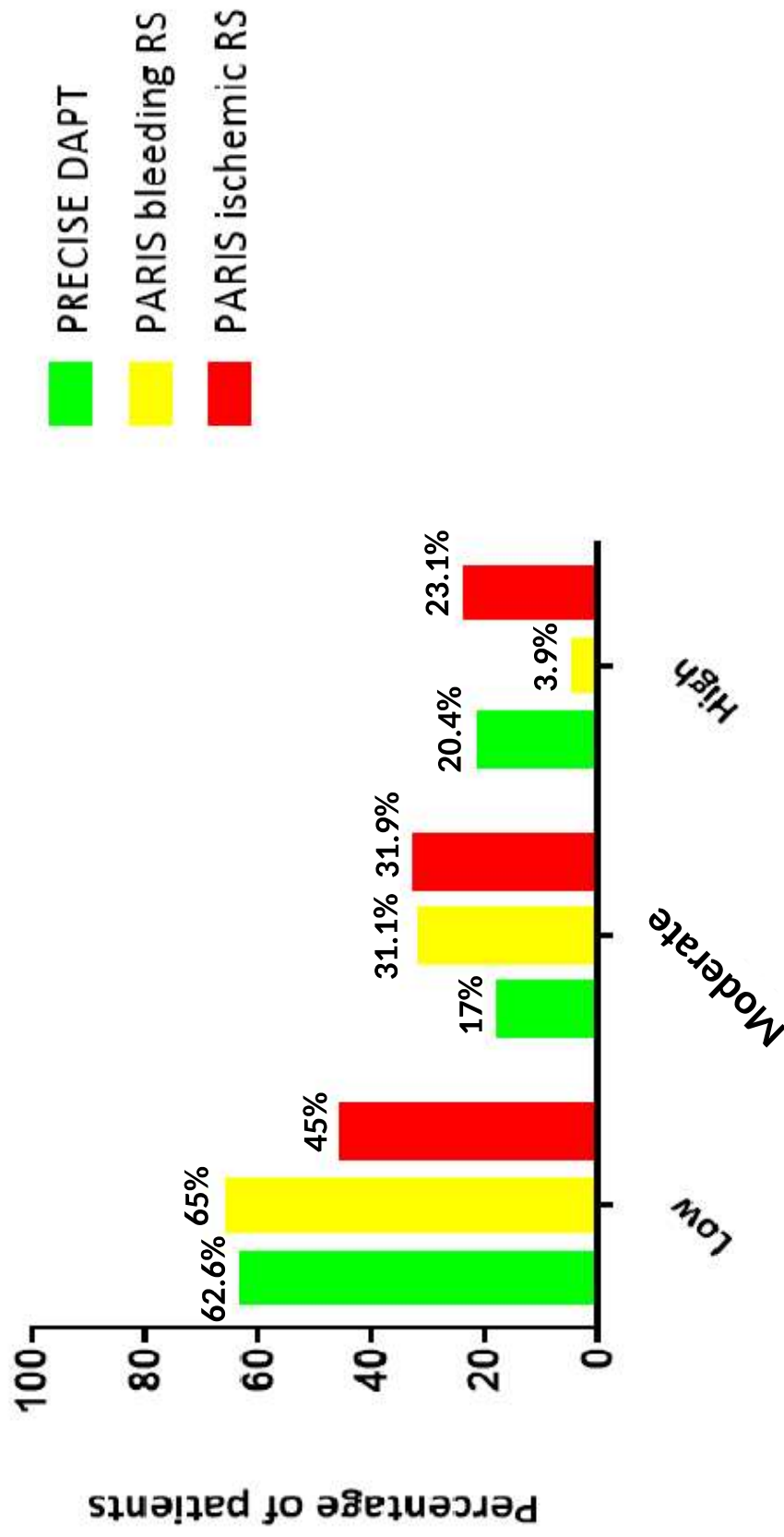


Figure 1. Patients risk class in the RENAMI registry using the PRECISE-DAPT, PARIS bleeding and PARIS ischemic risk scores.

