PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	How do type of preoperative P2Y12 receptor inhibitor and withdrawal time affect bleeding? – protocol of a systematic review and individual patient data meta-analysis.
AUTHORS	Schoerghuber, M.; Pregartner, Gudrun; Lindenau, I.; Zweiker, Robert; Voetsch, A.; Mahla, E.; Berghold, Andrea; Zirlik, Andreas

VERSION 1 – REVIEW

REVIEWER	Hibbert, Benjamin University of Ottawa Heart Institute
REVIEW RETURNED	09-Jan-2022

GENERAL COMMENTS	The submitted manuscript is a IPMA of withdrawal of P2Y12 and the impact of this on BARC4 bleeding. The protocol follows PICO format. The authors highlight PRISMA reporting and although not registered they highlight their plan to register the protocol. My only concern - if this is a IPMA - if studies are identified and individual patient level data cannot be obtained it is not strictly kosher to exclude. I would suggest a sensitivity analysis in which cumulative data including studies in which IP data was not obtained is included to ensure the results are not different.

REVIEWER	Hueb, Whady Universidade Federal de Sao Paulo
REVIEW RETURNED	13-Jan-2022

GENERAL COMMENTS	Assuming that surgical bleeding has multifactorial factors, involving heparinization, non-cauterized bleeding points, tissue trauma, it is fair to assume that every patient undergoing CABG will bleed. Thus, the volume of bleeding is directly related to these variables.. In addition, other unassessed variables may contribute to bleeding. Such as liver diseases, blood dyscrasias, von Willebrand disease among others. On the other hand, authors try to identify a possible association of bleeding in patients who used antiplatelet drugs but, discontinued. Assuming also that patients who discontinued drugs are free from their effect, any association between surgical bleeding and drug discontinuation time will be merely speculative. Thus, the only rationale of the study to be considered, would be the effect of the suspension for three days, for five days or for seven days, comparing with patients using drugs, thus indicating the safety of the time of suspension of the drug. Furthermore, responses should

	individualize groups (robust) of patients with single, double, or triple anti-platelet aggregation in a comparative analysis. For the study to be considered mechanistic, this reviewer suggests that authors include randomized clinical trials that did not require (or could not) discontinue antiplatelet drugs. Thus, perioperative bleeding would have its causes confirmed and not suggested.

REVIEWER	Mamas, Mamas Keele University
REVIEW RETURNED	19-Jan-2022

GENERAL COMMENTS	The authors propose an IPD meta-analysis studying the relationship between timing of P2Y12 receptor inhibitor discontinuation and clinical outcomes (BARC 4 bleeding, death, AMI) in patients undergoing CABG. This is an important study, as whilst guidelines exist, the practice varies significantly by institution. The methods seem appropriate but i have a number of comments 1) Has the review been registered on Prospero? 2) inclusion/ exclusion- it isnt clear to me whether inclusion is any patient referered for CABG on DAPT, or whether this is restricted to ACS cases. Patients may be on DAPT for example following PCI. another key point is whether this will only consider elective cardiac surgery or will emergency cardiac surgery be considered, for example as a bail out following a PCI complication. 3) How will the authors deal with other drugs given during the ACS admission / PCI procedure prior to the surgery that may impact on bleeding, such as GPIIB/IIIA inhibitors? or rivoroxaban 4) one factor not considered that would be important to protocolise, is how will the authors deal with timing of admission with ACS/ PCI vs timing of cardiac surgery. if a patient had a PCI several months ago and is still on DAPT, the impact of wihdrawing the P2Y12 receptor inhibitor will be far less than if it was withdrawn a few days after PCI, due to lack of strut endothelialisation. Simialr arguements can be used for ACS. taking into account how long the ACS/ PCI or whatever reason patient is on a P2Y12 receptor inhibitor will be key 5) will patients treated wih a VKA/ NOAC be excluded? such as those with chronic AF? 6) outcomes- please include stent thrombosis as an outcome. The authors should try and seperate events that occur pre-operatively and post operatively 7) where will data be stored? what is the data governance? how will anonymisation of data be maintained? how will data be protected? who will have access? what will happen to data at the end of study? This is important

VERSION 1 – AUTHOR RESPONSE

Please add a question mark to the title.

Answer: Done as suggested.

