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Original Article

# Impact of Dipyrone Administration on Postoperative Analgesia and Aspirin Effect in Patients Undergoing Coronary Artery Bypass Grafting: The Prospective Randomized DipASA Study

Walter Petermichl, MD*, Peter-Paul Ellmauer, MD*, Anne Benning, MD†, Florian Zeman, MD†, Christof Schmid, MD‡, Andrea Stadlbauer, MD‡, Susanne Heimerl, MD§, Timo Seyfried, MD‖, Sebastian Blecha, MD*,[1]

*Department of Anesthesiology, University Medical Center Regensburg, Regensburg, Germany
†Center for Clinical Studies, University Medical Center Regensburg, Regensburg, Germany
‡Department of Cardiothoracic Surgery, University Medical Center Regensburg, Regensburg, Germany
§Institute of Clinical Chemistry and Laboratory Medicine, University Medical Center Regensburg, Germany
‖Department of Anesthesiology, Hospital Vilshofen, Vilshofen, Germany

*Objective:* The aim of the study was to investigate the impact of dipyrone administration on postoperative analgesia and acetylsalicylic acid (ASA) effect in patients undergoing coronary artery bypass grafting (CABG).

*Design:* A prospective randomized study.

*Setting:* Single-university hospital setting.

*Participants:* Ninety-eight patients who underwent CABG between April 2022 and May 2023.

*Interventions:* The ASA effect was measured at 6 time points with impedance aggregometry (Multiplate) and thromboelastography (TEG6s Platelet Mapping). Patients were randomized to 1 of 3 groups: intravenous ASA and dipyrone at the same time (group 1), intravenous ASA and dipyrone with a 2-hour delay (group 2), and intravenous ASA alone (group 3). Postoperative analgesic effects (numeric rating scale) and the prevalence of potential ASA non-response (defined as ASPI >40 U and TEG-ASA inhibition <50%) were recorded.

*Measurements and Main Results:* Of 90 analyzed patients, 80 took ASA preoperatively. All patients received intravenous ASA 100 mg from postoperative day 1. The effect of ASA did not significantly differ between the study groups at any time for either platelet function test. NRS values did not differ between the study groups at any time ($p = 0.469$). Patients in group 3 received significantly more additional co-analgesics than patients who received dipyrone ($p = 0.005$). ASA non-response was detected in 38.9% and 67.8% on the seventh postoperative day, respectively.

*Conclusions:* Dipyrone given after CABG seems safe and did not show any significant effect on platelet inhibition after ASA administration. Patients taking dipyrone postoperatively need significantly fewer additional coanalgesics. The ASA effect on platelet function should be checked at least once after surgery.



*Key Words:* acetylsalicylic acid; anticoagulation; dipyrone; multiple electrode aggregometry (Multiplate); platelet function; thromboelastography (TEG)

AFTER CORONARY ARTERY BYPASS GRAFTING (CABG), patients need effective postoperative antiplatelet therapy to avoid graft failure. Acetylsalicylic acid (ASA), which irreversibly inhibits platelet cyclooxygenase-1 (COX-1), is the

[1]*Address correspondence to* Sebastian Blecha, MD, Department of Anesthesiology, University Medical Centre Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany.
*E-mail address:* Sebastian.Blecha@ukr.de (S. Blecha).

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gold standard for secondary prevention of graft occlusion and adverse cardiac events after CABG.[1,2] In case of intolerance (eg, stomach upset or non-response) or allergy to ASA, clopidogrel given daily is a reasonable alternative.[3,4]

Furthermore, patients after CABG need adequate postoperative analgesia due to the high risk of chronic pain disorder.[5,6] A multimodal analgesic regimen commonly consists of a combination of opioid and non-opioid analgesics. Guidelines of the European Society of Cardiology do not recommend the use of non-steroidal anti-inflammatory drugs (NSAIDs; especially ibuprofen or diclofenac) in patients with cardiovascular diseases.[7,8] Dipyrone was withdrawn from the market in the United States and in several European countries following reports of fatal agranulocytosis in users. However, dipyrone is still available by prescription and/or over-the-counter in many countries in Europe, South America, and Asia.[9] In Germany, dipyrone (metamizole) is often used as a comedication with opioids after CABG[10] because of its favorable analgesic, spasmolytic, and antipyretic effects; thus, the use of dipyrone in Germany more than doubled between 2008 and 2018.[11]

However, dipyrone should be used with caution in patients treated with ASA. In 2007, Hohlfeld and colleagues first described that dipyrone has a high potential to attenuate or prevent the antiplatelet effect of ASA.[12] Dipyrone and its active metabolite (4-methyl-aminoantipyrine) block the access of ASA into the substrate binding site of platelet COX-1. In a recent Germany-wide analysis, the administration of ASA and dipyrone together was associated with excess mortality and higher rates of myocardial infarction and strokes compared to ASA medication alone.[13] Another study recommended a strict order of ASA medication 30 minutes before dipyrone to preserve the antiplatelet effect of ASA in patients with coronary artery disease.[14] Whether differentiated dosing regimens, such as the recommended adherence to a minimum time interval of 30 minutes or longer between the administration of ASA and dipyrone, provide sufficient platelet aggregation has not been proved in clinical studies to date.

In this clinical study, we investigated the timing of dipyrone administration on the antiplatelet effect of ASA in patients up to 7 days after CABG. We hypothesized that dipyrone administered 2 hours after ASA does not affect the antiplatelet effects of ASA and reduces acute postoperative pain better than opioid-based treatment alone.

## Materials and Methods

### *Study Design*

This prospective, randomized, single-center, single-blind study (DipASA study: Impact of dipyrone administration on postoperative analgesia and aspirin effect in patients undergoing coronary artery bypass grafting) was approved by the local institutional review board (Protocol No. 21-2695-101, approved on 26 January 2022) and registered with the German Clinical Trials Register (DRKS00028161, prospectively registered on 17 February 2022). Written informed consent was obtained from study patients scheduled for elective CABG at the Department for Cardiac, Thoracic, and Cardiovascular Surgery at the University Medical Center Regensburg. All patients were recruited between April 2022 and May 2023. Main exclusion criteria were age older than 85 years, body mass index greater than 40 kg/m$^2$, American Society of Anesthesia physical status higher than III, emergency CABG, chronic pain, and rejection of study participation.