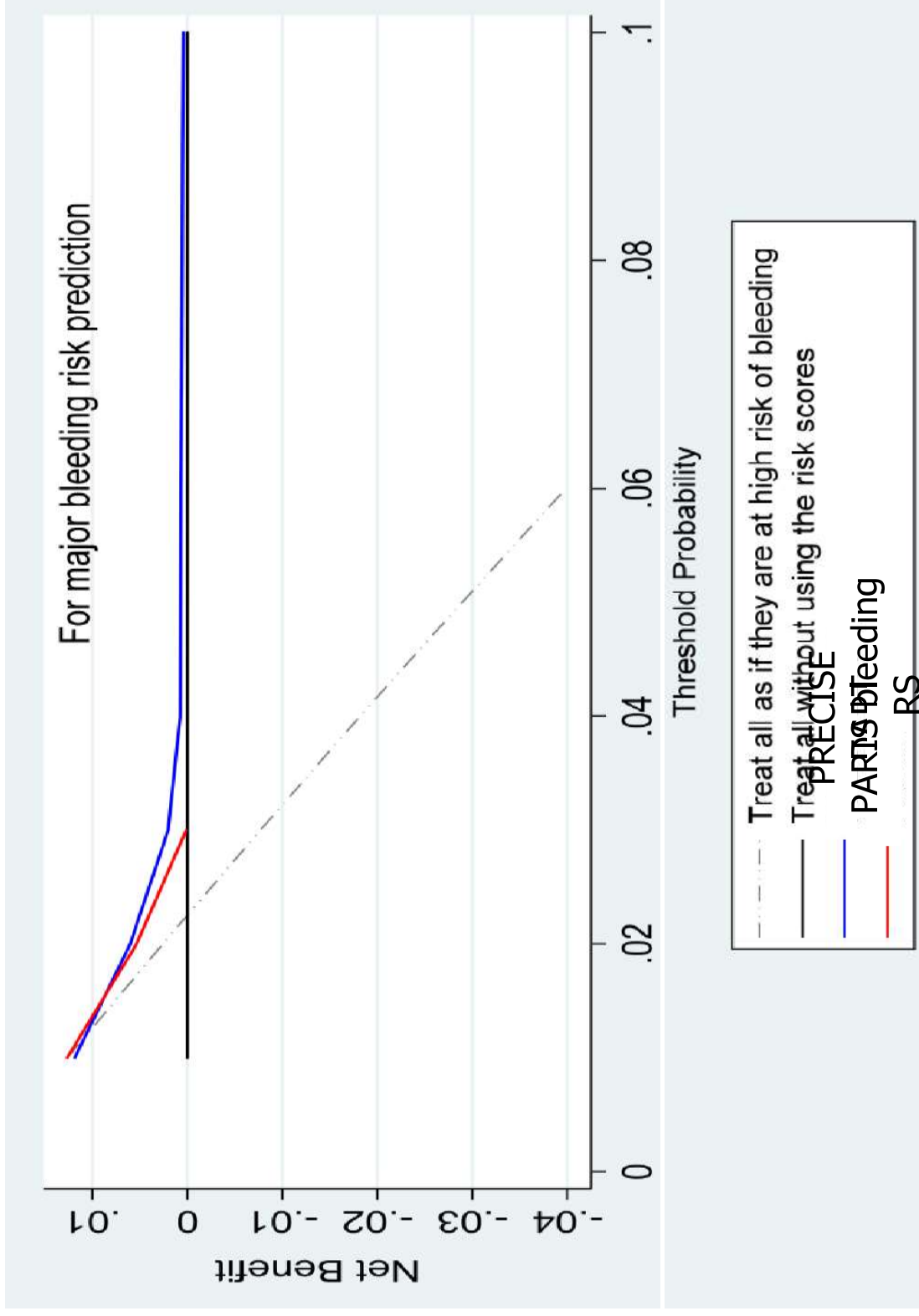


Figure 4: Decision curves for the PRECISE DAPT and PARIS bleeding RS derived risk thresholds for predicting MB bleeding.

	RENAMI	PRECISE-DAPT (derivation cohort)	PARIS (derivation cohort)
Number of patients	4424	14963	4190
Age (mean ± SD)	60.9 ± 11.5	---*	63.6±11.0
Age (median (IQR))	61.0 (53-69)	65.0 (56.9-73)	---*
Female, %	20.8	29.5	25.4
Weight, Kg	80.1 ± 13.8	74.0 (65-84)	---*
BMI (mean ± SD)	27.4 ± 4.1	---*	29.3±5.5
BMI median (IQR))	27 (25.0 - 29.0)	---*	---*
Active smoking, %	29.1	28	17.8
Hypertension (%)	54	71.9	81.4
Diabetes Mellitus (%)	29.9	27.8	34.1
LVEF (mean ± SD)	51.2 ± 9.4	---*	---*
Peripheral vascular disease,%	3.6	10.4	8
Prior MI,%	16.5	19.8	24.9
Prior PCI,%	17.9	---*	41.9
Prior CABG,%	0.9	---*	14.4
Prior stroke,%	5.2	3.6	3.5
Prior Bleeding,%	2.4	1.9	---*
Malignancy,%	4.5	---*	---*
UA,%	9	22.7	29.9
NSTEMI,%	33	14	7.9
STEMI,%	58	18.9	---*
Haemoglobin (mean ± SD)	14.1 ± 1.3		---*
Haemoglobin (median (IQR))	14 (13.2 - 14.5)	13.8 (12.7-14.9)	---*
Anaemia,%	1.9	---*	15
WBC count (10 ³ units/μL) (mean ±SD)	10602 ± 1381	---*	---*
WBC count (10 ³ units/μL) (median (IQR))	10.600 (8.200 - 12.335)	7.800 (6.300-10.200)	---*
CrCl (mL/min) (mean ±SD)	96.7 ± 37.3	79.1 (60.8-98.0)	---*
CrCl (mL/min) (median (IQR))	93 (71-118)		
CrCl <60 mL/min, %	15.9		17.8
DES,%	93	87.2	100
BMS,%	7	12.8	0
Treatment at discharge			
Aspirin,%	99.9	98.7	
Clopidogrel,%	0	87.7	92.1
Prasugrel,%	39	7.6	6.2
Ticagrelor,%	61	3.9	0
Statin,%	51	89.4	
ACE inhibitors/ARB II,%	34	66.7	
B-blocker,%	37	74.3	

Table 1: Baseline characteristics. LVEF= left ventricle ejection fraction. MI= myocardial infarction. PCI= percutaneous coronary intervention. CABG= coronary artery bypass graft. UA= unstable angina. NSTEMI=

non-ST segment elevated myocardial infarction. STEMI= ST segment elevated myocardial infarction.
ACE/ARB: ACE inhibitor or angiotensin-II receptor blocker. *Data not reported in the original study.

