IOSR Journal Of Pharmacy
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 11, Issue 11 Series. I (November 2021), PP. 14-25
www.iosrphr.org

Bridging anticoagulation therapy in patient undergoing coronary artery bypass graft: A systematic review

Wardati Mazlan-Kepli, Chuah Sim Mei, Haizun Athirah Ismail, Soo Pei Yean, Foo Yen See

Department of Pharmacy, Hospital Serdang, Ministry of Health Malaysia, Kajang, Malaysia
Corresponding Author: Wardati Mazlan-Kepli
Received 05 November 2021; Accepted 20 November 2021

Abstract: Patients undergoing coronary artery bypass grafting (CABG) remain at risk of subsequent major adverse cardiovascular and bleeding events. This study reviewed the available evidence on the safety of bridging anticoagulation therapy administered periprocedure CABG and the occurrence of major adverse cardiovascular events (MACE) and bleeding events. We systematically searched Ovid/MEDLINE, PubMed/MEDLINE, and Cochrane Library (Wiley) databases from inception until 8th April 2020. All randomized controlled trials (RCT) of participants (aged >18 years) undergoing CABG surgery and receiving perioperative - bridging anticoagulation therapy were included. Two investigators conducted title and abstract screening while another two investigators screened full text articles according to pre-specified inclusion criteria. The primary endpoint was a MACE, which consists of a composite of all-cause mortality, acute coronary syndrome (ACS), transient ischaemic attack (TIA) or stroke. This review identified 1688 citations and 53 full text articles which were then assessed for eligibility. We did not find any studies that were eligible to be included in this systematic review. Since there were no RCTs evaluating the safety of bridging anticoagulation therapy in patients undergoing CABG, thus, this finding shows that there is a lack of gold-standard studies (i.e. RCTs) to support valid conclusions. There were no RCTs evaluating safety and efficacy of bridging anticoagulant therapy in patients undergoing CABG surgery. This finding suggests that there is an urgent need for RCTs to assess safety and efficacy of bridging anticoagulant therapy in this population. This study was registered with PROSPERO (CRD42020190865).

Keywords: CABG, anticoagulant, major adverse cardiovascular event

I. INTRODUCTOION

The prevalence of coronary artery disease (CAD) is on the rise [1]. Following an acute coronary syndrome (ACS), the patient may receive percutaneous coronary intervention (PCI), which involves the placement of one or more stents in the narrowing artery [2], or coronary artery bypass grafting (CABG), if the patient has left main disease and a SYNTAX score of >32 [3]. After an ACS, stent placement, or while awaiting CABG, dual antiplatelet treatment (DAPT) is indicated.

The majority of patients arranged to undergo CABG are treated with aspirin with or without P2Y12 inhibitors [4]. This antiplatelet therapy will be stopped when the surgery is scheduled [4]. In patients with CAD, however, stopping antiplatelet medication has been linked to a 2 to 4-fold increase in the risk of death and recurrent myocardial infarction [5]. On the other hand, continuing antiplatelet therapy before surgery may increase the risk of bleeding and transfusions [6].

A systematic review and meta-analysis of antiplatelet discontinuation found that the risk of major adverse cardiac events (MACE) was three times higher before CABG [7]. Patients who received perioperative aspirin, on the other hand, had much lower postoperative in-hospital mortality than those who did not receive aspirin (1.7 % vs 4.4%) [8]. A study in Sweden found a 31% prevalence of severe bleeding with complications among patients who underwent CABG. They found that CABG-related significant bleeding was also shown to be high when ticagrelor or clopidogrel was stopped less than 24 hours before surgery [9]. Another study found that patients who received clopidogrel within 5 days following CABG had a substantially greater risk of severe bleeding [10].

Bridging with anticoagulation therapy is recommended to reduce the risk of MACE after CABG [11]. The administration of a brief course of anticoagulant is referred to as bridging anticoagulation therapy and must be modified to account for the risk of postoperative bleeding [12]. Recent meta-analyses and randomized trials have assessed the therapeutic benefits and risks of heparin bridging and managed to inform best practices

regarding 'how to bridge' [13-16]. However, these studies only include patients with atrial fibrillation, device implantation and those who undergo elective or minor surgeries. Uncertainty persists because the dose and type of anticoagulant used as a bridging regimen in patients undergoing CABG surgery are unclear. Therefore, in this study, we aim to systematically review randomized controlled trials that assess the effect of bridging anticoagulation therapy used to prevent MACE in patients undergoing CABG and the occurrences of bleeding.