### *Patient Cohort*

The patients were preoperatively randomized to 1 of 3 study groups, except for patients with known intolerance to dipyrone who were assigned directly to group 3 (Fig 1):

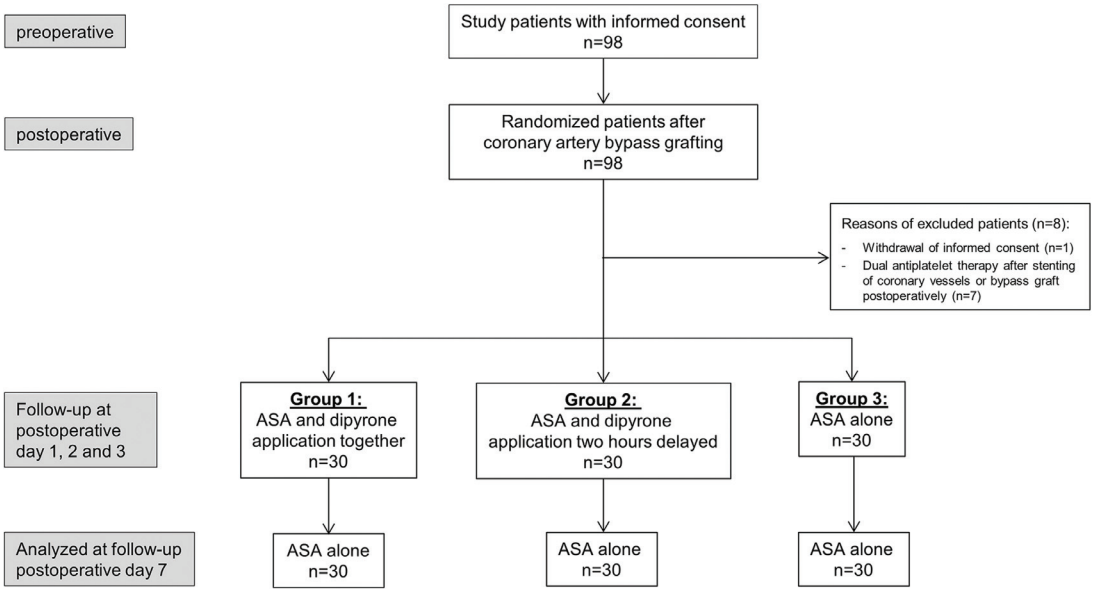


Fig 1. Patient flow chart of the DipASA-study.

- Group 1: intravenous administration of ASA 100 mg and dipyrone 1,000 mg at the same time on postoperative day 1 up to day 3; from postoperative day 4, intravenous administration of ASA alone once a day
- Group 2: intravenous administration of ASA 100 mg and dipyrone 1,000 mg with a 2-hour delay on postoperative days 1 to 3; from postoperative day 4, intravenous administration of ASA alone once a day
- Group 3: intravenous administration of ASA 100 mg alone once a day from postoperative day 1 (opioid-based pain treatment)

All study patients were observed for 7 days postoperatively. The study preliminarily included 98 patients. Postoperatively, 8 patients were excluded from analysis (dual antiplatelet therapy after postoperative stenting of coronary vessels or bypass [n = 7] or retroactive withdrawal of consent [n = 1]). Five patients with known intolerance to dipyrone were directly assigned to group 3.

### *Measurement of Platelet Function*

In this study, the effects of ASA on platelet function were measured with 2 different tests: Multiplate Analyzer (Roche Diagnostics, Basel, Switzerland) and thromboelastography (TEG6s Platelet Mapping, Haemonetics, Boston, MA). All blood samples were left to rest for 30 minutes before the respective platelet function test.

#### *Multiplate*

Multiple electrode platelet aggregometry with Multiplate Analyzer is an established, fast, convenient method of testing platelet function.[15] One of the Multiplate Analyzer testing options is the ASPI (platelet function stimulated by ASA) test, in which platelets are activated by arachidonic acid, which is converted to the potent platelet agonist thromboxane A2 by the platelet COX-1. Therefore, platelet activation in the ASPI test allows the sensitive and specific detection of ASA action (normal range of ASPI levels without ASA intake: 71-115 U). For the multiplate analysis, whole blood was collected in hirudin-anticoagulated blood tubes and analyzed by trained staff of the Institute of Clinical Chemistry and Laboratory Medicine of the University Medical Center Regensburg. The results were recorded in the laboratory information system (Lauris, Nexus/Swisslab GmbH, Offenbach, Germany).

#### *TEG6s*

The TEG6s Platelet Mapping whole blood assay measures clot strength as maximum amplitude and can provide a semi-quantitative analysis of platelet function by evaluating the contribution of the thromboxane A2 receptors to clot formation (normal range of TEG-ASA inhibition without ASA intake: 0% to 20%).[16,17] For TEG6s Platelet Mapping, heparinized blood tubes were used.

Both platelet function tests were performed at 6 different time points: preoperatively, 1 hour after surgery, 1 hour after ASA administration in study groups 1 and 3, and 1 hour after dipyrone administration in study group 2 on the first, second, and third postoperative day2. On day 7 after CABG, all study patients underwent platelet function testing 1 hour after ASA administration. In addition, adverse events (major postoperative bleeding, reoperation rate, ischemic complications, or death) and routine coagulation and hemostatic parameters were recorded at each measurement time point: platelet count, hemoglobin, leukocyte and fibrinogen values, creatine kinase [CK], CK-MB, quick value, and activated partial thromboplastin time. Furthermore, we recorded the preoperative ASA administration to identify potential ASA non-responders. ASA resistance was defined as ASPI $\geq$40 U by Multiplate and $<$50% ASA-induced whole blood inhibition by TEG6s Platelet Mapping.[18-22]

### *Postoperative Analgesia*

In all study patients, perioperative anesthesia was induced with sufentanil (initial bolus 0.5 μg/kg ideal body weight) before tracheal intubation and maintained with continuous sufentanil (0.5 μg/kg ideal body weight per hour) until 15 minutes before the end of surgery. Postoperatively, each patient in groups 1 and 2 received 1,000 mg of dipyrone intravenously 4 times a day from postoperative days 1 to 3. At the postoperative visits (days 1, 2, 3, and 7), each patient was interviewed about the current level of pain using the numeric rating scale (NRS). The questioner did not know which of the 3 groups the patient had been assigned to (single-blinded study). The NRS is a well-established tool for pain assessment tool that requires patients to rate their pain on a defined scale. The scale ranges from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable.[23] In addition, the doses of all postoperatively administered analgesics, especially opioids (fixed additional and cumulative opioid doses measured as morphine equivalents) and comedications (minimum one of the following substances: ibuprofen, paracetamol, ketamine, lidocaine, and dexmedetomidine), were recorded using the inhouse Metavision patient clinical information system (iMDsoft).

### *Study Aims*

The primary aim of the study was to investigate the influence of dipyrone on sufficient ASA antiplatelet inhibition defined by ASPI $<$40 U with Multiplate and $>$50% with TEG6s Platelet Mapping.