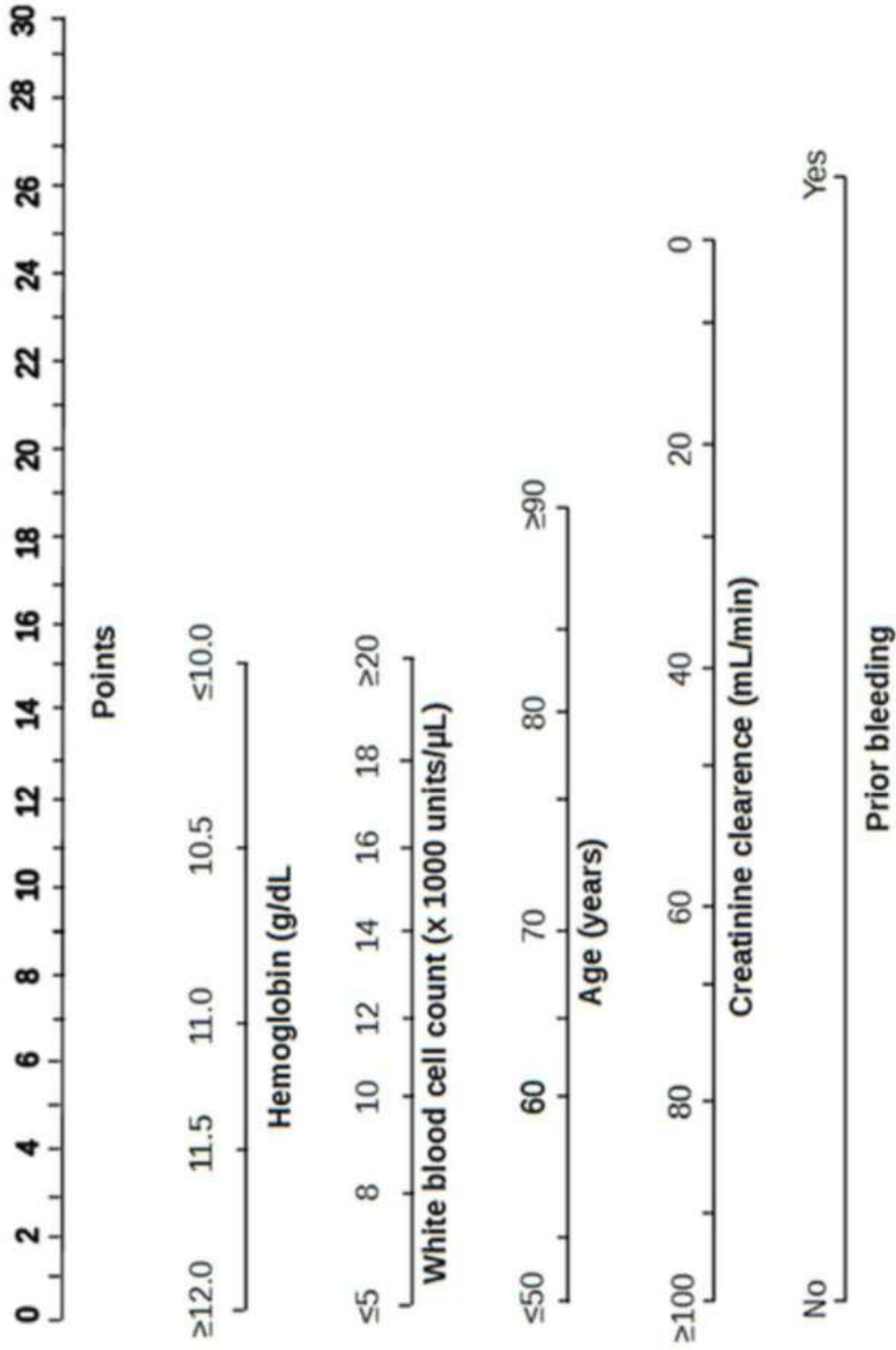
Discrimination capacity (C-statistic) for MB risk prediction by different DAPT durations		
	PRECISE DAPT	PARIS bleeding RS
Overall, n° of MB events= 83	0.653 (0.591-0.714)	0.593 (0.528-0.658)
12 months, n° of MB events= 44	0.624 (0.530-0.718)	0.526 (0.432-0.620)
More than 12 months, n° of MB events= 14	0.648 (0.491-0.805)	0.666 (0.514-0.818)
Less than 12 months, n° of MB events= 25	0.689 (0.596-0.782)	0.633 (0.517-0.749)
Discrimination capacity (C-statistic) for ischemic risk prediction by different DAPT durations		
	PRECISE DAPT	PARIS ischemic RS
Overall, n° of ischemic events= 133	0.568 (0.509-0.626)	0.604 (0.550-0.657)
12 months; n° of ischemic events= 54	0.525 (0.423-0.628)	0.571 (0.492-0.650)
More than 12 months; n° of ischemic events= 40	0.537 (0.431-0.643)	0.656 (0.564-0.755)
Less than 12 months n° of ischemic events= 39	0.648 (0.550-0.745)	0.597 (0.492-0.702)
Discrimination capacity (C-statistic) for MB risk prediction in STEMI patients		
	PRECISE DAPT	PARIS bleeding RS
n° of MB events in STEMI: 48	0.632 (0.547-0.717)	0.575 (0.487-0.663)
Discrimination capacity (C-statistic) for ischemic risk prediction in STEMI patients		
	PRECISE DAPT	PARIS ischemic RS
n° of ischemic events in STEMI: 70	0.574 (0.488-0.659)	0.629 (0.558-0.701)
Discrimination capacity (C-statistic) for MB risk prediction in NSTEMACS patients		
	PRECISE DAPT	PARIS bleeding RS
n° of MB events in NSTEMACS: 35	0.682 (0.597-0.767)	0.619 (0.524-0.713)
Discrimination capacity (C-statistic) for ischemic risk prediction in NSTEMACS patients		
	PRECISE DAPT	PARIS ischemic RS
n° of ischemic events in NSTEMACS: 63	0.551 (0.473-0.628)	0.569 (0.489-0.650)
Discrimination capacity (C-statistic) for MB risk prediction in prasugrel patients		
	PRECISE DAPT	PARIS bleeding RS
n° of MB events in prasugrel treated pts: 25	0.623 (.504-.743)	0.586 (0.460-0.713)
Discrimination capacity (C-statistic) for ischemic risk prediction in prasugrel patients		
	PRECISE DAPT	PARIS ischemic RS
n° of ischemic events in prasugrel treated pts: 49	0.525 (0.429-0.620)	0.639 (0.551-0.727)
Discrimination capacity (C-statistic) for MB risk prediction in ticagrelor patients		
	PRECISE DAPT	PARIS bleeding RS
n° of MB events in ticagrelor treated pts: 58	0.648 (0.576-0.719)	0.573 (0.499-0.6488)
Discrimination capacity (C-statistic) for ischemic risk prediction in ticagrelor patients		
	PRECISE DAPT	PARIS ischemic RS
n° of ischemic events in ticagrelor treated pts: 84	0.585 (0.514-0.657)	0.574 (0.505-0.642)
Discrimination capacity (C-statistic) for MB risk prediction in patients > 75 years		
	PRECISE DAPT	PARIS bleeding RS
n° of MB events in the 581 pts > 75 years: 21	0.621 (0.559 - 0.691)	0.603 (0.547 - 0.663)
Discrimination capacity (C-statistic) for MB risk prediction in patients with serum creatinine > 1.5 mg/dl		

	PRECISE DAPT	PARIS bleeding RS
n° of MB events in the 261 pts with serum creatinine > 1.5 mg/dl: 7	0.744 (0.626 - 0.864)	0.693 (0.587 - 0.803)