Please revise the abstract >> ethics and dissemination to include information about ethics approval and how study findings will be disseminated. As this is an individual patient data meta-analysis what ethics approval process and data sharing agreements need to be followed? (if not applicable then please explain why not here)

Answer: Done as requested. In the revised abstract it now reads “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.”

Please add the PROSPERO registration ID number to the manuscript, where applicable (the ID number starts with ‘CRD’).

Answer: Done as requested, CRD42022291946 added to the abstract of the revised manuscript.

Please revise the ‘Strengths and limitations’ section of your manuscript (after the abstract). This section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods. The novelty, aims, results or expected impact of the study should not be summarised here.

Answer: Bullet points are rewritten as requested.

The tense is inconsistent throughout the paper. As this is a study protocol can you please consistently use the future tense?

Answer: Future tense is now consistently used in the abstract and in the body of the manuscript as appropriate.

Please carefully check the paper for typographical errors e.g. page 8: “Clinicaltrails.gov” should be “ClinicalTrials.gov”.

Answer: Thank you, manuscript checked for typos.

Please remove the PRISMA checklist and instead provide a completed copy of the PRISMA-P checklist (http://www.prisma-statement.org/documents/PRISMA-P-checklist.pdf)

Answer: Thank you for pointing this out. We removed the PRISMA checklist and instead provide a completed copy of the PRISMA-P checklist.

Answers to Dr. Benjamin Hibbert, University of Ottawa Heart Institute, reviewer 1:

The protocol follows PICO format. The authors highlight PRISMA reporting and although not registered they highlight their plan to register the protocol.

Answer: The protocol was submitted to PROSPERO December 10th 2021. PROSPERO registration number is CRD42022291946 and is added to the revised abstract.

My only concern - if this is a IPMA - if studies are identified and individual patient level data cannot be obtained it is not strictly kosher to exclude. I would suggest a sensitivity analysis in which cumulative data including studies in which IP data was not obtained is included to ensure the results are not different.

Answer: We thank the reviewer for his valuable remark. In the data synthesis section we stated that “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.“ In the revised manuscript (page 17) we added „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.“

Answers to Dr. Whady Hueb, Universidade Federal de Sao Paulo, reviewer 2:
Assuming that surgical bleeding has multifactorial factors, involving heparinization, non-cauterized bleeding points, tissue trauma, it is fair to assume that every patient undergoing CABG will bleed. Thus, the volume of bleeding is directly related to these variables. In addition, other unassessed variables may contribute to bleeding. Such as liver diseases, blood dyscrasias, von Willebrand disease among others. On the other hand, authors try to identify a possible association of bleeding in patients who used antiplatelet drugs but, discontinued.
Assuming also that patients who discontinued drugs are free from their effect, any association between surgical bleeding and drug discontinuation time will be merely speculative. Thus, the only rationale of the study to be considered, would be the effect of the suspension for three days, for five

days or for seven days, comparing with patients using drugs, thus indicating the safety of the time of suspension of the drug.

Answer: Thank you Sir! There is evidence of an association between the extent of platelet inhibition and CABG related bleeding. This evidence stems from both large registries, demonstrating decreasing, though variable incidence of CABG related bleeding with increasing days off $P2Y_{12}$ receptor inhibitors, and smaller studies showing an association between direct measures of platelet inhibition and bleeding from our group and others (Holm, ATS 2019, Hansson EHJ 2016, Mahla ATS 2016, Voetsch ATS 2021). It is very doubtful that there will ever be a big RCT dealing with the optimal preoperative drug-specific withdrawal period resulting in a class I recommendation.
Therefore, the focus of this individual patient data meta-analysis in patients undergoing isolated on-pump coronary artery bypass grafting during dual antiplatelet therapy is to investigate the association between adherence to a class IIa recommendation of drug-specific preoperative withdrawal time of $P2Y_{12}$ receptor inhibitors and clinical and procedural variables on surgery-related bleeding (Valdimigli EHJ 2017). This focus is exemplified under the first two bullet points of the revised strength and limitations section as requested by the editor. Additionally, the definition of BARC-4 bleeding was added on page 12 of the revised manuscript.