Secondary aims included the postoperative analgesic effect of dipyrone compared to opioid-based analgesics, the use of other analgesic comedication, the rate of adverse events, and the frequency of potential ASA non-response.

### *Statistical Analyses*

#### *Sample Size Considerations*

Sample size was calculated according to the primary endpoint of platelet inhibition defined by ASPI $<$40 U (binary

endpoint yes *v* no) at any postoperative time point. We assumed a platelet inhibition of 95% in group 3, 90% in group 2, and 50% in group 1. Our primary hypothesis was that groups 3 and 2 have higher proportions of platelet inhibition than group 1. To detect a difference of 90% (group 2) versus 50% (group 1) with a power of 80% at a 2-sided significance level of 2.5% (adjusted for 2 tests), a total of 27 patients needed to be analyzed for both arms (groups 1 and 2). According to this calculation, we decided to also include 27 patients in group 3 to achieve the same group size. To account for about 10% of the patients to become dropouts, we included 30 patients per group. Sample size was calculated using G*Power.

### *Statistical Methods*

Data are shown as mean (± SD) or median (IQR) for continuous variables depending on the underlying distribution and as absolute and relative frequencies for categorical variables. A p-value <0.05 was considered significant. All analyses were performed using the software R (Version 3.5.1, www.r-project.org).

To analyze group differences, we used 1-way ANOVA for normally distributed variables, the Kruskal-Wallis test for non-normally distributed variables, and the chi-squared test of independence or the Fisher-exact-test for categorical variables.

For the primary and secondary endpoints, 2-way ANOVAs were used to analyze the effects of study group and time on routine laboratory parameters and platelet function. The chi-squared test of independence or the Fisher exact test was used to analyze group differences in the number of ASA non-responders at each time point. Two-way ANOVA was performed to analyze the effects of study group and time on NRS pain score and opioid dose. The Fisher exact test was performed to analyze differences in the treatment with additional analgesics between the study groups.

## Results

Of 98 randomized White patients, who had given their informed consent, 90 patients were eligible for statistical analysis. Patient characteristics and surgical details are listed in Table 1. Eighty patients (88.9%) were male; the mean age was 65 years (±9 years) with a mean body mass index of 28.6 kg/m$^2$ (±5.4 kg/m$^2$). The median duration of CABG was 210 (IQR 187-247) minutes, the median duration of cardiopulmonary bypass use was 94 (IQR 77-112) minutes, and the median duration of cross-clamp time on the heart-lung machine was 55 (IQR 44-66) minutes. All study patients were treated postoperatively in the ICU. The median length of the ICU stay was 2 (IQR 1-3) days, and the median hospital stay was 16 (IQR 13-19) days. All patients were prepared and waited a median of 5 (IQR 2-7) days for CABG surgery. The 3 study groups did not differ in any of the described parameters.

### *Platelet Function*

The Multiplate Analyzer showed a significant difference in ASPI values between the measurement time points ($p < 0.001$); the initial median ASPI value decreased after surgery and increased from the first to the seventh postoperative day. The ASPI values of each group are shown in Fig 2. No significant differences were found between the study groups. No interaction effect was found. As measured with TEG6s Platelet Mapping, the inhibitory effect of ASA on platelet function in each study group is shown in Fig 3. We found a significant effect of time on ASA inhibition on platelets ($p < 0.001$), with

Table 1
Patient Characteristics and Surgical and Clinical Details (N = 90)

| | Group 1 (n = 30) | Group 2 (n = 30) | Group 3 (n = 30) | p-Value |
|---|---|---|---|---|
| Age (y), mean (±SD) | 66 (±10) | 64 (±9) | 65 (±8) | 0.716[1] |
| Sex | | | | |
| Men, n (%) | 28 (93%) | 27 (90%) | 26 (87%) | 0.905[3] |
| Women, n (%) | 2 (7%) | 3 (10%) | 4 (13%) | |
| BMI (kg/m$^2$), mean (±SD) | 28.6 (±4.3) | 29.6 (±6.8) | 27.6 (±4.8) | 0.681[2] |
| SAPS II[a], mean (±SD) | 26 (±15) | 24 (±8) | 21 (±7) | 0.095[2] |
| Surgical and clinical details | | | | |
| Duration of CABG surgery [min], median (IQR) | 205 (184-240) | 215 (193-247) | 211 (189-254) | 0.765[2] |
| Duration of cardiopulmonary bypass [min], median (IQR) | 90 (70-100) | 94 (82-104) | 97 (81-122) | 0.294[2] |
| Duration of cross-clamp time [min], median (IQR) | 53 (41-60) | 53 (46-62) | 59 (44-74) | 0.412[1] |
| Duration of ICU stay [d], median (IQR) | 2 (1-3) | 2 (1-3) | 2 (1-3) | 0.935[2] |
| Duration of hospital stay [d], median (IQR) | 16 (12-21) | 16 (13-19) | 15 (13-18) | 0.824[2] |

Notes: *p < 0.05.
Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II.
Group 1: intravenous administration of ASA 100 mg and dipyrone 1,000 mg at the same time on postoperative days 1 to 3; group 2: intravenous administration of ASA 100 mg and dipyrone 1,000 mg with a 2-hour delay on postoperative days 1 to 3; group 3: postoperative intravenous ASA administration alone.
[a] Measured 24 hours after ICU admission.
[1] One-way ANOVA.
[2] Kruskal-Wallis test.
[3] Fisher exact test.

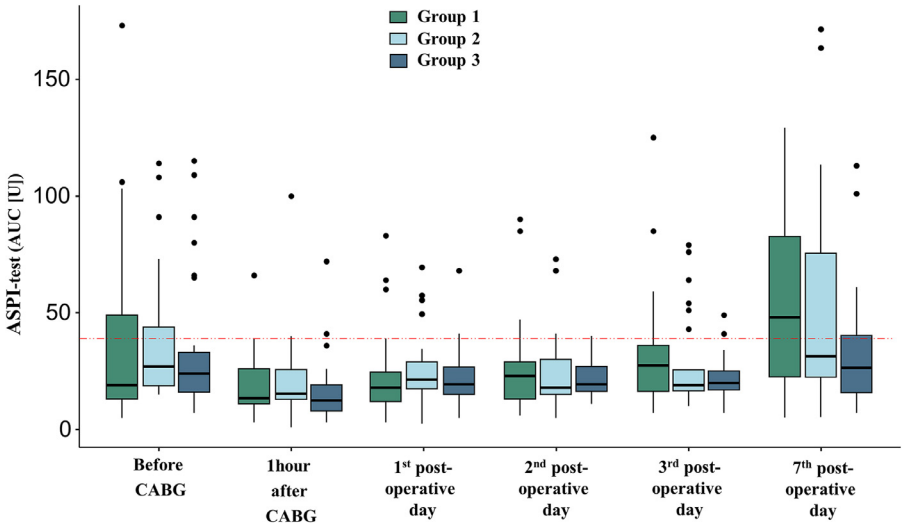


Fig 2. Median ASPI levels of each study group at the different measurement time points detected with the Multiplate Analyzer (N = 90, 30 patients in each group). Notes: Multiplate ASPI-test units: AUC [U]; CABG, coronary artery bypass grafting; group 1: intravenous administration of ASA 100 mg and dipyrone 1,000 mg at the same time on postoperative day 1 to 3, group 2: intravenous administration of ASA 100 mg and dipyrone 1,000 mg with a 2-hour delay on postoperative day 1 to 3, group 3: postoperative intravenous administration of ASA 100 mg alone; the red line designates an ASPI value of 40 U; no significant differences were found between study groups at any measuring time point.

the highest platelet inhibition immediately after surgery with a significant increase compared to preoperative level ($p < 0.001$). No significant differences were detected between the groups. No interaction effect was found.