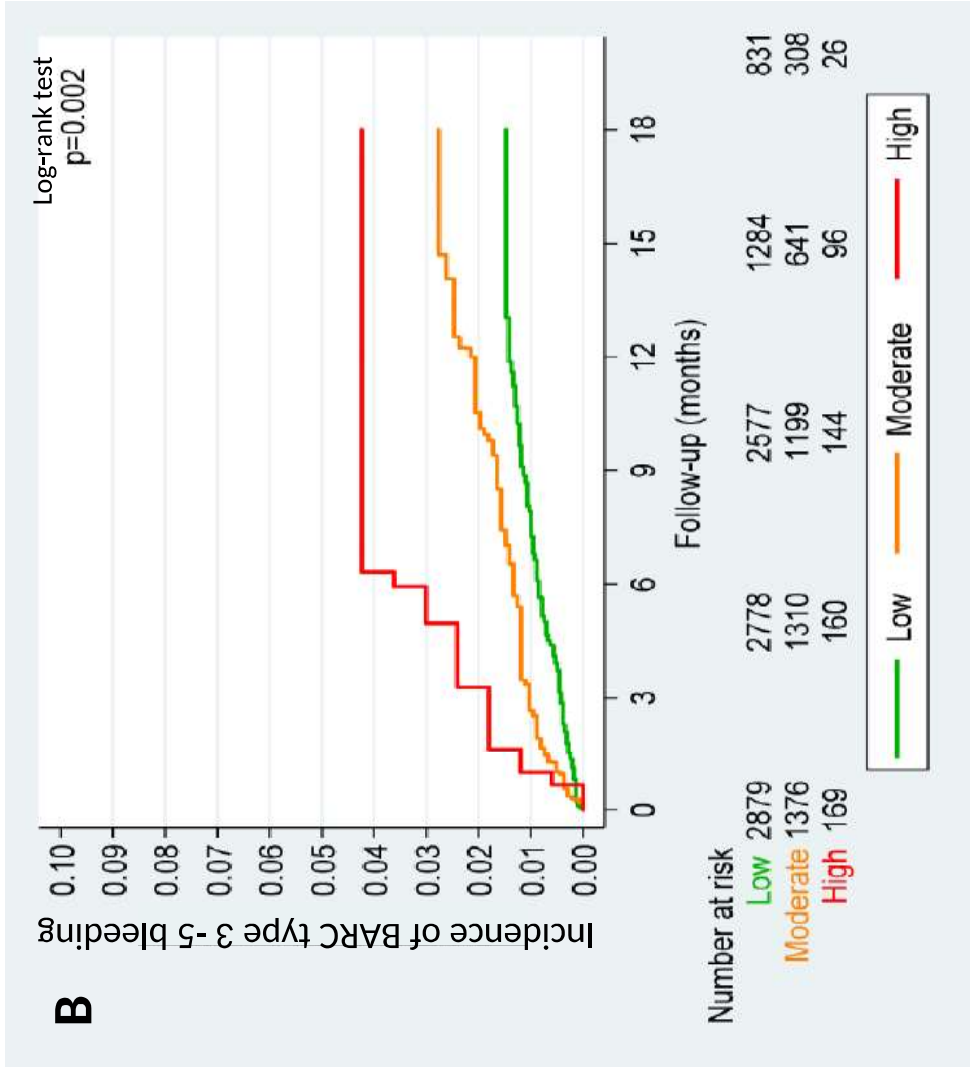
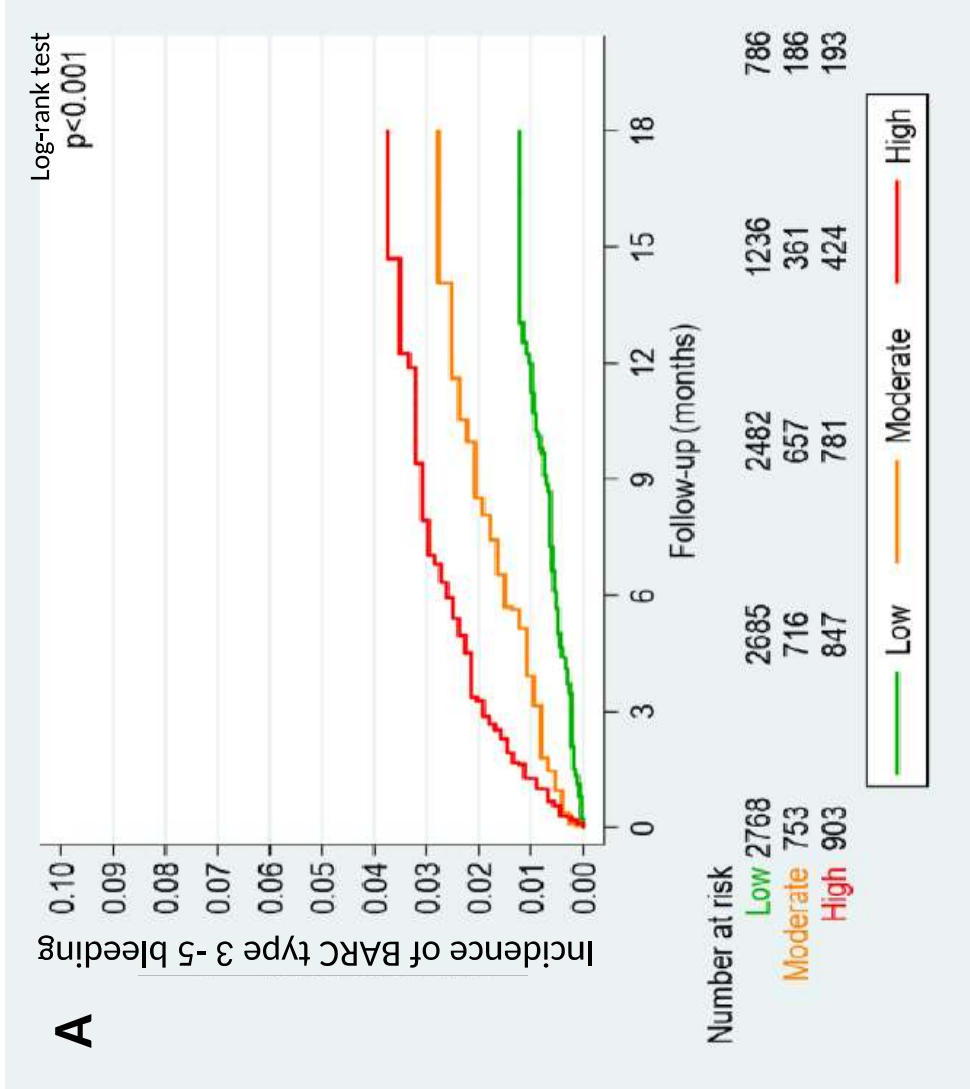
Table 2: C-statistic analysis for RSs accuracy for different subgroups of patients.