II. MATERIALS AND METHODS

2.1 Search strategy and selection criteria

We followed a detailed methodology that we describe in the protocol included in Appendix 1. This systematic review and meta-analysis is reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist (Appendix Table 1). This study was registered with PROSPERO (CRD42020190865). This study was registered with National Medical Research Register (NMRR), Ministry of Health Malaysia (NMRR-20-1409-55307). We conducted a search of Ovid/MEDLINE, Pubmed/MEDLINE, and Cochrane Library (Wiley) from their inception to April 2020. The search strategy combines relevant medical subject headings (MeSH) and keywords. The MeSH and keywords contain "coronary artery bypass", antithrombotic, anticoagulant, vitamin K antagonist, individual names of anticoagulants (heparin, low molecular weight heparin i.e. enoxaparin, dalteparin, tinzaparin; warfarin) including their brand names if relevant, and randomized controlled trial (Appendix Table 2).

Studies were eligible for inclusion if they consisted of patients 18 years old and above undergoing CABG surgery and receiving perioperative bridging anticoagulation therapy after temporary interruption of oral antiplatelet(s); if they compared intravenous anticoagulant regimen with placebo, regardless of unit of analysis and drug regimens. Bridging anticoagulation therapy included in this review were intravenous unfractionated heparin (UFH) or subcutaneous LMWH (enoxaparin, dalteparin or tinzaparin). Abstracts presented at conferences, reviews of other articles, letters to the editor, non-English language and non-published studies were excluded from the selection.

The primary endpoint of the study was a cardiovascular event, which consists of composite of all-cause mortality, ACS (MI or unstable angina), transient ischaemic attack (TIA) or stroke. The primary safety outcome was the incidence of major bleeding, defined as transfusion of 4 units of packed red blood cells (PRBCs) and/or a need for re-exploration. Other bleeding outcomes include non-life-threatening bleeding, defined as transfusion of 2 units but <4 units of PRBCs.

2.2 Data identification and extraction

All references were imported into EndNote X9 [17] for title and abstract screening. Two investigators (WMK and CSM) independently screened articles by title and abstract according to pre-specified inclusion criteria. The full text reports of potentially relevant studies were retrieved. Another two investigators (CSM and FYS) independently screened full text according to pre-specified inclusion criteria. Wherever possible, data on study and patient characteristics, treatment strategies, and results of all included studies were independently extracted using a data extraction form. Any discrepancies were resolved by consensus after consulting a third investigator (FYS).

2.3 Risk of bias and certainty assessment

Wherever possible the risk of bias using the approach outlined by the Cochrane Collaboration Risk of Bias Tool (RoB 2.0), which consists of five domains of bias that are relevant to the quality of RCTs was assessed. The risk of bias consists of the following five domains: (1) bias arising from the randomization process, (2) bias due to deviations from the intended interventions, (3) bias due to missing outcome data, (4) bias in the measurement of the outcome, and (5) bias in the selection of the reported result. The RoB 2.0 tool was to be used to assess the risk of bias in individually randomized crossover trials, wherein each trial was categorized into the one of the three groups: (1) high risk of bias; (2) some concerns; and (3) low risk of bias [18, 19].

2.4 Statistical analysis

Wherever possible, descriptive data for each trial as well as data for all pre-specified outcomes were to be tabulated. When trials were determined to be sufficiently similar in terms of descriptive characteristics, standard statistics were used to synthesize the data: odds ratios for binary outcomes and standardized mean differences for continuous outcomes. Wherever possible, 95% confidence intervals were to be generated throughout the review.

Where suitable, sensitivity analysis was to be done to assess the effect of differences in methodological quality, intervention type, and patient characteristics. Separate sensitivity analyses were to be performed where trials other than those comparing the impact of bridging anticoagulant treatment to placebo were included. A

narrative account of the trials included would be presented if statistical combining of different studies proved impossible.

