


# BMJ Open How do type of preoperative P2Y<sub>12</sub> receptor inhibitor and withdrawal time affect bleeding? Protocol of a systematic review and individual patient data meta-analysis

Michael Schoerghuber,<sup>1</sup> Gudrun Pregartner,<sup>2</sup> Andrea Berghold <sup>2</sup>, Ines Lindenau,<sup>1,3</sup> Robert Zweiker,<sup>4</sup> Andreas Voetsch,<sup>5</sup> Elisabeth Mahla,<sup>1</sup> Andreas Zirlik<sup>4</sup>

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For numbered affiliations see end of article.

## Correspondence to

Professor Andrea Berghold;  
[andrea.berghold@medunigraz.at](mailto:andrea.berghold@medunigraz.at)

## ABSTRACT

**Introduction** In order to reduce the risk of bleeding in patients on P2Y<sub>12</sub> receptor inhibitors presenting for non-emergent coronary artery bypass grafting (CABG), current guidelines recommend a preoperative discontinuation period of at least three, five and seven days for ticagrelor, clopidogrel and prasugrel, respectively, to allow for recovery of platelet function. However, there is still substantial interinstitutional variation in preoperative management and relevant covariates of CABG-related bleeding are largely elusive so far.

**Methods and analysis** We will search PubMed (July 2013 to November 2021) and EMBASE (January 2014 to November 2021) using the following terms, MeSH terms and their synonyms: clopidogrel, prasugrel, ticagrelor, dual antiplatelet, P2Y<sub>12</sub> receptor inhibitor, CABG, bleeding, haemorrhage. Two independent reviewers will screen all abstracts and full papers for eligibility. Disagreements will be solved by consulting with a third reviewer. The primary outcome is the incidence of Bleeding Academic Research Consortium type-4 bleeding depending on type of P2Y<sub>12</sub> receptor inhibitor and preoperative withdrawal period. The secondary outcomes are mortality and ischaemic events according to the Academic Research Consortium 2 Consensus Document. We will perform an individual patient data meta-analysis (IPD-MA) with drug-specific preoperative withdrawal time and adjust for demographic and procedural variables. Subgroup analyses will be performed for anaemic patients and patients undergoing non-emergent versus urgent/emergent surgery. **Ethics and dissemination** This IPD-MA consists of secondary analyses of existing non-identifiable data and meets the criteria for waiver of ethics review by the local Research Ethics Committee. Data sharing and transfer will be subject to a confidentiality agreement and a data use agreement. Findings will be disseminated through peer-reviewed publication and conference presentation. **PROSPERO registration number** CRD42022291946.

## BACKGROUND

In the 54 European Society of Cardiology (ESC) member countries, 34.9 million people

## Strengths and limitations of this study

- In patients undergoing coronary artery bypass grafting on P2Y<sub>12</sub> receptor inhibitors, an individual patient data meta-analysis (IPD-MA) can be a superior method to standard meta-analysis, as it allows us to identify clinical and procedural variables potentially associated with surgery-related bleeding in addition to drug-specific preoperative withdrawal time.
- This IPD-MA sets out to evaluate the association between the drug-specific preoperative withdrawal time of P2Y<sub>12</sub> receptor inhibitors and the incidence of Bleeding Academic Research Consortium (BARC) type-4 bleeding, a 'standardised' bleeding definition for patients on antithrombotic therapy and potential trade-offs in terms of ischaemic events comprising death, myocardial infarction and stent thrombosis according to Academic Research Consortium 2 Consensus Document.
- If we cannot get individual patient data for all identified studies, the risk of availability bias will be assessed by comparing study characteristics of those providing data and those that do not, and we will perform a sensitivity analysis.
- It is possible that in some studies not all information to calculate BARC-4 bleeding and the exact preoperative drug withdrawal period will be available but every attempt will be made to obtain these data.
- This IPD-MA will not be able to delineate a potential additional impact of anticoagulant agents on the incidence of BARC-4 bleeding.

lived with ischaemic heart disease in 2017. The median age-standardised prevalence per 1 000 000 inhabitants of each member country was 2270 (IQR 1508–2565) and was lower for females compared with males. In the 2018/2019 survey, these figures translated into a median of 2047 (IQR 1478–2588) percutaneous coronary interventions and

301.1 (IQR 245.0–440.0) coronary artery bypass grafting operations (CABGs) per one million inhabitants.<sup>1</sup>