*Adverse Events and Routine Laboratory*

In our study, we registered 6 cases of major postoperative bleeding with reoperation immediately after surgery (6.7%). Each of the patients had been treated with ASA preoperatively without any differences between the study groups. No adverse events were detected from the first postoperative day up to the end of the study observation (1 week after CABG). The routine parameters of each study group are shown in Table 2. We found significant differences between the time points but no significant differences between the study groups. No interaction effects were found except for the hemoglobin value ($p = 0.013$).

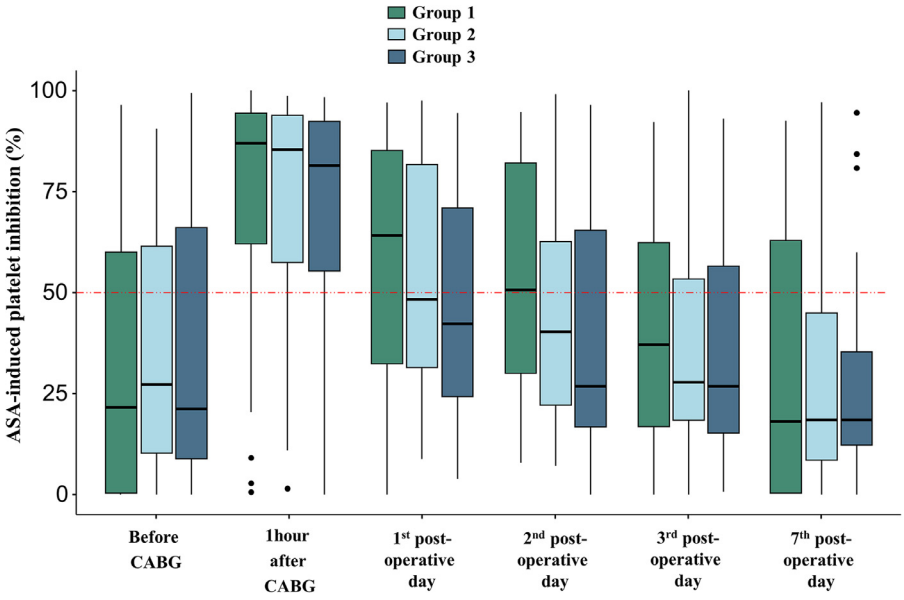


Fig 3. Median ASA inhibitory effect of each study group at the different measurement time points detected with TEG6s Platelet Mapping (N = 90, 30 patients in each group). Notes: TEG6s Platelet Mapping unit: percent; ASA, acetylsalicylic acid; CABG, Coronary artery bypass grafting; group 1: intravenous administration of ASA 100 mg and dipyrone 1,000 mg at the same time on postoperative day 1 to 3, group 2: intravenous administration of ASA 100 mg and dipyrone 1,000 mg with a 2-hour delay on postoperative day 1 to 3, group 3: postoperative intravenous administration of ASA 100 mg alone; the red line designates a platelet inhibition of 50%; no significant differences were found between study groups at any measuring time point.

Table 2
Median Standard Laboratory Parameters at the Different Measuring Time Points (N = 90, 30 patients in each group)