III. RESULTS AND DISCUSSION

The electronic database search identified 1,688 citations. After removal of duplicates, 886 citations remained. These were screened, and where a title clearly identified a study as not being relevant to this review, it was rejected. Abstracts of the remaining titles, where available, were checked for possible inclusion in the review. These totaled 886 abstracts. A total of 53 full texts were considered for inclusion but no studies meeting the stated criteria for inclusion could be identified (Figure). A total of 28 full texts could be clearly excluded on at least one criterion (Boldt 1994, Carrier 2003, Chakravathy 2017, Grima 2003, Hashimoto 1999, Hoenicka 2015, Kolluri 2016, Kozek-Langenecker 1998, Lax 2020, Meesters 2016, Merry 2004, Merry et al 2004, Mirhosseini 2013 Mirow 2001, Mullen 2002, Murase 1993, Nilsson 2012 Ovrum 1995, Pfisterer 1989, Pfisterer 1990, Radulovic 2015, Renda 2007, Shuhaibar 2004, Smedira 2006, Sun 2011, van der Meer 1993,Weiss 1996, Wilczynski 2014) while one study (Boldt 1995) was retracted. A total of 23 studies were rejected on two criteria (Aldea 1996, Aldea 1998, Baufreton 2002, Brinks 2001, Chen 2006, Chew 2008, Gargiulo 2018, Kincaid 2003, Koster 2007, Medalion 2003, Mirow 2008, Nenna 2016, Paparella 2005, Pocock 2010, Pothula 2004, Ranucci 2002, Riess 2007, Tanaka 2007, von Segesser 1990, von Segesser 1994, Weber 1990, Yli-Mäyry 1992) while one study was rejected on three criteria (Kao 2006). A summary of the excluded studies along with reasons for exclusion is provided in Appendix Table 3.

We could not conduct assessment of risk of bias or quality of reporting because there were no eligible studies found for inclusion.

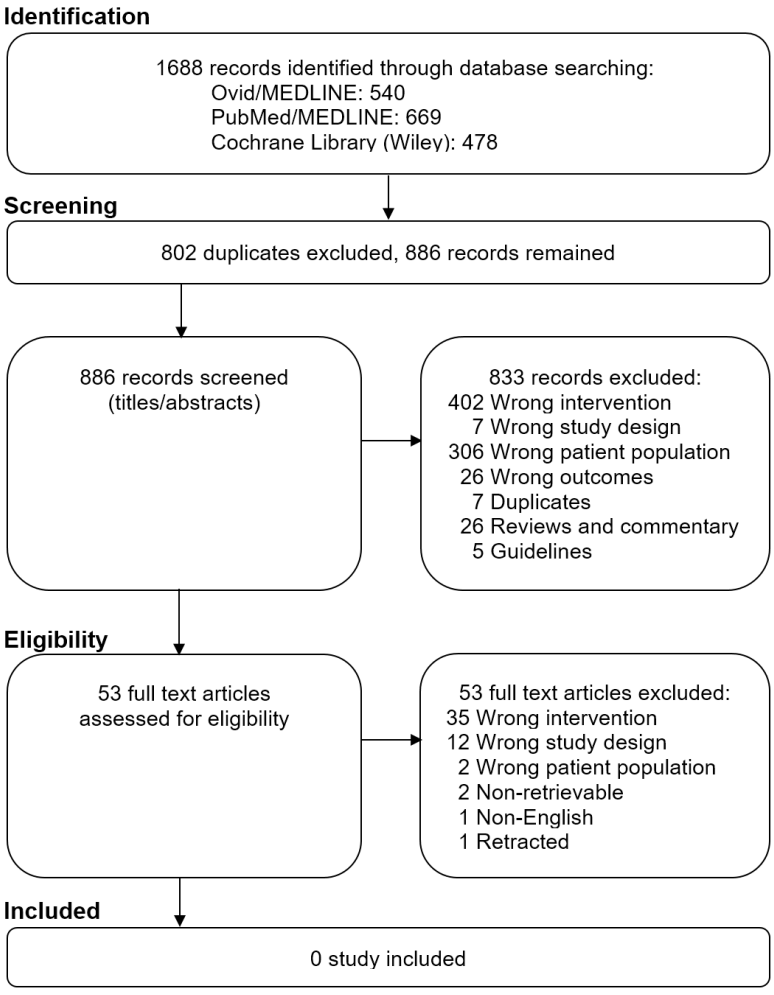

Fig : PRISMA flow diagram for the systematic review bridging anticoagulation therapy in patient undergoing coronary artery bypass graft.

This systematic review aimed to examine the effect of bridging anticoagulation therapy used to prevent MACE and the possible bleeding events in patients undergoing CABG surgery. No studies were identified that

specifically test bridging anticoagulant therapy in patients undergoing CABG surgery, and therefore an empty review is reported. An empty review is defined as a review that does not include any studies that meet the inclusion criteria [20]. The contribution of empty reviews to evidence-based practice is a hot topic of discussion. Reviews that do not include studies are a valuable source of evidence since they indicate knowledge gaps and can assist policymakers and researchers determine whether or not to pursue the topic further [20, 21]. An empty review may arise when review questions are asked about a field of practice with a limited research background. Empty reviews can also be caused by review questions that are more specific in terms of population, intervention, or outcome criteria than those asked in primary research studies [21].