Dual antiplatelet therapy (DAPT) with a P2Y<sub>12</sub> receptor inhibitor on top of aspirin is the cornerstone to prevent thrombotic complications in patients with acute coronary syndromes (ACS) and/or after percutaneous coronary interventions with stents, although at the risk of increased bleeding.<sup>2–5</sup>

Large observational studies have demonstrated an association between the severity of cardiac surgery-related bleeding and 30-day postoperative morbidity and mortality.<sup>6–10</sup> A substudy of the Transfusion Avoidance in Cardiac Surgery study demonstrated that two consensus-based scoring systems for assessing the severity of bleeding, the Universal Definition of Perioperative Bleeding in Adult Cardiac Surgery (UDPB) and the European Coronary Artery Bypass Grafting Bleeding Severity Grade instead of European Coronary Artery Bypass Graft (E-CABG), performed well in predicting 28-day mortality. Specifically, severe bleeding defined as either UDPB class 3 or E-CABG grade 2, both of which comprise transfusion of  $\geq 5$  units of red blood cells, was associated with about 40% relative increased risk of mortality.<sup>6</sup> Suggested mechanisms for bleeding-associated mortality are organ dysfunctions triggered by decreased oxygen delivery and hypotension following major blood loss in patients with atherosclerotic disease and adverse effects of transfusion.<sup>11 12</sup> Preventing perioperative blood loss may be more efficacious in improving outcome than mere reduction of allogenic blood components.<sup>7</sup>

Currently, almost 11% of patients presenting with ACS have to undergo aorto-coronary bypass grafting during DAPT.<sup>13</sup>

In order to reduce the risk of bleeding in patients on P2Y<sub>12</sub> receptor inhibitors presenting for non-emergent cardiac surgery, current ESC and American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend a 'standardised' preoperative discontinuation period of at least 3 days for ticagrelor, 5 days for clopidogrel and 7 days for prasugrel (II a recommendation) to allow for recovery of platelet function.<sup>2 14 15</sup> However, there is still substantial inter-institutional variation in preoperative management of ACS patients on DAPT, and there is heterogeneity in the definition and incidence of bleeding. Moreover, data on prasugrel are sparse.<sup>7 16</sup>

Two big registries used different bleeding definitions to evaluate the overall incidence of major CABG-related bleeding in patients on clopidogrel as compared with ticagrelor and the specific impact of preoperative withdrawal time.<sup>8 9</sup> The Swedish registry including 2244 patients with ACS who underwent CABG demonstrated a 5% lower incidence of Bleeding Academic Research Consortium (BARC) type-4 bleeding in patients on ticagrelor as compared with clopidogrel (12.9% vs 17.6%,  $p=0.033$ ). This difference was mainly driven by a sharp decline in bleeding after 72 hours withdrawal of ticagrelor as compared with a more gradual decrease with

clopidogrel. Importantly, incidence of BARC-4 bleeding was 38% and 31% when ticagrelor / clopidogrel was discontinued less than 24 hours, preoperatively.<sup>8</sup> In contrast, a subgroup analysis of 1376 patients from the E-CABG registry demonstrated a similar incidence of severe or massive UDPB (11.2% vs 8.7%,  $p=0.14$ ) and BARC-4 bleeding (13.2% vs 11.6%,  $p=0.38$ ) in clopidogrel and ticagrelor treated patients, and a similar decrease in bleeding with increasing days off P2Y<sub>12</sub> receptor inhibitors, compatible with time-dependent recovery of platelet function. In a propensity score-matched analysis, 4–5 days off clopidogrel reduced severe/massive UDPB class by 7.3% as compared with a 3-day preoperative withdrawal period ( $p=0.031$ ). Similarly, 3 days off ticagrelor reduced bleeding by 13.3% as compared with a 0–2 days preoperative withdrawal period ( $p=0.003$ ).<sup>9</sup>

However, the additional impact of covariates known to affect CABG-related bleeding, the potential bias introduced by preoperative anaemia, occurring in up to 40% of patients undergoing cardiac surgery, and the incidence of myocardial infarction in this particular patient population remain largely elusive so far.<sup>17–21</sup>

The proposed review is therefore needed to determine the effect of preoperative P2Y<sub>12</sub> receptor inhibitors and time of preoperative withdrawal in patients undergoing on-pump CABG on primary (BARC-4 bleeding) and secondary outcomes (all-cause mortality and myocardial infarction) in studies published from July 2013 to November 2021. Studies published until June 2013 have been included in a prior pooled meta-analysis which demonstrated that late preoperative discontinuation of P2Y<sub>12</sub> receptor inhibitors (<5 days) was associated with a 2.5-fold and 1.5-fold increased risk of reoperation for bleeding and death, respectively, as compared with early ( $\geq 5$  days) preoperative discontinuation.<sup>21</sup>