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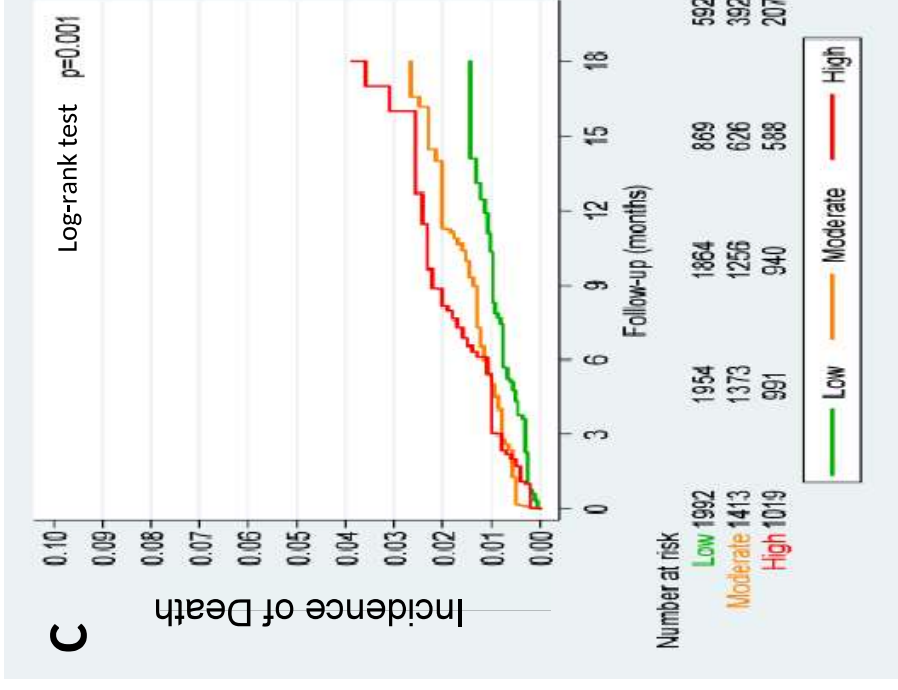
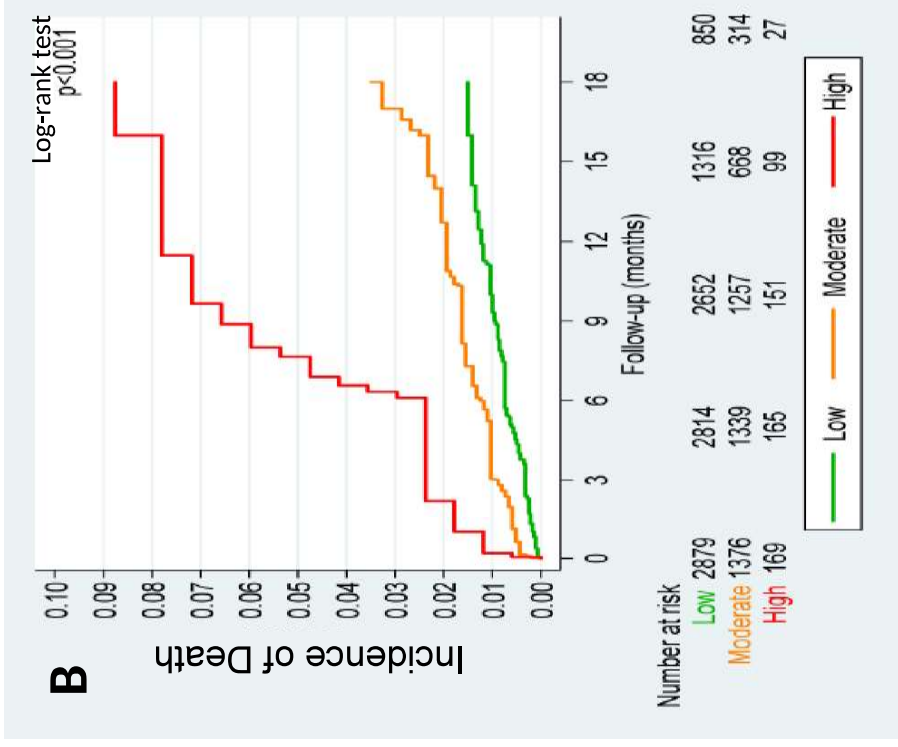
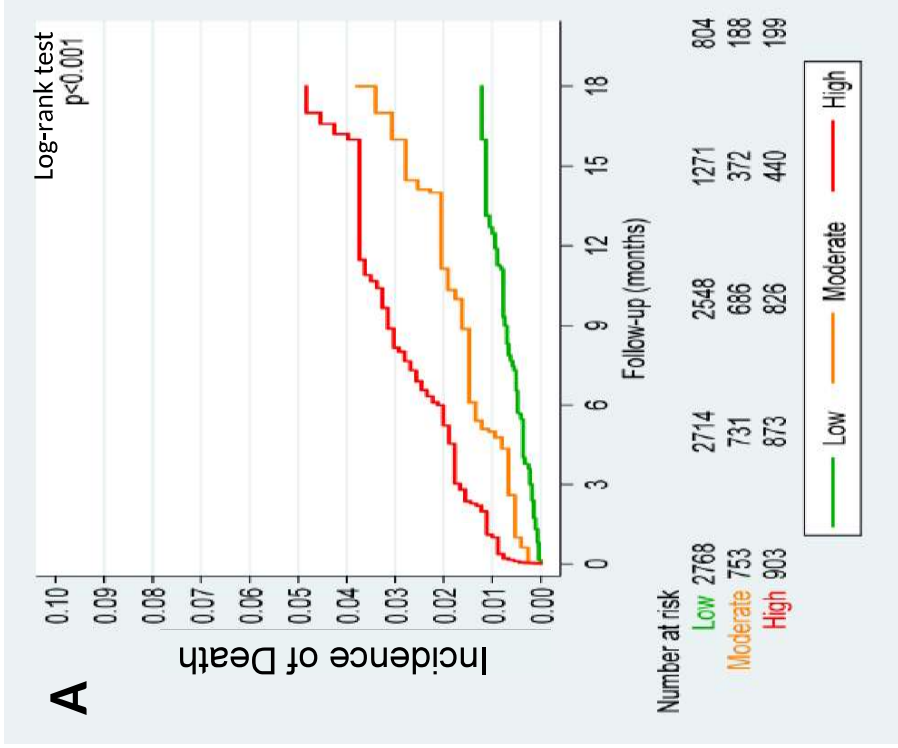
None of the other authors have any conflict of interests to declare