Peri-procedural bridging therapy with heparin or low molecular weight heparin (LMWH) in patients undergoing surgery is a common clinical practice to ensure some antithrombotic protection after interruption of antiplatelet(s) temporarily. A meta-analysis by Du et.al found that perioperative bridging therapy with heparin or LMWH was associated with increased risk of bleeding events and concluded that, continuous OAC in patients undergoing implantation of cardiac implantable electronic devices might offer the best combination of acceptable risk of bleeding complications especially pocket hematoma with lesser thromboembolism [15]. A recent meta-analysis by Kuo et.al found that bridging anticoagulation was associated with increased bleeding risk compared to non-bridging and they do not support routine use of bridging during anticoagulation interruption in patients undergone any invasive procedures or surgery [22]. These studies, however, only involved in patients undergone device implantation and any surgeries; and its safety and efficacy are not yet established in patients undergoing CABG surgery.

The aim of this study was to review all regimens of bridging anticoagulation therapy used to prevent MACE and bleeding events in patients undergoing CABG surgery. Not including grey literature and non-English articles is a limitation of our review, as some important data might be missed. There could have been potential biases in the review process since only randomized controlled trials were included in the protocol. The lack of clinically controlled trials is likely to be the results of complicated procedure, the overall shortage of cardiothoracic surgeons and a lack of adequate funding for larger-scale research endeavors. Of total 436 clinical trials related to CABG surgery and registered at ClinicalTrials.gov, only 11 clinical trials (less than 3%) are related to anticoagulants in patients undergone CABG [23].

IV. CONCLUSION

The findings of this study support the need for a standardized bridging anticoagulation therapy to prevent MACE and to lower the risk of bleeding in patients undergoing CABG surgery. Overall, the study findings suggest that there is an urgent need for RCTs to compare bridging and non-bridging anticoagulation therapy in patients undergoing CABG surgery and more evidence on safety and efficacy of anticoagulation therapy is warranted in this population.

ACKNOWLEDGEMENTS

We would like to thank the Director General of Health Malaysia for his permission to publish this article.

Abbreviations

ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; CAD: coronary artery disease; DAPT: dual antiplatelet treatment; LMWH: low molecular weight heparin; MACE: major adverse cardiovascular event; PRBCs: packed red blood cells; PCI: percutaneous coronary intervention; RCT: randomized controlled trials; TIA: transient ischaemic attack; UFH: unfractionated heparin

REFERENCES

[1]. Celermajer DS, Chow CK, Marijon E, Anstey NM, Woo KS. Cardiovascular Disease in the Developing World: Prevalences, Patterns, and the Potential of Early Disease Detection. J Am Coll Cardiol 2012; 60: 1207-16.

[2]. Doenst T, Haverich A, Serruys P, Bonow RO, Kappetein P, Falk V, Velazquez E, Diegeler A, Sigusch H. PCI and CABG for Treating Stable Coronary Artery Disease: JACC Review Topic of the Week. J Am Coll Cardiol 2019; 73: 964-76.

[3]. Sousa-Uva M, Neumann F-J, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, Group ESCSD. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2019; 55: 4-90.

