


## ORIGINAL ARTICLE

# Blood loss after coronary artery bypass by aspirin responsiveness assessed with preoperative VerifyNow aspirin testing

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## Funding information

The POPular CABG trial was funded by AstraZeneca. AstraZeneca had no role in the study design, data collection, data analysis, data interpretation, or writing of the report of the trial or this substudy.

**Handling Editor:** Dr Cihan Ay

## Abstract

**Background:** Aspirin is important for preventing thrombotic events but also increases bleeding complications. Minimizing bleeding while preventing thrombotic events remains challenging in patients undergoing coronary artery bypass grafting (CABG). Establishing the patient's preoperative aspirin response could distinguish patients at risk for perioperative blood loss.

**Objective:** Aim was to compare 12-h blood loss after CABG between aspirin-sensitive and aspirin-resistant patients.

**Patients/Methods:** The primary analysis of this substudy of the POPular CABG trial (NCT02352402) included patients that used aspirin monotherapy preoperatively. A preoperative platelet function test by the VerifyNow aspirin assay was performed before CABG and patients were classified as aspirin-sensitive or aspirin-resistant based on an aspirin reaction units cutoff value of 550. The primary end point was 12-hour blood loss after CABG. The secondary end point was, among others, clinical bleeding events after CABG.

**Results:** A total of 128 patients were included in the primary analysis. Of these, 116 patients were aspirin sensitive and 12 were aspirin resistant. Mean blood loss 12 hours after CABG was  $555 \pm 278$  mL in aspirin-sensitive patients and  $406 \pm 110$  mL in aspirin-resistant patients ( $P = .04$ ). All bleeding events ( $n = 15$ ; 11.7%) occurred in aspirin-sensitive patients.

**Conclusions:** In patients who are on aspirin preoperatively, aspirin sensitivity was associated with 12-hour blood loss after CABG, suggesting that preoperative VerifyNow aspirin testing could identify patients undergoing CABG at high risk for perioperative bleeding.

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**KEYWORDS**

aspirin, cardiovascular surgical procedures, coronary artery bypass, platelet function tests, blood loss, surgical

**Essentials**

- Balancing thrombotic and bleeding complications is a challenge in coronary artery bypass grafting (CABG).
- Our aim was to compare 12-hour blood loss between aspirin-sensitive and aspirin-resistant patients.
- Twelve-hour blood loss did differ between aspirin-sensitive and aspirin-resistant patients.
- VerifyNow aspirin testing could identify patients undergoing CABG at risk for perioperative bleeding.

## 1 | INTRODUCTION

Relevant guidelines, including the 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines on myocardial revascularization, recommend initiating or continuing aspirin throughout the perioperative period in both stable and unstable patients undergoing coronary artery bypass grafting (CABG),<sup>1-3</sup> as early postoperative use of aspirin is associated with a reduction in death and ischemic complications involving heart, brain, kidneys, and the gastrointestinal tract.<sup>4</sup> Nonetheless, the advantages of perioperative aspirin use are accompanied by a higher risk of perioperative and postoperative bleeding complications.<sup>5-8</sup>

Not all patients display the same level of inhibitory response to aspirin. A proportion of patients, ranging from 10% to 90% (depending on the platelet function test used and timing of platelet function testing<sup>9</sup>) demonstrate insufficiently suppressed platelets after CABG despite optimal perioperative aspirin administration. This phenomenon is known as aspirin resistance.<sup>9,10</sup> Although it is hypothesized that aspirin-resistant patients are at increased risk of thrombotic events,<sup>11</sup> they might also have a lower bleeding risk, whereas aspirin-sensitive patients might have lower risk of thrombotic events but increased bleeding risks. Quickly and correctly identifying the preoperative, baseline response to aspirin could be an important factor in distinguishing patients at risk for perioperative blood loss in cardiovascular surgical procedures.

Therefore, the aim of this study was to determine if aspirin responsiveness, determined by preoperative VerifyNow aspirin assay testing (Accumetrics, San Diego, CA, USA), is associated with blood loss within 12 hours after CABG.