Although not yet validated regarding the risk of CABG-associated morbidity and mortality, we decided to use the BARC-4 bleeding definition because BARC bleeding has been introduced as a standardised bleeding endpoint for patients receiving antithrombotic therapy.<sup>22</sup>

To fill the gaps in the knowledge as outlined above, we will aim to conduct an individual patient data meta-analysis (IPD-MA). The primary objective will be to assess the incidence of BARC-4 bleeding depending on type of P2Y<sub>12</sub> receptor inhibitors and drug-specific preoperative withdrawal period. Furthermore, the effect of preoperative P2Y<sub>12</sub> receptor inhibitors on in-hospital/30-day all-cause mortality and myocardial infarction in on-pump CABG patients will be evaluated. We will correct for demographic and procedural variables and we will perform subgroup analyses to identify the influence of preoperative anaemia and non-emergent CABG versus urgent/emergent CABG on outcome.

**Table 1** Search strategy for PubMed

ID	Query
#1	(clopidogrel OR Prasugrel OR Ticagrelor OR dual antiplatelet OR dual-antiplatelet OR P2Y12 receptor inhibitor OR p2y12 receptor antagonist OR p2y12 Inhibitor OR p2y12-inhibitor OR P2Y12 inhibit* OR P2Y12-Inhibit* OR platelet aggregation inhibitor* OR thienopyridine OR ADP receptor blocking agent OR ADP receptor antagonist OR ADP-receptor antagonist OR Adenosine diphosphate receptor antagonist OR ADP-Receptor* OR ADP Receptor* OR Purinergic P2Y Receptor Antagonists [MeSH])
#2	(cabg OR cardiac surgery OR coronary artery bypass OR Coronary artery surgery OR coronary surgery OR Coronary bypass surgery OR heart surgery OR “on pump” OR on-pump OR Coronary revascularization OR Coronary revascularisation OR myocardial revascularization OR myocardial revascularisation OR (coronary OR cardiac) AND (bypass OR surgery OR surgical OR operation OR operative)) OR Coronary Artery Bypass [MeSH] OR myocardial revascularization [MeSH])
#3	(bleeding OR bleed* OR hemorrhage OR hemorrhag* OR haemorrhage OR haemorrhag* OR barc OR Blood loss OR Blood Loss, Surgical [MeSH] OR hemorrhage (MeSH Terms))
#4	#1 AND #2 AND #3
#5	#4 AND July 2013–November 2021
#6	#5 AND English

## METHODS AND ANALYSES

The review will be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data (PRISMA-IPD) Statement.<sup>23</sup>

### Sources of evidence and search strategy

We will search PubMed (July 2013 to November 2021, search strategy see [table 1](#)) and EMBASE (2014–2021, search strategy see [table 2](#)) for a combination of terms, MeSH terms and their synonyms in titles and abstracts like ‘clopidogrel’, ‘prasugrel’, ‘ticagrelor’, ‘dual antiplatelet’, ‘P2Y<sub>12</sub> receptor inhibitor’, ‘CABG’, ‘bleeding’, ‘haemorrhage’. Vocabulary and syntax will be adjusted across databases. This strategy was reviewed by a librarian of the Medical University of Graz. Two researchers (IL and MS) will search separately according to the search strategy as described in [tables 1 and 2](#). We will also search the Cochrane Library and will carry out a hand search. Unpublished ongoing clinical studies will be searched

from WHO International Clinical Trials Registry Platform, ClinicalTrials.gov and Prospero (until November 2021).

### Inclusion and exclusion criteria

We will include randomised controlled trials (RCTs) and observational trials that evaluate the effect of different P2Y<sub>12</sub> receptor inhibitors (clopidogrel, prasugrel and ticagrelor) and drug-free period prior to surgery on any of the defined outcome measures (BARC-4 bleeding, mortality, non-fatal myocardial infarction), to assess differences depending on

1. The individual P2Y<sub>12</sub> receptor inhibitor.
2. Preoperative withdrawal time.

We will include adult female and male patients of any age undergoing on-pump CABG during DAPT with aspirin and a P2Y<sub>12</sub> receptor inhibitor.

### Inclusion criteria are

- Full text articles in English.