There may be some residual platelet inhibition due to variable on-treatment platelet reactivity and platelet function recovery after the recommended preoperative waiting period of 3, 5 and 7 days for ticagrelor, clopidogrel and prasugrel, respectively. However, this residual platelet inhibition is unlikely to be below 208 platelet reactivity units, the defined cutoff for “high platelet reactivity” (Tantry, JACC 2013, Price RECOVERY trial JACC 2012, Gurbel ONSET OFFSET Circulation 2009). Moreover, preoperative platelet function testing, targeted at achieving “high platelet reactivity”, has been demonstrated to be non-inferior to a standardized 5 - 7 days preoperative withdrawal period in patients on clopidogrel in terms of chest output drainage as has been shown by our group and others (Mahla, TARGET CABG, Circ intervention 2012, Nakashima JACC 2011).
Furthermore, responses should individualize groups (robust) of patients with single, double, or triple anti-platelet aggregation in a comparative analysis.

Answer: The focus of this IPD-MA including patients undergoing isolated on-pump CABG during dual antiplatelet therapy is only to investigate the association of clinical and procedural variables on BARC-4 bleeding (CABG-related bleeding) in addition to adherence to a class IIa recommendation of drug-specific preoperative withdrawal time of $P2Y_{12}$ receptor inhibitors.

Among patients undergoing coronary artery surgery, the administration of preoperative aspirin resulted in neither a lower risk of death or thrombotic complications nor a higher risk of bleeding than with placebo. A primary ischemic outcome event occurred in 202 patients in the aspirin group (19.3%) and in 215 patients in the placebo group (20.4%) (relative risk, 0.94; 95% confidence interval, 0.80 to 1.12; P = 0.55). Major hemorrhage leading to reoperation occurred in 1.8% of patients in the aspirin

group and in 2.1% of patients in the placebo group (P = 0.75), and cardiac tamponade occurred at rates of 1.1% and 0.4%, respectively (P = 0.08). (ATACAS trial; Myles, NEJM 2016)

Regarding triple therapy, we would like to refer to answer 5 of reviewer 3 and the last bullet point under the revised “Strengths and Limitations section”.

“drug-specific withdrawal time” was added to the Methods and Analysis section of the revised abstract.

In the revised protocol it now reads: “Intervention: CABG with a drug-specific preoperative withdrawal time of $P2Y_{12}$ 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 $P2Y_{12}$ receptor inhibitors (clopidogrel, prasugrel or ticagrelor) according to the ESC and AHA / ACC guidelines.”

For the study to be considered mechanistic, this reviewer suggests that authors include randomized clinical trials that did not require (or could not) discontinue antiplatelet drugs. Thus, perioperative bleeding would have its causes confirmed and not suggested.

Answer: To the best of the authors’ knowledge there are only 2 RCTs dealing with perioperative management in patients undergoing CABG during dual antiplatelet therapy. The first is the study by Nakashima (JACC 2021) showing non-inferiority in bleeding in patients after recommended preoperative waiting as compared to platelet function testing-based waiting. The second is Rapid CABG, the data of which have been presented at AHA, Nov 2021. Early surgery 2-3 days after ticagrelor cessation was non-inferior in incurring severe or massive perioperative bleeding compared to waiting 5-7 days.
To the best of the authors’ knowledge there are no RCTs in patients that did not or could not discontinue P2Y12 receptor inhibitors.
We will ask the study authors for the exact days since withdrawal of clopidogrel, ticagrelor or prasugrel. We will use drug-specific preoperative withdrawal periods to compare patients from the identified studies, with a discontinuation period shorter than suggested by guidelines vs. a discontinuation period adhering to the guidelines. Additionally, we will compare the incidence of BARC-4 bleeding stratified by the days since withdrawal of clopidogrel, ticagrelor or prasugrel thereby also addressing those patients without preoperative $P2Y_{12}$ receptor withdrawal.

In the revised manuscript on page 17 in now reads:

“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.”

Answers to Dr. Mamas Mamas, Keele University, reviewer 3

The authors propose an IPD meta-analysis studying the relationship between timing of P2Y12 receptor inhibitor discontinuation and clinical outcomes (BARC 4 bleeding, death, AMI) in patients undergoing CABG. This is an important study, as whilst guidelines exist, the practice varies significantly by institution. The methods seem appropriate but i have a number of comments

1) Has the review been registered on Prospero?

Answer: We submitted our protocol December 10th 2021 and received the registration number on January 10th 2022. The number is CRD42022291946 and is added to the abstract of the revised version of the manuscript.