## 2 | METHODS

### 2.1 | Study design

This was a post hoc substudy from the POPular CABG trial (Effect of Adding Ticagrelor to Standard Aspirin on Saphenous Vein Graft Patency in Patients Undergoing Coronary Bypass Grafting; NCT02352402). The study was designed in compliance with the Declaration of Helsinki and was approved by the relevant ethics committees and review boards. The POPular CABG was a

randomized, double-blind, placebo-controlled trial that investigated the effect of ticagrelor in addition to standard aspirin on saphenous vein graft (SVG) patency 1 year after CABG. The rationale and design of the trial have been published, as well as the results of the primary end point.<sup>12,13</sup>

### 2.2 | Population

Patients who underwent planned CABG with one or more SVGs were eligible for participation. Major exclusion criteria were, among others, use of oral anticoagulation after CABG or a definite indication for use of a P2Y<sub>12</sub> inhibitor or antithrombotic agent other than aspirin after CABG. All patients provided written informed consent for the POPular CABG trial, and patients who wanted to participate in this substudy also provided oral informed consent for the blood sampling. In the main study, patients were randomized in the two study groups after a second screening after CABG to ensure that patients did receive a SVG during surgery as planned. Patients who were not included in the POPular CABG trial because they did not meet the criteria of this second screening, but did consent to the trial and underwent blood sampling preoperatively, were included in this substudy. For this substudy, all patients who used a P2Y<sub>12</sub> inhibitor within 48 hours before CABG were excluded, as P2Y<sub>12</sub> inhibition before cardiac surgery is a well-known risk factor for blood loss.

### 2.3 | Platelet function testing by the VerifyNow assay

Blood was sampled using venipuncture with 21-gauge needles before CABG. After a 5 mL discard tube, 1 Greiner Bio-One partial fill Vacuette vacuum collection tube of whole blood (2 mL), anticoagulated with 3.2% sodium citrate, was withdrawn from each subject. The tubes were gently rotated at least 5 times to ensure complete mixing of the citrate with blood. The assay was performed according to manufacturer's instructions. All platelet function analyses were performed between 30 minutes and 4 hours after blood sampling. Results of the preoperative VerifyNow assay remained unknown to all operation personnel. Based on the results of the preoperative VerifyNow assay, patients were classified as aspirin sensitive (aspirin

reaction units [ARU] value <550) or aspirin resistant (ARU value  $\geq$ 550). This cutoff value for aspirin-responsiveness is set by the manufacturer<sup>14</sup> and has been accepted in the medical literature.<sup>15-17</sup>

## 2.4 | Blood loss

The primary end point of this study was blood loss 12 hours after CABG, defined as 12-hour chest tube production. We also evaluated total drain production 12 hours after CABG (chest tube + leg drainage), as well as chest tube and total drain production at 1 hour and 6 hours after CABG and clinical bleeding events 12 hours after CABG. All bleeding events, except for chest tube output, were defined according to the universal definition of perioperative bleeding in cardiovascular surgical procedures<sup>18</sup> (Table S1). As packed red blood cell transfusions were often supplied during surgery to correct for a low baseline hemoglobin or induced hemodilution as a consequence of cardiopulmonary bypass (CPB) and not always for bleeding, it was decided to exclude class 1 bleeding events.

## 2.5 | Statistical analysis

Continuous data are presented as mean  $\pm$  standard deviation (SD) for normally distributed data, and median and interquartile range for nonnormally distributed data. Categorical data are presented as numbers and percentages. To compare independent continuous variables between groups for normally and nonnormally distributed variables, the Student's *t* test and the Mann-Whitney *U* test were used. For categorical data the chi-squared test or Fisher's exact test was used.

Statistical significance was assumed when the *P* value was  $<.05$ . All statistical analyses were performed using SPSS statistical software for Windows version 24 (IBM Corporation, Armonk, NY, USA).

## 3 | RESULTS

### 3.1 | Trial population

Table 1 shows baseline and procedural characteristics of patients and procedures, respectively. Of 128 patients included, 12 patients displayed a preoperative ARU value of  $\geq$ 550 ARU and were classified as aspirin resistant. In the total population, the mean age was 69 years, and 87% were men. Indication for CABG was acute coronary syndrome in 24% of cases, and CABG was performed with CPB in 99% of cases. No significant differences in the baseline characteristics of aspirin-resistant and aspirin-sensitive patients were identified. Preoperative and direct postoperative hemoglobin, hematocrit, and platelet count were comparable in both groups (Table 1). All patients used aspirin preoperatively. None of the patients used preoperative anticoagulation therapy. Five patients used a P2Y<sub>12</sub> inhibitor >48 hours before CABG. Four patients used ticagrelor, this was

discontinued 5 days preoperatively in one patient, and 3 days preoperatively in three patients. One patient used clopidogrel; this was halted 5 days preoperatively. All five patients were aspirin sensitive and none of the patients used antithrombotic therapy other than aspirin or anticoagulation therapy within 12 hours after CABG (as this was an exclusion criterion for the trial).