| Parameter | | Before CABG Surgery | 1 Hour after CABG | 1st Postoperative Day | 2nd Postoperative Day | 3rd Postoperative Day | 7th Postoperative Day | p-Values |
|---|---|---|---|---|---|---|---|---|
| Leukocyte count (n/nL) | Group 1 | 8.2 (±2.9) | 11.6 (±5.3) | 10.4 (±4.0) | 10.8 (±4.7) | 10.1 (±5.1) | 9.1 (±3.3) | 0.224 |
| | Group 2 | 7.6 (±1.5) | 11.3 (±3.7) | 10.5 (±2.5) | 10.3 (±3.1) | 9.3 (±3.5) | 9.5 (±2.9) | |
| | Group 3 | 8.8 (±1.9) | 11.7 (±4.0) | 11.1 (±3.0) | 12.5 (±2.9) | 10.7 (±2.3) | 9.2 (±2.2) | |
| | All | 8.2 (±2.2) | 11.5 (±4.4) | 10.7 (±3.2) | 11.2 (±3.7) | 10.0 (±3.8) | 9.3 (±2.8) | |
| Platelet count (n/nL) | Group 1 | 242 (±84) | 164 (±55) | 177 (±54) | 161 (±50) | 168 (±51) | 288 (±98) | 0.670 |
| | Group 2 | 248 (±62) | 166 (±53) | 179 (±51) | 155 (±46) | 157 (±50) | 283 (±104) | |
| | Group 3 | 272 (±79) | 168 (±48) | 182 (±42) | 175 (±37) | 176 (±38) | 307 (±86) | |
| | All | 254 (±76) | 166 (±52) | 179 (±49) | 163 (±45) | 167 (±47) | 293 (±96) | |
| Hemoglobin (g/dL) | Group 1 | 13.8 (±1.4) | 10.3 (±1.3) | 9.9 (±1.2) | 9.3 (±1.0) | 9.1 (±0.9) | 9.9 (±1.1) | 0.013* |
| | Group 2 | 13.9 (±1.8) | 10.0 (±1.5) | 10.4 (±1.4) | 9.8 (±1.3) | 9.4 (±1.3) | 10.8 (±2.0) | |
| | Group 3 | 14.3 (±1.5) | 10.1 (±1.1) | 10.1 (±1.4) | 9.5 (±1.5) | 9.3 (±1.5) | 9.7 (±1.3) | |
| | All | 14.0 (±1.6) | 10.1 (±1.3) | 10.1 (±1.3) | 9.5 (±1.3) | 9.3 (±1.3) | 10.1 (±1.6) | |
| Fibrinogen (mg/dL) | Group 1 | N/A | 273 (±90) | 343 (±81) | 529 (±111) | 624 (±92) | 618 (±127) | 0.387 |
| | Group 2 | N/A | 269 (±122) | 359 (±104) | 518 (±109) | 616 (±130) | 629 (±166) | |
| | Group 3 | N/A | 287 (±74) | 368 (±87) | 520 (±99) | 590 (±129) | 601 (±121) | |
| | All | N/A | 277 (±95) | 357 (±91) | 522 (±105) | 610 (±117) | 616 (±138) | |
| Creatine kinase (U/L) | Group 1 | 241 (±805) | 287 (±170) | 423 (±236) | 627 (±799) | 477 (±762) | 83 (±63) | 0.314 |
| | Group 2 | 115 (±80) | 340 (±136) | 636 (±607) | 746 (±772) | 488 (±613) | 100 (±95) | |
| | Group 3 | 91 (±78) | 343 (±162) | 466 (±254) | 466 (±268) | 390 (±362) | 104 (±119) | |
| | All | 149 (±469) | 323 (±157) | 508 (±410) | 613 (±662) | 453 (±601) | 96 (±95) | |
| CK-MB (ng/mL) | Group 1 | 21.3 (±99.2) | 18.2 (±12.1) | 18.9 (±20.5) | 8.7 (±9.4) | 3.9 (±3.9) | 1.8 (±1.0) | 0.169 |
| | Group 2 | 3.3 (±3.8) | 20.7 (±13.1) | 39.0 (±70.7) | 15.4 (±28.6) | 5.8 (±9.7) | 1.9 (±1.1) | |
| | Group 3 | 2.5 (±1.7) | 20.5 (±15.3) | 30.0 (±52.0) | 11.0 (±15.5) | 4.2 (±4.5) | 1.6 (±1.0) | |
| | All | 9.1 (±57.3) | 19.8 (±13.5) | 29.3 (±52.1) | 11.7 (±19.5) | 4.6 (±6.5) | 1.7 (±1.0) | |
| NT-proBNP (pg/mL) | Group 1 | 918 (±1,352) | 756 (±1,202) | 2,096 (±3,096) | 2,230 (±1,474) | 3,122 (±2,609) | 2,516 (±1,828) | 0.307 |
| | Group 2 | 1026 (±2,090) | 1,330 (±2,568) | 2,762 (±3,343) | 5,849 (±12,958) | 5,502 (±8,694) | 4,235 (±6,729) | |
| | Group 3 | 1,034 (±1,167) | 1,059 (±878) | 2,191 (±1718) | 4,277 (±4,135) | 4,572 (±4,213) | 3,827 (±4,215) | |
| | All | 992 (±1,570) | 1,052 (±1,714) | 2,365 (±2,800) | 4073 (±7852) | 4,381 (±5,782) | 3,550 (±4,803) | |
| Quick value (%) | Group 1 | 96.4 (±7.2) | 77.4 (±12.8) | 84.7 (±10.7) | 91.3 (±9.7) | 97.5 (±5.4) | 97.5 (±4.6) | 0.134 |
| | Group 2 | 98.0 (±4.5) | 72.0 (±12.6) | 85.6 (±9.8) | 88.9 (±10.1) | 95.4 (±6.8) | 94.7 (±9.9) | |
| | Group 3 | 97.3 (±4.4) | 76.3 (±12.5) | 85.1 (±12.7) | 90.6 (±9.8) | 95.3 (±6.5) | 93.9 (±8.9) | |
| | All | 97.2 (±5.5) | 75.2 (±12.7) | 85.1 (±11.0) | 90.2 (±9.8) | 96.1 (±6.3) | 95.4 (±8.2) | |
| Activated partial thromboplastin time (s) | Group 1 | 36.0 (±16.8) | 39.9 (±9.8) | 40.7 (±10.8) | 38.7 (±10.5) | 33.6 (±5.7) | 30.1 (±8.3) | 0.264 |
| | Group 2 | 35.1 (±17.3) | 44.8 (±13.0) | 38.1 (±9.4) | 37.3 (±8.2) | 34.1 (±7.3) | 31.0 (±9.4) | |
| | Group 3 | 30.9 (±9.0) | 44.7 (±19.6) | 40.4 (±16.7) | 36.9 (±6.6) | 35.1 (±6.5) | 33.6 (±12.6) | |
| | All | 34.0 (±14.9) | 43.1 (±14.7) | 39.7 (±12.6) | 37.6 (±8.7) | 34.3 (±6.5) | 31.8 (±10.1) | |

Notes: Entries depict the mean (±SD), and p-values compare the 3 treatment arms using repeated-measures ANOVA.
*$p < 0.05$.
Abbreviations: CABG, coronary artery bypass grafting; CK-MB, creatine kinase-MB; N/A, not available; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Group 1: intravenous administration of ASA 100 mg and dipyrone 1,000 mg at the same time on postoperative day 1 to 3, group 2: intravenous administration of ASA 100 mg and dipyrone 1,000 mg with a 2-hour delay on postoperative day 1 to 3, group 3: postoperative intravenous administration of ASA 100 mg alone.

### *ASA Non-responders*

Eighty patients (88.9%) took ASA before CABG surgery. Of the 80 patients (28.8%) under Multiplate testing who had taken ASA preoperatively, 23 showed an inadequate ASA effect (ASPI level ≥40 U). The distribution of potential ASA non-response for all patients and in each group is shown in Table 3. On the seventh postoperative day, 38.9% (35 of 90) of patients with ASA medication showed reduced ASA inhibition. No significant differences in the number of ASA non-responders were found between the groups. As measured with TEG6s Platelet Mapping, 75% (60 of 80) of patients showed reduced ASA inhibition before surgery (Table 4). On the seveth postoperative day, 67.8% (61 of 90) of patients with ASA medication showed reduced ASA inhibition. No significant differences in the ASA effect were found between the groups at any of the measurement time points.