**Table 2** Search strategy for Embase

ID	Query
#1	clopidogrel OR Prasugrel OR Ticagrelor OR dual antiplatelet* OR dual-antiplatelet* OR P2Y12 receptor inhibitor OR p2y12 receptor antagonist OR p2y12 Inhibitor OR p2y12-inhibitor OR P2Y12 inhibit* OR P2Y12-Inhibit* OR platelet aggregation inhibitor* OR thienopyridine* OR ADP receptor blocking agent* OR ADP receptor antagonist* OR ADP-receptor antagonist* OR Adenosine diphosphate receptor antagonist OR ADP-Receptor* OR ADP Receptor*
#2	cabg OR cardia* surg* OR coronary artery bypass OR Coronary artery surg* OR coronar* surg* OR Coronary bypass surg* OR heart surg* OR on pump OR on-pump OR Coronar* revasculari* OR myocardial revasculari*
#3	bleed* OR hemorrhag* OR haemorrhag* OR barc OR Blood los*
#4	Blood adj3 los
#5	#3 OR #4
#6	#1 AND #2 AND #5
#7	#6 AND English language
#8	#7 AND 2014–current

- ▶ Isolated on-pump CABG.
- ▶ Patients on DAPT (irrespective of type of P2Y<sub>12</sub> inhibitor) with the withdrawal period being equal to or shorter than 7 days.
- ▶ At least one BARC-4 criteria documented.

#### Exclusion criteria are

- ▶ Off-pump CABG.
- ▶ Complex surgery (eg, CABG+valve).
- ▶ Timing of surgery based on preoperative platelet function.

#### Intervention

Intervention: CABG with a drug-specific preoperative withdrawal time of P2Y<sub>12</sub> receptor inhibitors (clopidogrel, prasugrel or ticagrelor) shorter than suggested by ESC and AHA/ACC guidelines.

Comparison: CABG with a drug-specific preoperative withdrawal period of P2Y<sub>12</sub> receptor inhibitors (clopidogrel, prasugrel or ticagrelor) according to the ESC and AHA/ACC guidelines.

#### OUTCOMES

##### Primary outcome

BARC-4 bleeding, defined as any of the following<sup>22</sup>:

(A) Perioperative intracranial bleeding within 48 hours, (B) reoperation after closure of sternotomy for the purpose of controlling bleeding, (C) transfusion of 5 units or more of packed RBCs within 48 hours or (D) 24-hour chest tube drainage of 2000 mL or more.

##### Secondary outcomes

- ▶ Mortality (in-hospital mortality/30-day mortality).
- ▶ Ischaemic end points defined according to the Academic Research Consortium-2 Consensus Document comprising death, myocardial infarction and stent thrombosis.<sup>24</sup>

##### Languages

English.

##### Time

Study start April 2021; anticipated study end March 2023.

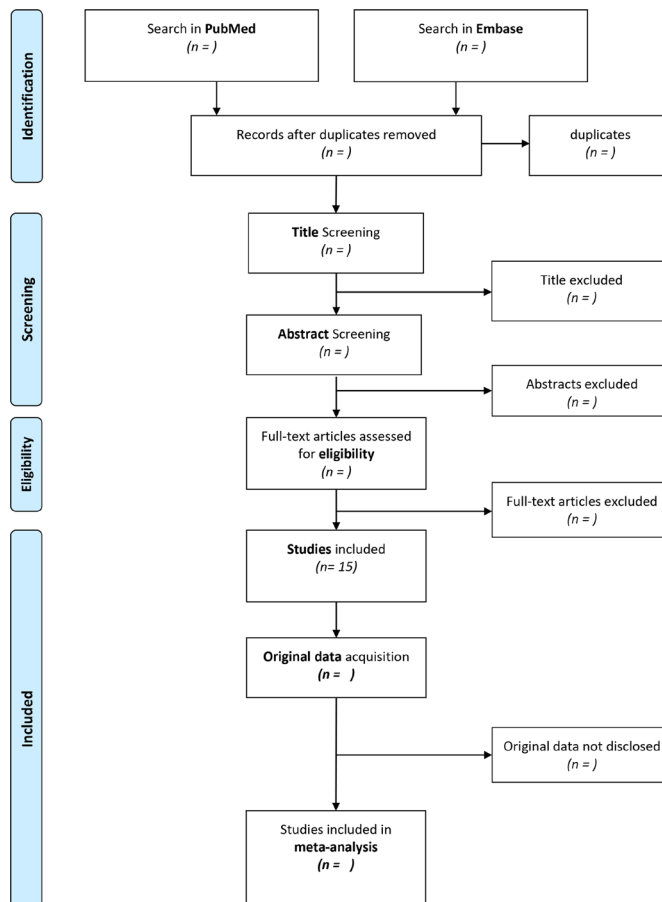
#### STUDY RECORDS

##### Data management

All search results will be downloaded into a compatible version of MS Excel (MS Office Professional Plus 2016) from the interfaces. We will transfer these results into a common Excel file for deduplication. For manual deduplication we will have two criteria, title and author, to unambiguously recognise duplicates. Finally, we will do a cross check of the number of included studies.