### 3.2 | Primary outcome

Mean blood loss 12 hours after CABG was  $555 \pm 278$  mL in the aspirin-sensitive group and  $406 \pm 110$  in the aspirin-resistant group ( $P = .04$ ; Table 2, Figure 1). Individual ARU values and 12-hour blood loss are plotted in Figure 2.

### 3.3 | Secondary outcomes

Total drain production at 12 hours was  $631 \pm 302$  mL in the aspirin-sensitive group and  $458 \pm 128$  in the aspirin-resistant group ( $P = .04$ ). Results of chest tube and total drain production at 1 hour were comparable between aspirin-resistant and aspirin-sensitive groups. At 6 hours, both results of chest tube and total drain production differed between aspirin-sensitive and aspirin-resistant groups. All secondary outcomes rendered higher blood loss in the aspirin-sensitive group (Table 2). In total, 15 patients (11.7%) experienced bleeding events during or up to 12 hours after CABG, 12 events were categorized as class 2 events and 3 events as class 3. All patients experiencing bleeding events were classified as aspirin sensitive.

## 4 | DISCUSSION

This substudy of the POPular CABG randomized controlled trial investigated whether preoperative platelet function testing of aspirin responsiveness with the VerifyNow aspirin assay was associated with blood loss after CABG. We found a significant association between VerifyNow aspirin responsiveness and blood loss in patients who used aspirin preoperatively. In addition, all bleeding complications occurred in the aspirin-sensitive group.

Some studies have investigated the relationship between aspirin responsiveness as measured with the VerifyNow aspirin assay and postoperative blood loss in cardiovascular surgical procedures. Takiuchi et al<sup>19</sup> enrolled 114 Japanese patients undergoing cardiac surgery, of which 30 underwent off-pump CABG, of which 11 used only aspirin preoperatively (11 used aspirin + clopidogrel, 1 used aspirin + cilostazol, 1 used warfarin, 1 used aspirin + warfarin, and 4 used no antithrombotic medication). In these patients undergoing CABG, they established a weak inverse correlation ( $r_s = -0.18$ ), between preoperative ARU values and 24-hour blood loss, but this was not significant, probably because of the small sample size. Welsh et al<sup>20</sup> retrospectively enrolled 88 patients that underwent cardiac surgery (12.5% CABG) and had VerifyNow aspirin testing.