### *Postoperative Analgesia*

A median NRS pain score of 4 (IQR 2-6) on the first postoperative day was the highest postoperative pain score, which continuously decreased during follow-up (Table 5). The 3 study groups did not significantly differ in pain levels ($p = 0.963$). Nevertheless, pain decreased significantly over time ($p < 0.001$). No interaction effect was found ($p = 0.469$). A significant difference in the fixed dose of opioids ($p = 0.002$) was found between the time points, but there was no main effect in relation to group ($p = 0.694$). Nevertheless, the difference between the treatment groups changed over time (interaction term: $p = 0.015$). Furthermore, patients in

Table 3
Number (and Percentage) of Patients with Multiplate ASPI Level ≥40 U (N = 90)

| | Before CABG Surgery | 1 Hour after Surgery | 1st Postoperative Day | 2nd Postoperative Day | 3rd Postoperative Day | 7th Postoperative Day |
|---|---|---|---|---|---|---|
| Group 1 | 8 (8.9%) | 2 (2.2%) | 3 (3.3%) | 5 (5.6%) | 7 (7.8%) | 15 (16.7%) |
| Group 2 | 9 (10%) | 2 (2.2%) | 5 (5.6%) | 3 (3.3%) | 6 (6.7%) | 13 (14.4%) |
| Group 3 | 6 (6.7%) | 2 (2.2%) | 2 (2.2%) | 1 (1.1%) | 2 (2.2%) | 7 (7.8%) |
| All | 23 (25.6%) | 6 (6.7%) | 10 (11.1%) | 9 (10%) | 15 (16.7%) | 35 (38.9%) |
| p-Values | 0.616[1] | >0.99[2] | 0.592[2] | 0.231[2] | 0.191[2] | 0.094[1] |

Note: *p < 0.05.
Abbreviations: ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting.
Group 1: intravenous administration of ASA 100 mg and dipyrone 1,000 mg at the same time on postoperative days 1 to 3, group 2: intravenous administration of ASA 100 mg and dipyrone 1,000 mg with a 2-hour delay on postoperative days 1 to 3, group 3: postoperative intravenous administration of ASA alone.
[1] Chi-squared test of independence.
[2] Fisher exact test.

group 3 required significantly more additional coanalgesics than patients who received dipyrone (p = 0.005).

## Discussion

This study analyzed the timing of dipyrone administration on the inhibitory effect of ASA on platelet function up to 7 days after CABG surgery. The main findings were (1) platelet function was maximally decreased immediately after surgery and (2) the timing of postoperative dipyrone administration did not influence the inhibitory effect of ASA. Secondary findings were (1) patients without postoperative dipyrone medication required more analgesic comedication and (2) over one-third of the patients showed an inadequate inhibitory effect of ASA on platelet function after surgery.

The administration of dipyrone for 3 days immediately after CABG surgery seems to be safe and has potential benefits. Thus, the hypotheses underlying this study could be partially confirmed. However, patients treated with CABG still have a notable risk of subsequent major ischemic cardiac and cerebrovascular events up to 12 months after surgery.[24] Therefore, the postoperative administration of dipyrone should be as short as possible to avoid interaction with ASA.

### *Platelet Function*

A consensus statement of the International Society for Minimally Invasive Cardiothoracic Surgery recommends that preoperative ASA administration may be continued until surgery.[25] The optimal dose and timing of ASA for the

Table 4
Number (and Percentage) of Patients with ASA Inhibition <50% with TEG6s Platelet Mapping (N = 90)

| | Before CABG Surgery | 1 Hour after Surgery | 1st Postoperative Day | 2nd Postoperative Day | 3rd Postoperative Day | 7th Postoperative Day |
|---|---|---|---|---|---|---|
| Group 1 | 19 (21.1%) | 7 (7.8%) | 12 (13.3%) | 14 (15.6%) | 17 (18.9%) | 19 (21.1%) |
| Group 2 | 21 (23.3%) | 7 (7.8%) | 15 (16.7%) | 18 (20%) | 20 (22.2%) | 21 (23.3%) |
| Group 3 | 20 (22.2%) | 6 (6.7%) | 18 (20%) | 21 (23.3%) | 21 (23.3%) | 21 (23.3%) |
| All | 60 (66.7%) | 20 (22.2%) | 45 (50%) | 53 (58.9%) | 58 (64.4%) | 61 (67.8%) |
| p-Values | p = 0.861 | p = 0.962[1] | p = 0.301[1] | p = 0.174[1] | p = 0.405[1] | p = 0.656[1] |

Note: *p < 0.05.
Abbreviations: ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; TEG6s, thromboelastography.
Group 1: intravenous administration of ASA 100 mg and dipyrone 1,000 mg at the same time on postoperative day 1 to 3, group 2: intravenous administration of ASA 100 mg and dipyrone 1,000 mg with a 2-hour delay on postoperative day 1 to 3, group 3: postoperative intravenous administration of ASA alone.
[1] Chi-squared test of independence.

Table 5
Postoperative Numeric Rating Scale (NRS) Pain Scores (N = 90)

| NRS Value | 1st Postoperative Day | 2nd Postoperative Day | 3rd Postoperative Day | 7th Postoperative Day |
|---|---|---|---|---|
| Group 1 | 4.5 (3.5-6) | 3 (1-5) | 2 (0-4) | 0 (0-2) |
| Group 2 | 4 (2-6) | 3 (2-3.75) | 2 (0.5-3) | 0.5 (0-2) |
| Group 3 | 3 (0.75-5.25) | 3 (1-4) | 2 (0.25-3.75) | 1 (0-2) |
| All | 4 (2-6) | 3 (1-4) | 2 (0-3) | 0.5 (0-2) |

Notes: NRS values are shown as median (IQR); group 1: intravenous administration of ASA 100 mg and dipyrone 1,000 mg at the same time on postoperative day 1 to 3, group 2: intravenous administration of ASA 100 mg and dipyrone 1,000 mg with a 2-hour delay on postoperative day 1 to 3, group 3: postoperative intravenous administration of ASA alone; no significant differences were found between the study groups at any measuring time point.
Abbreviation: ASA, acetylsalicylic acid.

antiplatelet therapy of patients after CABG ares controversial. Early initiation of ASA administration after CABG is associated with a reduced risk of death and ischemic complications.[26] Currently, ASA is mostly administered without assessing its effect on platelet function. After CABG, daily low-dose ASA is a uniformly accepted strategy for secondary prevention in patients with cardiovascular disease.[27] On the other hand, a systematic review described higher doses of ASA (≥300 mg) that resulted in a higher ASA treatment effect and a lower prevalence of ASA resistance.[28] But higher ASA dosage is a potential risk factor for postoperative bleeding.[29] This is one of the reasons why platelet inhibition should be monitored with specific blood tests. The incorporation of point-of-care platelet function tests into transfusion management algorithms is associated with reduced blood loss and transfusion requirements in cardiac surgery patients.[30] In a Polish study, patients received ASA 300 mg immediately after CABG but before dipyrone, followed by ASA 150 mg daily. Comparable to our results, that study showed no effect on ASPI values between the dipyrone/opioid and opioid groups.[31] In our study, all patients were treated with low-dose ASA (100 mg intravenously once per day) starting on the first postoperative day. Using the Multiplate test, ASPI levels were lowest nearly 2 hours after CABG surgery, reflecting the negative effect of a heart-lung machine on platelet function. This fact could be a possible explanation for the 6 cases of postoperative bleeding and the necessity of operative revision. Between the first and seventh postoperative days, the ASPI values increased slowly but continuously under ASA treatment, with the highest values one week after CABG (Fig 2). In a retrospective study of nearly 500 patients after heart surgery, ASPI values <40 U were associated with higher postoperative drainage, and values <27 U were associated with higher postoperative red blood cell concentrate usage.[32]