2) inclusion/ exclusion- it isnt clear to me whether inclusion is any patient referered for CABG on DAPT, or whether this is restricted to ACS cases. Patients may be on DAPT for example following PCI. another key point is whether this will only consider elective cardiac surgery or will emergency cardiac surgery be considered, for example as a bail out following a PCI complication.

Answer: We will include any study, identified by our search strategy as presented in table 1 and table 2. According to the inclusion criteria as listed on page 11 of the manuscript we will include patients on DAPT (irrespective of type of $P2Y_{12}$ inhibitor) with the withdrawal period being equal to or shorter than 7 days. Subgroup analysis is planned for patients undergoing non-emergent CABG vs patients undergoing urgent / emergent CABG because of ACS as has been stated on page 17 of the manuscript.

3) How will the authors deal with other drugs given during the ACS admission / PCI procedure prior to the surgery that may impact on bleeding, such as GPIIB/IIIA inhibitors? or rivoroxaban

Answer: Other drugs like heparin, bivalirudin or GPIIb/IIIa-blockers are given at the discretion of the cardiologists in charge of the individual patient. Due to the generally short half-lives (with the exception of abciximab which rarely comes to use) those drugs should cause limited interference with platelet function at the time of surgery. As an example, the most commonly used drug eptifipatide has a half-life of 2,5 hours. It has been tested by the PURSUIT-Study against placebo in almost 10,000 patients. 752 of them underwent CABG, major bleedings occurred in 8,2% in both treatment arms. (NEJM 1998) In our collective, GPIIb/IIIa usage was extremely low with a rate of 1,7% (Voetsch ATS 2016)
Regarding oral antagonists please see answer to question 5

4) one factor not considered that would be important to protocolise, is how will the authors deal with timing of admission with ACS/ PCI vs timing of cardiac surgery. if a patient had a PCI several months ago and is still on DAPT, the impact of wihdrawing the P2Y12 receptor inhibitor will be far less than if

it was withdrawn a few days after PCI, due to lack of strut endothelialisation. Simialr arguements can be used for ACS. taking into account how long the ACS/ PCI or whatever reason patient is on a P2Y12 receptor inhibitor will be key

Answer: The authors assume that this question addresses the risk of ischemic events due to discontinuation of $P2Y_{12}$ receptor inhibitors. In the 2018 ESC/EACTS Guidelines on myocardial revascularization it reads “in the absence of randomized data, optimal timing for non-emergent CABG in NSTE-ACS patients should be determined individually. The risk of ischaemic events possibly related to suboptimal antiplatelet therapy while awaiting surgery is 0.1% while the risk of bleeding complications is 10%” (Neumann EHJ 2018, Malm BJA 2016). Furthermore “strategies aiming to improve the outcomes by preventing perioperative blood loss may be more efficacious than targeting only a reduction of the exposure to allogenic blood.”(Biancari EHJ European Heart Journal - Quality of Care and Clinical Outcomes, 2018)
We therefore wish to address the association between bleeding and platelet inhibition as primary endpoint and potentially amenable target to improve outcome and the incidence of myocardial infarction, as defined by the authors of the included studies, and death as secondary endpoint.
Based on a previous pooled meta-analysis by Siller Matula (EHJ Acute Cardiovascular care 2015), we expect an around 3% incidence of myocardial infarction. However, both the expected low incidence and the observational nature of the studies included in this meta-analysis will prohibit a more detailed analysis like differentiation between pre- and postoperative MI, as requested by this author.
We discussed this issue with our cardiology coauthors (Robert Zweiker and Andreas Zirlik) before starting our meta-analysis and screened all RCTs included in a recent systematic meta-analysis (Kahn, circulation 2020, n= 79,073). Out of all these studies only global Leaders (n=15,968) report that 21 patients needed urgent surgery during DAPT.

5) will patients treated wih a VKA/ NOAC be excluded? such as those with chronic AF?