##### Selection process

Using the results of the above searches, two authors (IL and MS) will independently screen all titles and abstracts



**Figure 1** Flow chart diagram presenting the selection of articles for systemic review and meta-analysis of incidence of BARC-4 bleeding depending on type of P2Y<sub>12</sub> receptor inhibitor and preoperative withdrawal period. BARC, Bleeding Academic Research Consortium.

for eligibility. Each of the two authors will document the reason for exclusion of each trial to be excluded. All records deemed potentially relevant by at least one author will be obtained in full text format and assessed according to eligibility criteria independently by IL and MS. In a second step, these evaluations will be discussed with a third researcher (EM) to resolve disagreements. The selection process will be plotted in a flow diagram in accordance with the PRISMA-P statement (figure 1).<sup>23 25</sup>

##### Data extraction and management

We will independently extract study characteristics such as study design (RCTs, observational trials), authors, year of publication and setting of study. We will aim to perform an IPD-MA for the review questions because the main outcome of interest, BARC-4 bleeding, is not generally reported in the literature. IPD-MA would furthermore allow for the direct incorporation of demographic and procedural variables that were previously identified as potential confounders of increased bleeding into the analysis.<sup>7 16 26</sup>

Following the selection process, we will address the first author or, if unavailable, the corresponding author of each identified study. All authors will be asked to provide a selection of parameters from their original datasets in a

**Table 3** Parameters requested from individual studies

	Parameter	Categories/unit
Demographics	Age*	years
	Gender*	M/F
	Weight	kg
	Height	m
	BMI	kg/m <sup>2</sup>
	Creatinine	mg/dL or µmol/L
	Creatinine clearance*	mL/min
	Diabetes mellitus	y/n
	Liver disease	y/n
	LVEF*	%
	Euroscore 2	
	UFH or LMWH or fondaparinux (within 24 hours preop)	y/n
Procedural variables	Urgency*	Elective/urgent/emergency/salvage
	CABG indication	Stable CAD/NSTEMI/STEMI
	CPB time	minutes
	No of arterial grafts	
	No of distal anastomoses	
	Tranexamic acid during surgery	y/n
	Hb preoperative	g/L
	Platelets preoperative	x10 <sup>9</sup> /L
	Institutional protocol for treating postpump bleeding	y/n
	ASS perioperative continuation	y/n
	ASS cessation prior to surgery	days
	Clopidogrel preoperative	y/n
	Clopidogrel cessation prior to surgery	days
	Prasugrel preoperative	y/n
	Prasugrel cessation prior to surgery	days
	Ticagrelor preoperative	y/n
	Ticagrelor cessation prior to surgery	days
Outcome	Chest tube drainage volume within 24 hours†	ml
	Reoperation due to bleeding	y/n
	Intracranial bleeding within 48 hours perioperatively	y/n
	No of transfused red blood cell units within 48 hours from incision	
	Postoperative MI	y/n
	In-hospital mortality	y/n
	30-day mortality	y/n

\*Part of euroscore II.

†If unavailable chest tube drainage volume obtained during shorter observation period (define observation period).

ASS, Aspirin; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, Coronary Artery Disease; CPB, Cardiopulmonary Bypass; Hb, Haemoglobin; LMWH, Low Molecular Weight Heparin; LVEF, Left ventricular ejection fraction ; MI, Myocardial infarction; NSTEMI, Non-ST-Elevation Myocardial Infarction; STEMI, ST-Elevation Myocardial Infarction; UFH, Unfractionated heparin.

pseudonymised fashion that does not allow identification of individual identities. We will provide an Excel sheet outlining the requested parameters (see [table 3](#)). After accepting the invitation to collaborate and signing both a confidentiality and data transfer agreement, the authors will be asked to share their data via a secure server of the Medical University of Graz. This uploading process is encrypted. The stored data will be protected by access

authorisation. The received data will be reviewed to assess the completeness and accuracy of the dataset.