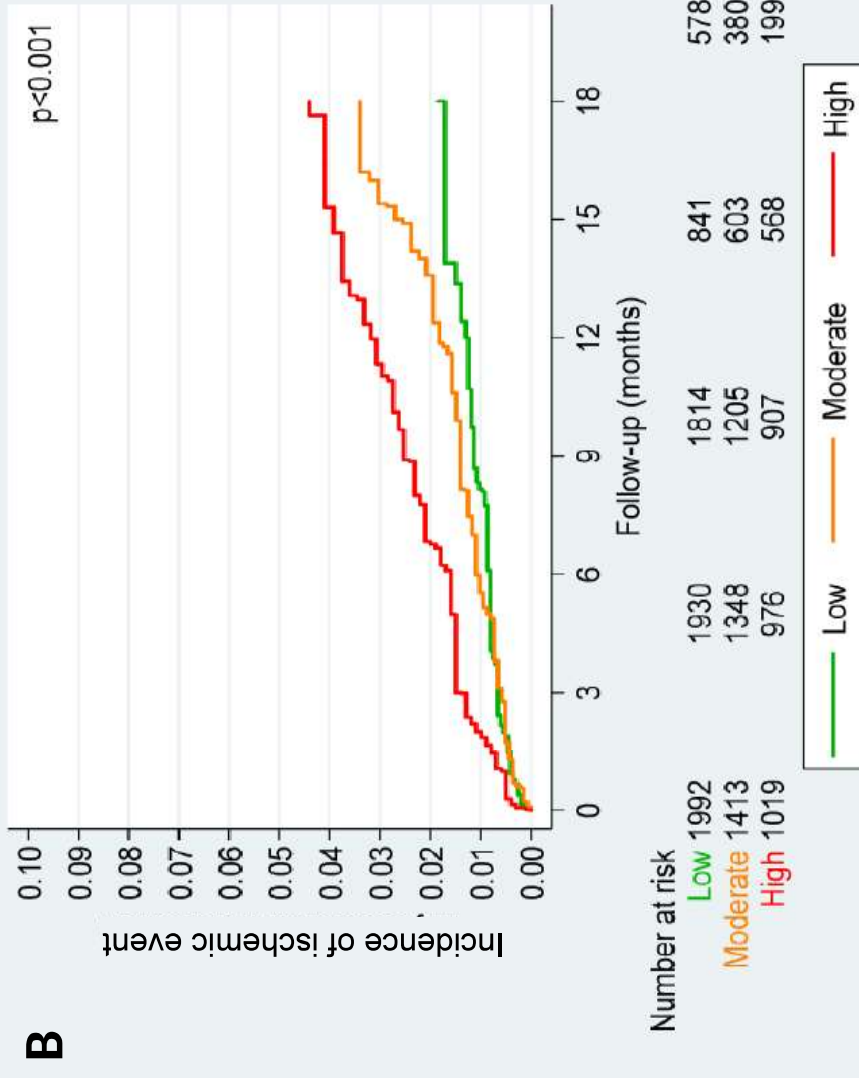
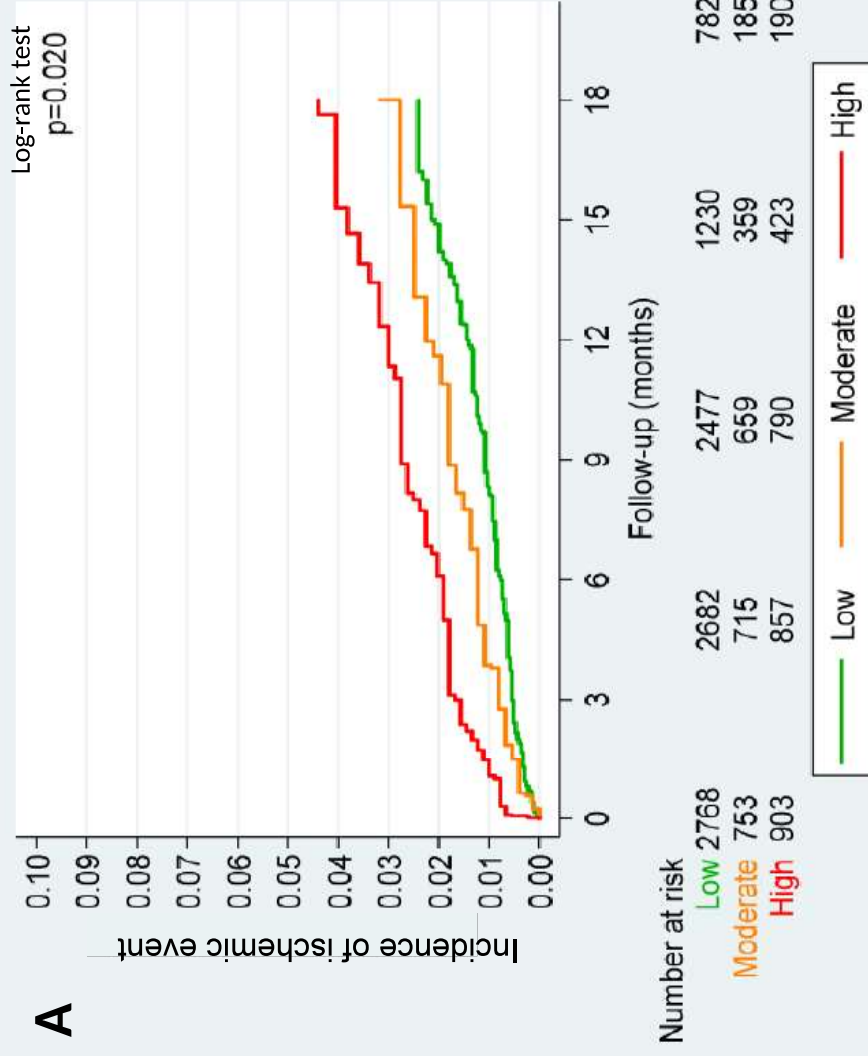
Supplementary materials figure 1: variables comprising the PRECISE-DAPT bleeding risk score.