Answer: Before starting the literature search according to the defined search terms we repeatedly cross-checked the literature on cardiac surgery-related bleeding and potential covariates of bleeding, being one of our main scientific interests (Mahla, Gurbel Anesthesiology 2020). There is much inconsistency regarding 1. reporting of preoperative intake of oral anticoagulants (vitamin K antagonists / NOACs), 2. reported number of patients on oral anticoagulants, and 3. perioperative management in terms of time of preoperative withdrawal or bridging with heparin. And even if the number of patients on oral anticoagulants is reported, as for instance in the studies of Holm and Hansson (Holm, ATS 2019; Hansson EHJ 2016), it remains elusive whether or not oral anticoagulants were preoperatively discontinued according to the suggested discontinuation periods or antagonized with vitamin K or factor concentrates. Even if oral anticoagulants were antagonized with factor concentrates / Idaruzizumab, “anticoagulation” may recur due to limited half-life of the respective substances.
After a check of studies familiar to the authors and a rough cross-check of a preliminary screening, we identified only 5 patients on novel oral anticoagulants in the E-CABG register (Holm ATS 2019) and

only 28 patients on GP IIb/IIIa antagonists on the whole. We cannot exclude some impact of anticoagulants other than $P2Y_{12}$ receptor inhibitors on bleeding as has been shown for heparin but not for LMWH, fondaparinux or vitamin K antagonists in univariate analysis (Hansson EHJ 2016). We address this limitation in the revised manuscript.
The last bullet point under the revised "Strengths and Limitations section" now reads:

- "This IPD-MA will not be able to delineate a potential additional impact of anticoagulant agents on the incidence of BARC-4 bleeding."

6) outcomes- please include stent thrombosis as an outcome. The authors should try and seperate events that occur pre-operatively and post operatively

Answer: please see answer to question 4 above.

7) where will data be stored? what is the data governance? how will anonymisation of data be maintained? how will data be protected? who will have access? what will happen to data at the end of study? This is important

Answer: Thank you Sir! The respective sentences are added to the Section "Data extraction and management" of the revised manuscript on page 14 and 15.

"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."

"Individual datasets will be pre-processed and merged into a single datafile for analysis. At the end of the study all original individual datasets will be deleted."

VERSION 2 – REVIEW

REVIEWER	Hibbert, Benjamin University of Ottawa Heart Institute
REVIEW RETURNED	14-Feb-2022

GENERAL COMMENTS	My concerns have been addressed. I look forward to the study results.

REVIEWER	Hueb, Whady Universidade Federal de Sao Paulo
REVIEW RETURNED	14-Feb-202

GENERAL COMMENTS	NA

REVIEWER	Mamas, Mamas Keele University
REVIEW RETURNED	14-Feb-2022

GENERAL COMMENTS	The authors have addressed most of my comments. They should reconsider my point re studying stent thrombosis as an outcome- premature DAPT discontinuation is a known risk factor for stent thrombosis, and as such ischemic events including stent thrombosis would be an important safety signal. There is lots of literature around this and citing the ESC guidelines out of context is not really adequate as a rebuttal.

VERSION 2 – AUTHOR RESPONSE

reviewer 3:

The authors have addressed most of my comments. They should reconsider my point re studying stent thrombosis as an outcome- premature DAPT discontinuation is a known risk factor for stent thrombosis, and as such ischemic events including stent thrombosis would be an important safety signal. There is lots of literature around this and citing the ESC guidelines out of context is not really adequate as a rebuttal.

Answer: We thank this reviewer for pointing at the important topic of ischemic events like myocardial infarction and stent thrombosis as potential trade-offs after early discontinuation of DAPT in patients after stenting and/or ACS. We, therefore, decided to adapt the protocol by integrating the ARC-2-Consensus for Definition of Endpoints in Coronary Intervention Trials as follows:

In the abstract – methods and analysis - of the revised manuscript it now reads:
“The secondary outcomes are mortality and ischemic events according to the Academic Research Consortium 2 Consensus Document.”

The second bullet point of the Strengths and Limitations section is amplified by “and potential tradeoffs in terms of ischemic events comprising death, myocardial infarction and stent thrombosis according to Academic Research Consortium 2 Consensus Document.”

“Ischemic end points defined according to the Academic Research Consortium 2 Consensus Document comprising death, myocardial infarction, stent thrombosis” are added to the secondary outcomes on page 11 of the revised manuscript.

VERSION 3 – REVIEW

REVIEWER	Mamas, Mamas Keele University
REVIEW RETURNED	23-Feb-2022

GENERAL COMMENTS	the authors have fully addressed my concerns, thank you