**TABLE 1** Baseline and procedural characteristics

	Total population (N = 128)	Aspirin-sensitive patients (N = 116)	Aspirin-resistant patients (N = 12)	P value
<b>Demographic characteristics</b>				
Age, y, mean $\pm$ SD	69 $\pm$ 8	69 $\pm$ 8	67 $\pm$ 9	.49
Male sex, n (%)	111 (86.7)	100 (86.2)	11 (91.7)	1.0
Body mass index, kg/m <sup>2</sup> , mean $\pm$ SD	27.2 $\pm$ 3.9	27.2 $\pm$ 3.9	26.6 $\pm$ 4.2	.61
eGFR < 60, mL/min/1.73 m <sup>2</sup> , n (%)	24 (18.8)	22 (19.0)	2 (16.7)	1.0
Current smoker, <sup>a</sup> n (%)	19 (14.8)	15 (13.0)	4 (33.3)	.08
<b>Indication for CABG</b>				
Acute coronary syndrome, n (%)	31 (24.2)	30 (28.3)	1 (9.1)	.28
Chronic coronary syndrome, n (%)	86 (67.2)	76 (71.7)	10 (90.9)	
<b>Medical history</b>				
Diabetes mellitus, n (%)	28 (21.9)	25 (21.6)	3 (25.0)	.72
Hypertension, n (%)	79 (61.7)	74 (63.8)	5 (41.7)	.21
Hypercholesterolemia, <sup>b</sup> n (%)	56 (43.8)	48 (41.4)	8 (66.7)	.09
Prior PCI, n (%)	28 (21.9)	26 (22.4)	2 (16.7)	1.0
Prior CABG, n (%)	2 (1.6)	2 (1.7)	0 (0)	NA
<b>Preoperative laboratory results</b>				
Hemoglobin, mmol/L, mean $\pm$ SD	9.0 $\pm$ 0.8	9.0 $\pm$ 0.8	9.0 $\pm$ 0.9	.99
Hematocrit, L/L, mean $\pm$ SD	0.42 $\pm$ 0.04	0.42 $\pm$ 0.04	0.42 $\pm$ 0.04	.71
Platelet count, ( $\times 10^3$ per mm <sup>3</sup> , mean $\pm$ SD	241 $\pm$ 59	242 $\pm$ 59	231 $\pm$ 64	.71
<b>Medication</b>				
Start of aspirin <5 days preoperatively, n (%)	11 (8.6)	10 (8.6)	1 (8.3)	1.0
Use of P2Y <sub>12</sub> inhibitor >48 h before CABG	5 (3.9)	5 (4.3)	0 (0)	1.0
<b>Intraoperative characteristics</b>				
On-pump CABG, n (%)	127 (99.2)	115 (99.1)	12 (100.0)	1.0
Time on cardiopulmonary bypass, hh:mm, mean $\pm$ SD	01:28 $\pm$ 00:25	01:27 $\pm$ 00:23	01:35 $\pm$ 00:37	.61
Administering of tranexamic acid, n (%)	183 (64.8)	75 (64.7)	8 (66.8)	1.0
Intraoperative RBC transfusion, <sup>c</sup> n (%)	7 (5.5)	7 (6.0)	0 (0)	NA
Cellsaver transfusion, mL, -mean $\pm$ SD	322 (269)	321 (270)	333 (268)	.89
<b>Direct postoperative laboratory results<sup>d</sup></b>				
Hemoglobin, mmol/L, mean $\pm$ SD	6.6 $\pm$ 0.9	6.6 $\pm$ 0.8	7.0 $\pm$ 1.0	.10
Hematocrit, L/L, mean $\pm$ SD	0.32 $\pm$ 0.07	0.31 $\pm$ 0.07	0.33 $\pm$ 0.05	.11
Platelet count, $\times 10^3$ per mm <sup>3</sup> , mean $\pm$ SD	153 $\pm$ 40	153 $\pm$ 39	156 $\pm$ 51	.82

Note: Plus-minus values are means  $\pm$  SD.

Abbreviations: CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; NA, not available; PCI, percutaneous coronary intervention; RBC, red blood cell; SD, standard deviation.

<sup>a</sup>Defined as current smoker or quit smoking < 3 months.

<sup>b</sup>Defined as diagnosis in medical history or low-density lipoprotein  $\geq$  2.5 mmol/L, high-density lipoprotein < 1.1 mmol/L, total cholesterol > 6.5 mmol/L, and/or triglycerides  $\geq$  2.2 mmol/L.

<sup>c</sup>Defined as administered intraoperatively or <1 h after operation.

<sup>d</sup>Defined as first lab results after CABG, in 90% of cases within 1 h after CABG.

Of 88 patients in this study, 11 (12.5%) had significant bleeding during or after surgery. Five of these patients were aspirin sensitive ( $P = .32$ ). VerifyNow ARU values for patients with significant bleeding did not significantly differ from patients without significant bleeding (546.5  $\pm$  61.2 vs 519.1  $\pm$  77.2). The study of Kim et al<sup>21</sup> prospectively included 220 aspirin-taking patients undergoing elective

off-pump CABG. Patients who used other antiplatelet or anticoagulant medication were excluded from the study. The patients were divided in aspirin responders and aspirin nonresponders according to the VerifyNow aspirin assay. They identified 181 aspirin responders (82.3%) and 39 aspirin nonresponders (17.7%). Blood loss 12 hours after surgery, defined as the volume of the mediastinal

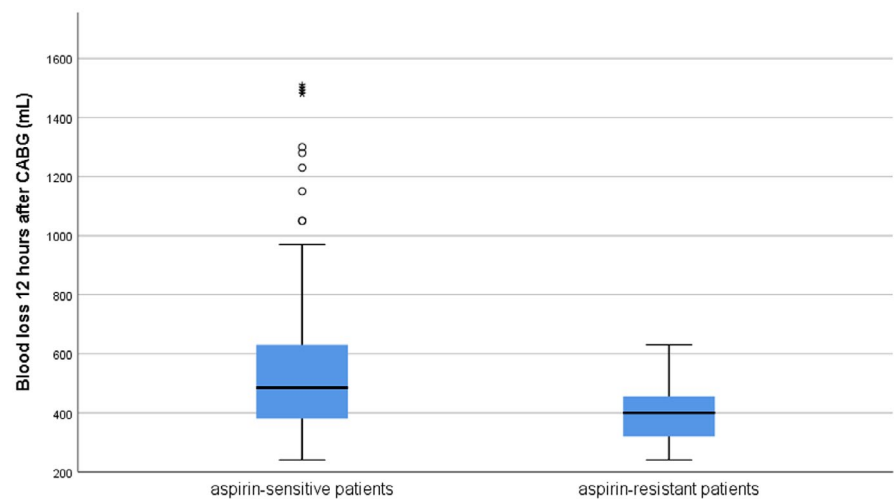
**TABLE 2** Primary and secondary outcomes regarding chest tube and total drain production over time