Plausibility checks of the received data will be performed by comparing summary measures of the IPD with the published data as well as by checking plausibility of the individual values in a clinical context. Any implausibilities will be resolved with the original authors through queries. Individual datasets will be preprocessed and merged into

a single datafile for analysis. At the end of the study, all original individual datasets will be deleted.

### RISK OF BIAS

Two authors (IL and MS) will assess the risk of bias for each trial independently. Possible disagreements will be resolved by consensus, or with consultation of a third party (EM).

For RCTs, we will assess risk of bias using the Cochrane Collaboration's tool.<sup>27</sup> We will use the following bias criteria:

- ▶ Random sequence generation (selection bias).
- ▶ Allocation concealment (selection bias).
- ▶ Blinding (performance bias and detection bias), separately for blinding of participants and personnel and blinding of outcome assessment.
- ▶ Incomplete outcome data (attrition bias).
- ▶ Selective reporting (reporting bias).
- ▶ Other bias.

We will judge risk of bias criteria as 'low risk', 'high risk' or 'unclear risk' as described in the Cochrane Handbook for Systematic Reviews of Interventions.<sup>27</sup>

For observational studies, the quality of each study will be assessed using the Robins-I Tool as suggested by the Cochrane Handbook for Systematic Reviews of Interventions.<sup>27</sup>

The following domains will be assessed:

- ▶ Bias due to confounding.
- ▶ Bias in selection of participants into the study.
- ▶ Bias in classification of interventions.
- ▶ Bias due to deviations from intended interventions.
- ▶ Bias due to missing data.
- ▶ Bias in measurement of outcomes.
- ▶ Bias in selection of the reported result.

### DATA SYNTHESIS

The primary analysis will be performed as a two-stage IPD-MA. For this approach, each study will first be individually analysed according to a prespecified regression model for each type of P2Y<sub>12</sub> inhibitor including drug specific preoperative withdrawal time as well as relevant confounders (see table 3). The results of these analyses will be presented as odds ratios (OR) and 95% confidence intervals (CI) and can be displayed in a forest plot. For the second stage, these results will be pooled using standard meta-analytic methods, in our case random-effects models.

If we cannot get individual patient data for all identified studies, the risk of availability bias will be assessed by comparing study characteristics of those providing data and those that do not. For studies not providing individual patient data but presenting the respective outcomes, we will incorporate these results in a sensitivity analysis to test the robustness of the IPD findings. Furthermore, the equivalent to the well-known Funnel plot will be visually assessed.

Additionally, subgroup analyses are planned for:

- ▶ Patients undergoing non-emergent CABG versus patients undergoing urgent/emergent CABG because of ACS.
- ▶ Patients preoperatively presenting with anaemia according to the WHO-definition of less than 13 g/dL for men and less than 12 g/dL for women versus preoperatively non-anaemic patients.

Furthermore, sensitivity analyses will test the robustness of our findings for the analysis of the primary outcome. They will be performed for study quality and drug-specific preoperative withdrawal periods for each single day of withdrawal, including no preoperative withdrawal.

The analyses will be performed using a current version of R. No imputation for missing data is planned. The analyses are performed in accordance with the handbook of the Cochrane collaboration and results will be presented according to the PRISMA-IPD statement.<sup>23</sup>

### Author affiliations

<sup>1</sup>Division of Anesthesiology for Cardiovascular Surgery and Intensive Care Medicine, Medical University of Graz, Graz, Austria

<sup>2</sup>Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria

<sup>3</sup>Department of Anesthesiology and Intensive Care Medicine, Hospital Hochsteiermark, Steiermarkische Krankenanstaltengesellschaft mbH, Leoben, Austria

<sup>4</sup>Division of Cardiology, Department of Internal Medicine, Medical University of Graz, Graz, Austria

<sup>5</sup>Department of Cardiovascular and Endovascular Surgery, Paracelsus Medical University Salzburg, Salzburg, Austria

**Contributors** MS: study design, bibliographic research, design of data entry forms, data management, conduct of study, protocol and manuscript writing. GP: study design, data management, statistical analysis, protocol and manuscript writing and review. AB: study design, statistical analysis, protocol and manuscript writing and review. IL: bibliographic search, design of data entry forms, data management, conduct of study, protocol and manuscript review. RZ: Scientific coordination, protocol and manuscript writing and review. AV: Scientific coordination, protocol and manuscript review. EM: study design, scientific coordination, protocol and manuscript writing and review. AZ: Scientific coordination, protocol and manuscript review

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### ORCID iD

Andrea Berghold <http://orcid.org/0000-0001-5187-9105>

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