Along with standard laboratory testing, the use of TEG can significantly reduce the amount of blood products given to patients undergoing CABG as well as the rate of reoperation.[33] Furthermore, the TEG allows the detection of the platelet inhibitory effect of ASA. Platelet mapping has been proved to be a valuable tool for assessing the level of platelet inhibition of ASA and detecting potential "non-responders."[34] A study by Lee and colleagues has also shown that it is possible to detect platelet disorders with TEG.[35] Therefore, TEG is a suitable tool for detecting a potential reduction of platelet inhibition when dipyrone is administered. In our study, we found no interaction of dipyrone with the inhibitory effect of ASA between the study groups, but an increased rate of patients with postoperative ASA inhibition <50%, which is consistent with previous findings.[36]

### *ASA Non-responders*

The terms ASA non-responder or resistance have been used to describe two different phenomena. One is the inability of ASA to inhibit platelet aggregation as demonstrated by platelet function tests (named biochemical ASA resistance). However, the term has also been used to describe the occurrence of cardiovascular events under therapeutic ASA medication (named clinical treatment failure). No consensus exists on whether the terms should be based on laboratory evidence, clinical outcomes, or both.[37,38] For biochemical ASA resistance, the rate of ASA non-response is influenced by the definition of the cut-off value. There is no universal cut-off for ASA response and non-response in the Multiplate Analyzer. Most studies used a cut-off value of 40 U to define ASA response and non-response.[18–21] Furthermore, the ASA effect of platelet inhibition is dose-dependent as described here. In our study, we investigated the effect of ASA on platelet inhibition in 90 patients who received 100 mg ASA once daily up to 7 days postoperatively. Using 2 different platelet function tests, we found a biochemical ASA resistance in 38.9% and 67.8% of the patients on the seventh postoperative day. These findings were comparable with a previous review that described ASA resistance between 10% and over 90% after CABG.[39] In our study, 28.8% and 75.0% of patients receiving preoperative ASA medication also showed a reduced ASA effect. ASA dosage and the biochemical method of defining ASA resistance strongly influence estimated prevalence.[28]

### *Postoperative Analgesia*

Immediately after CABG surgery, patients reported the highest level of pain, which gradually decreased after hospital discharge.[5,40] In addition, patients after cardiac surgery with persistently high pain levels had longer hospital stays.[41] In a study by Lahtinen and colleagues, patients reported postoperative pain as severe (NRS 7-10) in 49% at rest, in 78% when coughing, and in 62% when moving (on postoperative day 4).[42] In our study, the highest pain level was recorded on postoperative day 1 (median NRS of 4; moderate pain 4 to 6) with a continuous decrease until postoperative day 7.

The predominant pain management strategy immediately after CABG is the use of prescribed opioid medication.[40] In our study, patients in groups 1 and 2 received dipyrone as non-opioid analgesic medication on postoperative days 1 to 3, 4 times a day, in addition to opioids, which were adapted to the individual patient's level of pain. Patients without dipyrone medication (group 3) needed significantly more coanalgesics.

### *Strengths and Limitations*

The strengths of the present study are its prospective design with 6 measurement time points, the large number of included patients with a follow-up of 1 week postoperatively, and the detection of platelet function with 2 different tests. The number of dropouts in this study was low but may result in small selection bias. Furthermore, 5 patients with known intolerance to dipyrone were directly assigned to group 3, which could be a selection bias. Despite the previously calculated sample size, the effect of dipyrone on the platelet inhibitory effect of ASA could be underestimated. Furthermore, this study is not powered to show the relationship between ASA resistance and demographic variables. The NRS is a subjective tool for detecting the level of pain of patients after surgery.

## Conclusion

In summary, dipyrone administration immediately after CABG until the third postoperative day seems to be safe and has no significant effect on the antiplatelet effect of ASA. Patients who receive dipyrone after surgery need significantly fewer fixed opioids and additional coanalgesics. Because of the potential risk of ASA resistance, the effect of ASA on platelet function should be checked at least once after surgery. Further (prospective) larger studies are needed to better quantify the potential risks of dipyrone administration in patients treated with ASA after CABG.

## Trial Registration

German Clinical Trials Register (DRKS00028161, prospectively registered 17-02-2022). URL https://drks.de/search/de/trial/DRKS00028161

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## CRediT authorship contribution statement

**Walter Petermichl:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Peter-Paul Ellmauer:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Anne Benning:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Data curation. **Florian Zeman:** Writing – review & editing, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Christof Schmid:** Writing – review & editing, Validation, Project administration, Methodology, Investigation, Formal analysis. **Andrea Stadlbauer:** Writing – review & editing, Validation, Software, Project administration, Investigation, Data curation. **Susanne Heimerl:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Timo Seyfried:** Writing – review & editing, Validation, Supervision, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Sebastian Blecha:** Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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## References