	Total population (N = 128)	Aspirin-sensitive patients (N = 116)	Aspirin-resistant patients (N = 12)	P value
Chest tube production at 1 h after CABG, mL, mean $\pm$ SD	103 $\pm$ 76	105 $\pm$ 78	78 $\pm$ 40	.36
Total drain production 1 h after CABG, mL, mean $\pm$ SD	159 $\pm$ 121	163 $\pm$ 124	122 $\pm$ 81	.40
Chest tube production at 6 h after CABG, mL, mean $\pm$ SD	375 $\pm$ 220	386 $\pm$ 226	265 $\pm$ 88	.05
Total drain production 6 h after CABG, mL, mean $\pm$ SD	438 $\pm$ 239	451 $\pm$ 245	316 $\pm$ 114	.06
Chest tube production 12 h after CABG, mL, mean $\pm$ SD	541 $\pm$ 271	555 $\pm$ 278	406 $\pm$ 110	.04
Total drain production 12 h after CABG, mL, mean $\pm$ SD	615 $\pm$ 294	631 $\pm$ 302	458 $\pm$ 128	.04

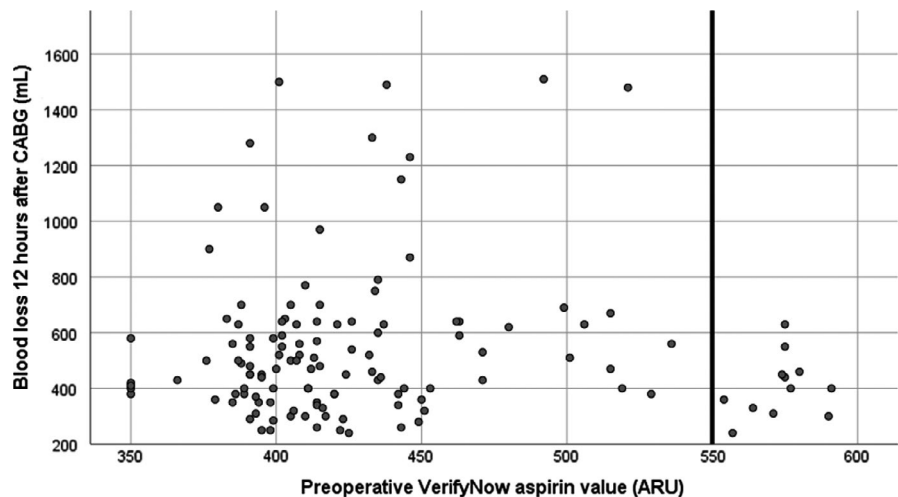
Note: Plus-minus values are means  $\pm$  SD.

Abbreviation: CABG, coronary artery bypass grafting.

**FIGURE 1** Boxplot of 12-h blood loss after CABG by aspirin-resistant or aspirin-sensitive patients. The horizontal black line is the median value; boxes extend from the 25th to the 75th percentile of each group's distribution of values; whiskers represent 1.5 times the interquartile range; dots denote outliers (observations outside the range of 1.5 times the interquartile range) and asterisks denote extremes (observations more than 3 times the interquartile range). CABG, coronary artery bypass grafting



**FIGURE 2** Scatterplot of 12-h blood loss (mL) after CABG by individual ARU values. The vertical line at 550 ARU is the cutoff value for aspirin resistance. ARU, aspirin reaction units; CABG, coronary artery bypass grafting



and pleural chest tube drainage, did not differ between both groups (858  $\pm$  530 mL in the aspirin-responder group, 883  $\pm$  474 mL in the aspirin-nonresponder group,  $P = .52$ ), nor did transfused packed red blood cells and the rate of reexploration for bleeding.