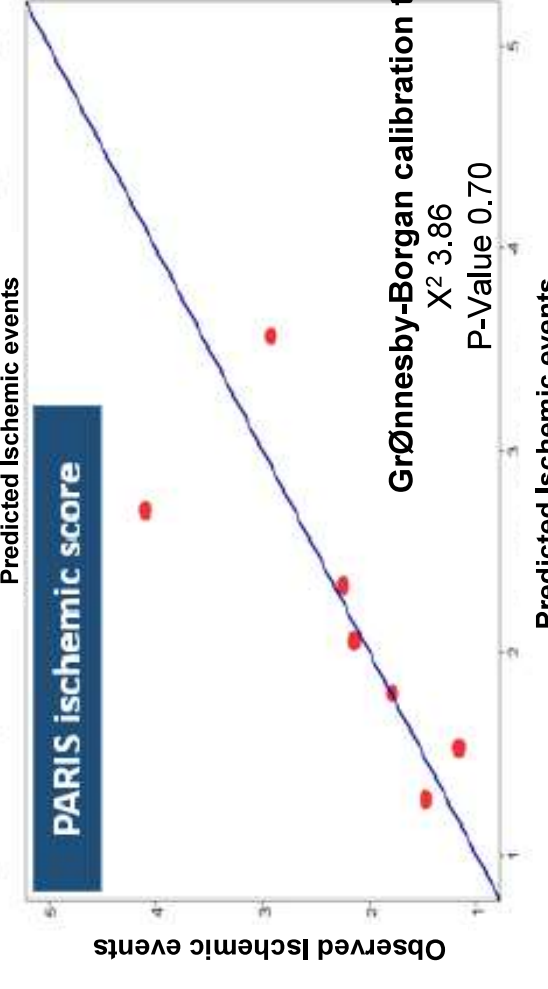
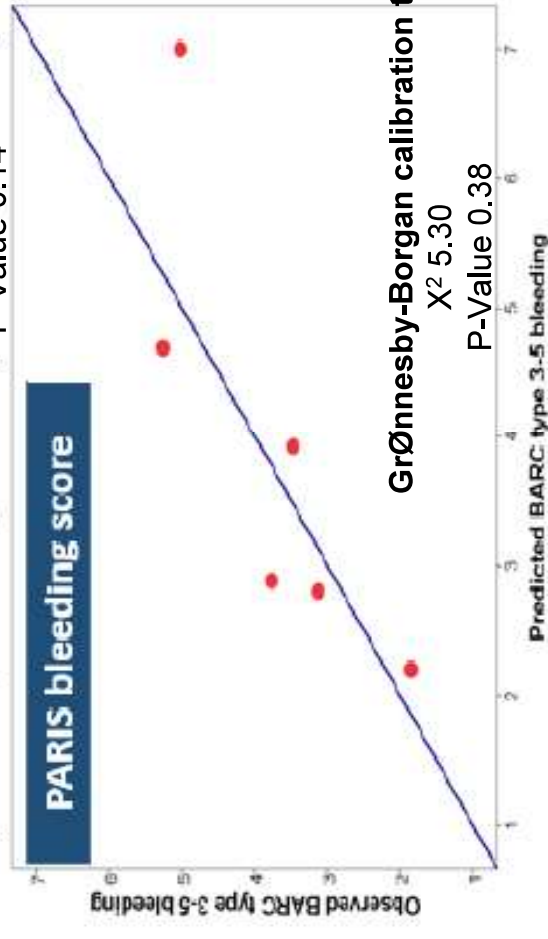
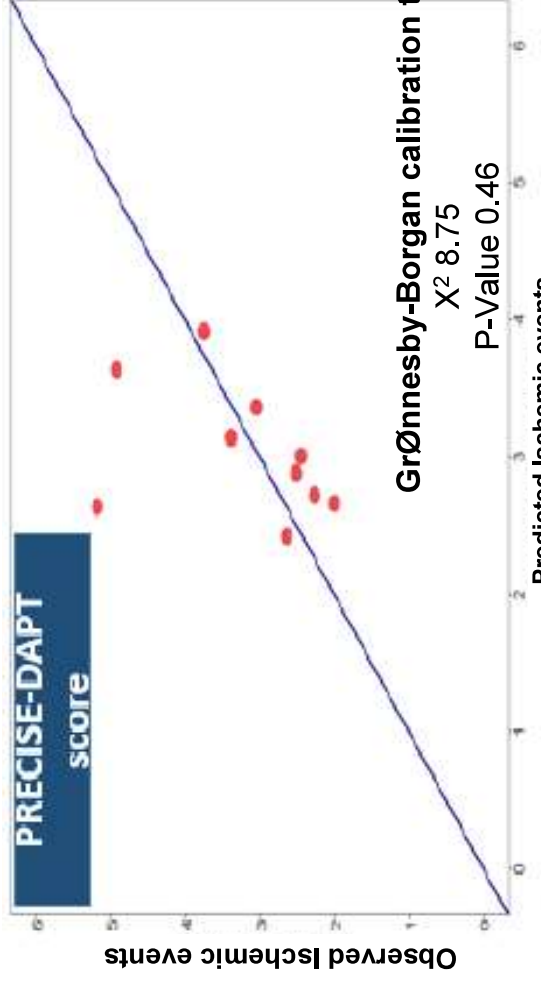
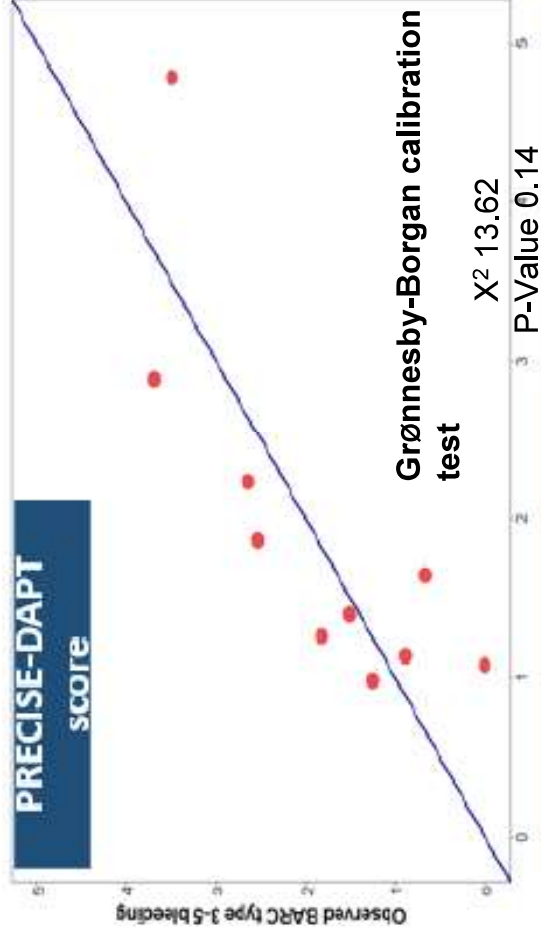
Supplementary Figure 2. Kaplan-Meier curves for BARC type 3 or 5 bleeding. A) Using PRECISE-DAPT classification system, and B) using PARIS bleeding risk classification system.