1 Kulik A, Ruel M, Jneid H, et al. Secondary prevention after coronary artery bypass graft surgery. A scientific statement from the American Heart Association. Circulation 2015;131:927–64.
2 Patel MR, Calhoon JH, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease. A report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. J Am Coll Cardiol 2017;69:2212–41.
3 Hillis LD, Smith PK, Anderson JL, et al. Special Articles. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: executive summary: A report of the American College of Cardiology FoundatioN/American Heart Association Task Force on Practice Guidelines. Anesth Analg 2012;114:11–45.
4 Hombach V. Neuentwicklungen in der Thrombozytenaggregationshemmung - sinnvolle Alternativen für ASS/Clopidogrel-Non-Responder? Clin Res Cardiol Suppl 2009;4:184–91.
5 Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain. Risk factors and prevention. Lancet 2006;367:1618–25.
6 Krakowski JC, Hallman MJ, Smeltz AM. Persistent pain after cardiac surgery. Prevention and management. Semin Cardiothorac Vasc Anesth 2021;25:289–300.
7 McMurray JJV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.
8 Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease. The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949–3003.
9 Andrade S, Bartels DB, Lange R, et al. Safety of metamizole. A systematic review of the literature. J Clin Pharm Ther 2016;41:459–77.
10 Dabbagh A, Esmailian F, Aranki S. Postoperative Critical Care for Adult Cardiac Surgical Patients. Cham: Springer International Publishing; 2018.
11 Schwabe U, Paffrath D, Ludwig W-D, et al. Arzneiverordnungs-Report 2018. Berlin, Heidelberg: Springer Berlin Heidelberg; 2018. https://doi.org/10.1007/978-3-662-57386-0.
12 Hohlfeld T, Zimmermann N, Weber A-A, et al. Pyrazolinone analgesics prevent the antiplatelet effect of aspirin and preserve human platelet thromboxane synthesis. J Thromb Haemost 2008;6:166–73.
13 Polzin A, Dannenberg L, Helten C, et al. Excess mortality in aspirin and dipyrone (metamizole) co-medicated in patients with cardiovascular disease: A nationwide study. J Am Heart Assoc 2021;10:e022299. https://doi.org/10.1161/JAHA.121.022299.
14 Dannenberg L, Petzold T, Achilles A, et al. Dose reduction, oral application, and order of intake to preserve aspirin antiplatelet effects in dipyrone co-medicated chronic artery disease patients. Eur J Clin Pharmacol 2019;75:13–20.
15 Tóth O, Calatzis A, Penz S, et al. Multiple electrode aggregometry. A new device to measure platelet aggregation in whole blood. Thromb Haemost 2006;96:781–8.
16 Hartmann J, Curzen N. Modified thromboelastography for peri-interventional assessment of platelet function in cardiology patients. A narrative review. Semin Thromb Hemost 2023;49:192–200.
17 Bochsen L, Wiinberg B, Kjelgaard-Hansen M, et al. Evaluation of the TEG® platelet mapping™ assay in blood donors. Thrombosis J 2007;5:3. https://doi.org/10.1186/1477-9560-5-318.
18 Al-Azzam SI, Alzoubi KH, Khabour O, et al. The prevalence and factors associated with aspirin resistance in patients premedicated with aspirin. Acta Cardiol 2012;67:445–8.

19 Kazimi AU, Weber CF, Keese M, et al. The pre- and postoperative prevalence and risk factors of ASA nonresponse in vascular surgery. Clin Appl Thromb Hemost 2021;27:10760296211044723.
20 Wand S, Adam EH, Wetz AJ, et al. The prevalence and clinical relevance of ASA nonresponse after cardiac surgery. A prospective bicentric study. Clin Appl Thromb Hemost 2018;24:179–85.
21 Davidson S. Monitoring of antiplatelet therapy. Methods Mol Biol 2023;2663:381–402. https://doi.org/10.1007/978-1-0716-3175-1_25.
22 Tantry US, Bliden KP, Gurbel PA. Overestimation of platelet aspirin resistance detection by thrombelastograph platelet mapping and validation by conventional aggregometry using arachidonic acid stimulation. J Am Coll Cardiol 2005;46:1705–9.
23 Haefeli M, Elfering A. Pain assessment. Eur Spine J 2006:(Suppl 1): S17–24.
24 Lamy A, Devereaux PJ, Prabhakaran D, et al. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. N Engl J Med 2013; 368:1179–88.
25 Menkis AH, Martin J, Cheng DCH, et al. Drug, devices, technologies, and techniques for blood management in minimally invasive and conventional cardiothoracic surgery. A consensus statement from the International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS) 2011. Innovations (Phila) 2012;7:229–41.
26 Mangano DT. Aspirin and mortality from coronary bypass surgery. N Engl J Med 2002;347:1309–17.
27 Gurbel PA, Bliden KP, DiChiara J, et al. Evaluation of dose-related effects of aspirin on platelet function. Results from the Aspirin-Induced Platelet Effect (ASPECT) study. Circulation 2007;115:3156–64.
28 Hovens MMC, Snoep JD, Eikenboom JCJ, et al. Prevalence of persistent platelet reactivity despite use of aspirin. A systematic review. Am Heart J 2007;153:175–81.
29 Ferraris VA, Ferraris SP, Moliterno DJ, et al. The Society of Thoracic Surgeons practice guideline series. Aspirin and other antiplatelet agents during operative coronary revascularization (executive summary). Ann Thorac Surg 2005;79:1454–61.
30 Corredor C, Wasowicz M, Karkouti K, et al. The role of point-of-care platelet function testing in predicting postoperative bleeding following cardiac surgery. A systematic review and meta-analysis. Anaesthesia 2015;70:715–31.
31 Wilczyński M, Wybraniec MT, Sanak M, et al. Metamizole and platelet inhibition by aspirin following on-pump coronary artery bypass grafting. J Cardiothorac Vasc Anesth 2018;32:178–86.
32 Kuliczkowski W, Sliwka J, Kaczmarski J, et al. Predicting bleeding risk by platelet function testing in patients undergoing heart surgery. Clin Cardiol 2015;38:679–83.
33 Redfern RE, Naimy G, Kuehne M, et al. Retrospective analysis of thromboelastography-directed transfusion in isolated CABG. Impact on blood product use, cost, and outcomes. J Extra Corpor Technol 2020; 52:103–11.
34 Lee I, Suarez S, Hall R, et al. Optimizing platelet inhibition in peripheral artery disease: A comparison of mono-antiplatelet therapy and dual-antiplatelet therapy using thromboelastography. Vascular 2024: 17085381241237005. https://doi.org/10.1177/17085381241237005.
35 Lee RH, Rudran T, Bergmeier W. Utility of thromboelastography with platelet mapping for monitoring platelet transfusion in qualitative platelet disorders. J Thromb Haemost 2024;22:2873–8. https://doi.org/10.1016/j.jtha.2024.06.021.
36 Agarwal S, Johnson RI, Kirmani BH. Pre- and post-bypass platelet function testing with multiple electrode aggregometry and TEG platelet mapping in cardiac surgery. J Cardiothorac Vasc Anesth 2015; 29:1272–6.
37 Hankey GJ, Eikelboom JW. Aspirin resistance. BMJ 2004;328:477–9.
38 Michos ED, Ardehali R, Blumenthal RS, et al. Aspirin and clopidogrel resistance. Mayo Clin Proc 2006;81:518–26.
39 Zimmermann N, Gams E, Hohlfeld T. Aspirin in coronary artery bypass surgery. New aspects of and alternatives for an old antithrombotic agent. Eur J Cardiothorac Surg 2008;34:93–108.
40 Sethares KA, Chin E, Costa I. Pain intensity, interference and patient pain management strategies the first 12 weeks after coronary artery bypass graft surgery. Appl Nurs Res 2013;26:174–9.
41 Mori M, Brooks C, Dhruva SS, et al. Trajectories of pain after cardiac surgery: Implications for measurement, reporting, and individualized treatment. Circ Cardiovasc Qual Outcomes 2021;14:e007781. https://doi.org/10.1161/CIRCOUTCOMES.120.007781.
42 Lahtinen P, Kokki H, Hynynen M. Pain after cardiac surgery. A prospective cohort study of 1-year incidence and intensity. Anesthesiology 2006;105:794–800.