These results are not in line with the results of our study, as we can establish a significant difference when analyzing aspirin responders versus nonresponders. We can only speculate on the reasons why these studies do not demonstrate a relation between aspirin responsiveness and blood loss after cardiovascular surgical procedures.

First, the study of Takiuchi et al<sup>19</sup> is conducted in Japanese patients, and the study of Kim et al<sup>21</sup> is conducted in Korean patients, while our study population exists of European patients. These populations are not necessarily comparable. Vascular disease seems to manifest differently in Asians (higher stroke incidences but lower incidences of acute myocardial infarction).<sup>22</sup> Genetic differences may cause a dissimilar bleeding risk (and risk factors for bleeding) as well as changes in the aspirin metabolism,<sup>23</sup> as is the case with clopidogrel resistance.<sup>24</sup>

Second, opposed to our study (>99% on-pump surgery), the study population of Takiuchi et al<sup>19</sup> and Kim et al<sup>21</sup> consists of patients undergoing off-pump CABG (the study of Welsh et al<sup>20</sup> does not comment on the type of CABG). Although the effect of off-pump surgery on blood loss remains a topic for discussion,<sup>25,26</sup> the difference in thrombocyte (dys)function and (transient) aspirin resistance between on-pump and off-pump CABG might explain some of the discrepancies between the outcomes of our studies.

Finally, the study of Kim et al<sup>21</sup> is the only study that selected a similar study population with regard to preoperative antithrombotic and anticoagulation drugs (Welsh et al<sup>20</sup> do not mention preoperative medication use, and as mentioned the population of Takiuchi et al<sup>1</sup> differs in medication use). These other drugs might have influenced blood loss. Given our results, it could be proposed that preoperative testing of aspirin responsiveness might have value in predicting blood loss in patients undergoing cardiovascular surgical procedures who use aspirin preoperatively. Whether this difference in blood loss between aspirin-sensitive and aspirin-resistant patients is clinically meaningful can aid in determining the timing of surgery,<sup>27</sup> and whether classification according to aspirin responsiveness with the preoperative VerifyNow aspirin assay can help identify patients undergoing CABG at risk for high blood loss and eventually could prevent bleeding events needs to be further investigated.

The following limitations should be considered. First, this is a relatively small study, with a small proportion of patients that were aspirin-resistant. Second, no correction for the aforementioned other possible factors influencing blood loss was made. Therefore, it cannot be excluded that these factors influenced the results. Third, although results of the preoperative VerifyNow aspirin assay were unknown to all except the study team, blood transfusion management was left to the discretion of treating physicians, which could have influenced postoperative blood loss.

## 5 | CONCLUSIONS

In patients who used aspirin preoperatively, aspirin responsiveness as classified by preoperative platelet function testing by the VerifyNow aspirin assay was associated with 12-hour blood loss after CABG. Further investigation is needed to determine if and in which population preoperative VerifyNow aspirin testing can identify patients undergoing CABG at high risk for perioperative bleeding and whether this can prevent clinically relevant bleeding events.

### AUTHOR CONTRIBUTIONS

LMW, PWAJ, E-JvdD, CMH, and JMtB designed the study. LMW, EAV, and CDV collected study data. LMW, PWAJ drafted the manuscript. KZ and JCK supported the data analysis. PGN, PK, CMH, and JMtB supervised the study. All authors critically interpreted study data. All authors read and critically revised the manuscript and approved submission.

### RELATIONSHIP DISCLOSURE

LMW was coordinating investigator of the POPular CABG trial, which was conducted with funding from AstraZeneca. PK declares consultancy and proctoring fees Edwards Lifesciences and BioVentric Inc., and receiving a grant for conducting a clinical trial from Edwards Lifesciences, all unrelated to this work. JMtB reports institutional research grants from ZonMw (government institution) and AstraZeneca and being lecturer for AstraZeneca, Eli Lilly, Daiichi Sankyo, The Medicines Company, Accumetrics, Boehringer Ingelheim, BMS, Pfizer, Bayer, and Ferrer. EAV, PWAJ, CDV, KZ, JCK, PN, EJvdD, and CMH declare no conflicts of interest.

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### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Willemsen LM, Vlot EA, Janssen PWA, et al. Blood loss after coronary artery bypass by aspirin responsiveness assessed with preoperative VerifyNow aspirin testing. *Res Pract Thromb Haemost*. 2021;5:e12623. doi:[10.1002/rth2.12623](https://doi.org/10.1002/rth2.12623)