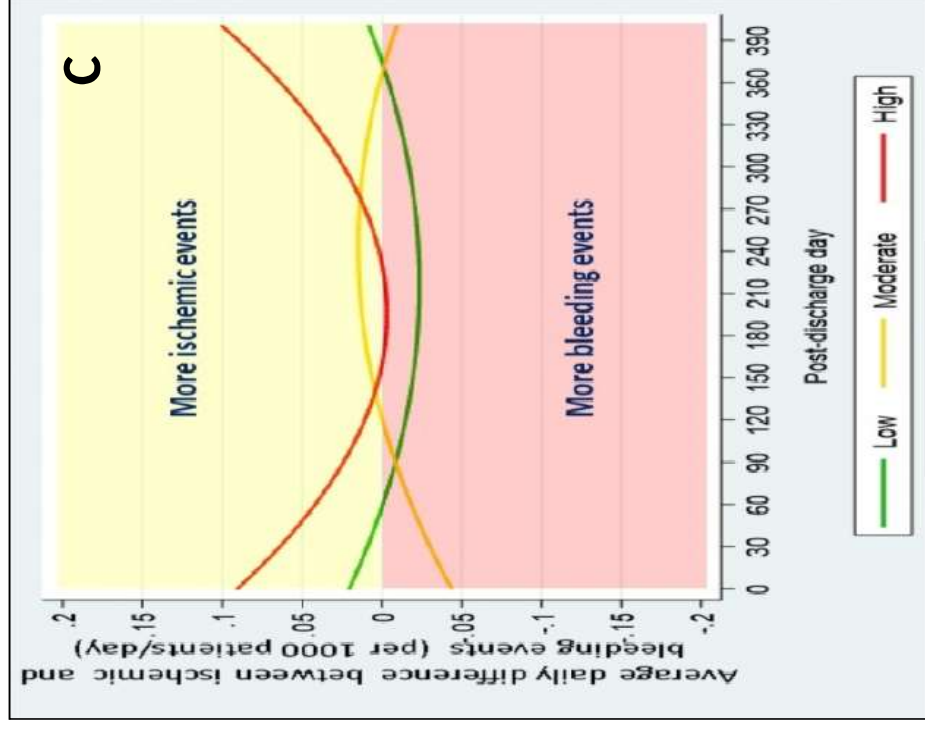
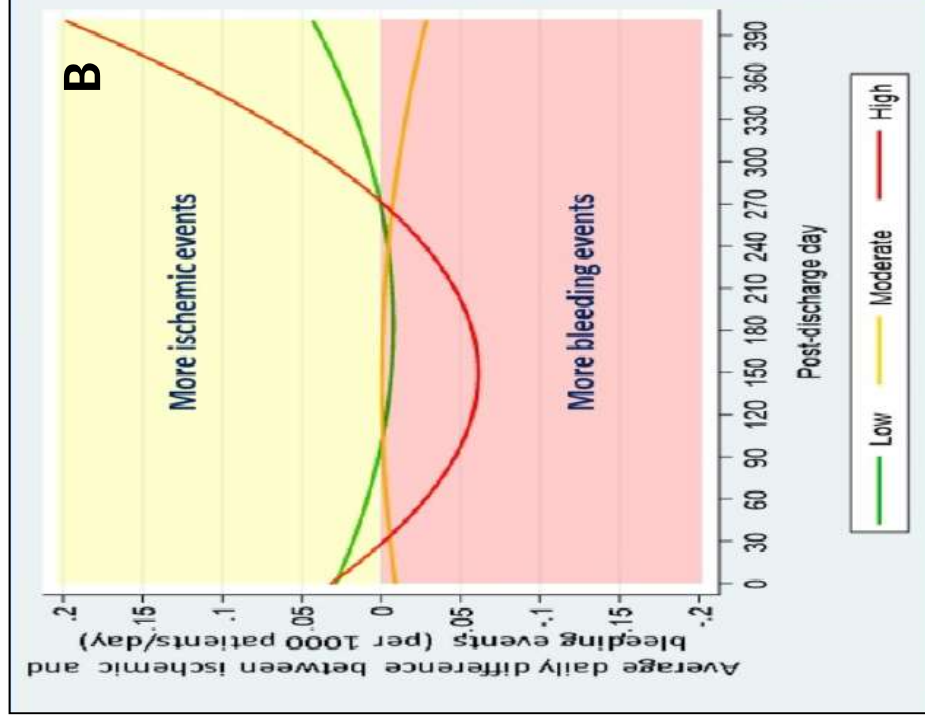
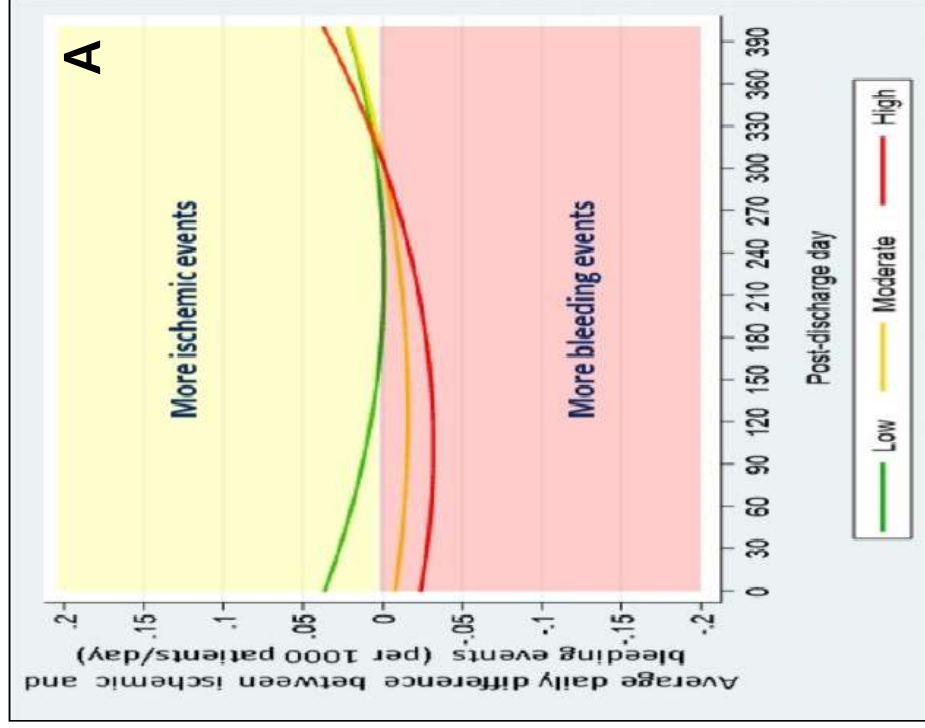
Supplementary materials figure 3. Kaplan-Meier curves for cardiovascular death. A) Using PRECISE-DAPT risk strata. B) Using PARIS ischemic risk strata. C) Using PARIS RS risk strata.



Supplementary materials figure 4. Kaplan-Meier curves for Myocardial infarction/stent thrombosis. A) Using PRECISE-DAPT risk strata. B) Using PARIS ischemic RS risk strata.



- Supplementary Figure 5: Calibration of predicted against observed MB and ischemic events (MI and ST) with RSs.



Supplementary materials figure 6. Average daily difference between ischemic and bleeding events. A) Using PRECISE-DAPT B) Using PARIS bleeding RS risk. C) Using PARIS ischemic RS.