[4]. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the

European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018; 39: 213-60.
[5]. Collet JP, Montalescot G, Blanchet B, Tanguy ML, Golmard JL, Choussat R, Beygui F, Payot L, Vignolles N, Metzger JP, Thomas D. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. Circulation 2004; 110: 2361-67.
[6]. Sousa-Uva M, Head SJ, Milojevic M, Collet J-P, Landoni G, Castella M, Dunning J, Gudbjartsson T, Linker NJ, Sandoval E, Thielmann M, Jeppsson A, Landmesser* U. 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. Eur J Cardiothorac Surg 2018; 53: 5-33.
[7]. Biondi-Zoccai GGL, Lotrionte M, Agostoni P, Abbate A, Fusaro M, Burzotta F, Testa L, Sheiban I, Sangiorgi G. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50 279 patients at risk for coronary artery disease. Eur Heart J 2006; 27: 2667-74.
[8]. Bybee KA, Powell BD, Valeti U, Rosales AG, Kopecky SL, Mullany C, Wright RS. Preoperative aspirin therapy is associated with improved postoperative outcomes in patients undergoing coronary artery bypass grafting. Circulation 2005; 112: I286-92.
[9]. Hansson EC, Jidéus L, Åberg B, Bjursten H, Dreifaldt M, Holmgren A, Ivert T, Nozohoor S, Barbu M, Svedjeholm R, Jeppsson A. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study. Eur Heart J 2016; 37: 189-97.
[10]. Blais DM, Zukkoor SM, Hayes C, 3rd, Pickworth KK, Porter K, Firstenberg MS. Bleeding outcomes associated with coronary artery bypass graft surgery and recent clopidogrel exposure. Heart Surg Forum 2013; 16: E70-7.
[11]. Wysokinski WE, McBane RD, 2nd. Periprocedural bridging management of anticoagulation. Circulation 2012; 126: 486-90.
[12]. BRIDGE Study Investigators. Bridging anticoagulation: is it needed when warfarin is interrupted around the time of a surgery or procedure? Circulation 2012; 125: e496-8.
[13]. Sant'anna RT, Leiria TL, Nascimento T, Sant'anna JR, Kalil RA, Lima GG, Verma A, Healey JS, Birnie DH, Essebag V. Meta-analysis of continuous oral anticoagulants versus heparin bridging in patients undergoing CIED surgery: reappraisal after the BRUISE study. Pacing Clin Electrophysiol 2015; 38: 417-23.
[14]. Birnie DH, Healey JS, Wells GA, Verma A, Tang AS, Krahn AD, Simpson CS, Ayala-Paredes F, Coutu B, Leiria TLL, Essebag V. Pacemaker or Defibrillator Surgery without Interruption of Anticoagulation. N Engl J Med 2013; 368: 2084-93.
[15]. Du L, Zhang Y, Wang W, Hou Y. Perioperative anticoagulation management in patients on chronic oral anticoagulant therapy undergoing cardiac devices implantation: a meta-analysis. Pacing Clin Electrophysiol 2014; 37: 1573-86.
[16]. Di Biase L, Burkhardt JD, Santangeli P, Mohanty P, Sanchez JE, Horton R, Gallinghouse GJ, Themistoclakis S, Rossillo A, Lakkireddy D, Reddy M, Hao S, Hongo R, Beheiry S, Zagrodzky J, Rong B, Mohanty S, Elayi CS, Forleo G, Pelargonio G, Narducci ML, Dello Russo A, Casella M, Fassini G, Tondo C, Schweikert RA, Natale A. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. Circulation 2014; 129: 2638-44.
[17]. The EndNote Team. EndNote. EndNote X9. 2013.
[18]. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.
[19]. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.
[20]. Yaffe J, Montgomery P, Hopewell S, Shepard LD. Empty reviews: a description and consideration of Cochrane systematic reviews with no included studies. PLoS One 2012; 7: e36626-e26.
[21]. Slyer JT. Unanswered questions: implications of an empty review. JBI Evidence Synthesis 2016; 14.
[22]. Kuo HC, Liu FL, Chen JT, Cherng YG, Tam KW, Tai YH. Thromboembolic and bleeding risk of periprocedural bridging anticoagulation: A systematic review and meta-analysis. Clin Cardiol 2020; 43: 441-49.
[23]. National Library of Medicine (NLM). Search results for: coronary artery bypass graft | Interventional Studies | Anticoagulant (46 records). July 9. https://clinicaltrials.gov/ct2/results?cond=&term=coronary+artery+bypass+graft&intr=Anticoagulant&cn

try=&state=&city=&dist=&Search=Search&type=Intr.
[24]. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.

Appendix 1. Study protocol

Bridging Anticoagulation Therapy in Patient Undergoing Coronary Artery Bypass Graft: A Systematic Review Protocol

Wardati Mazlan-Kepli, Chuah Sim Mei, Haizun Athirah Ismail, Soo Pei Yean

Method and Design

This protocol, which outlines methods for the proposed systematic review, was designed in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) Guidelines. The protocol is registered in the PROSPERO database (CRD42020190865). The items of this protocol are presented in accordance with the PRISMA-P checklist.

Review Question

This systematic review protocol outlines the procedures for a systematic literature review that is intended to answer the question: What is the impact of bridging anticoagulation therapy on the incidence of major adverse cardiac events (MACEs) and bleeding risks in patient undergoing CABG?

Eligibility criteria

The components of population, intervention, comparator, and outcome (PICO) are as follows:

Types of participants

Participants will include adults aged 18 years old and above undergoing CABG surgery and receiving perioperative bridging anticoagulation therapy after temporary interruption of oral antiplatelet(s).

Types of interventions

Interventions of interest are bridging anticoagulation therapy with intravenous unfractionated heparin (UFH) or subcutaneous LMWH (enoxaparin, dalteparin or tinzaparin), regardless of dose and duration of treatment.

Types of comparator

The comparator is no bridging anticoagulation (matching placebo)

Types of outcome

The primary endpoint of the study is a cardiovascular event, which consists of composite of all-cause mortality, ACS (MI or unstable angina), transient ischaemic attack (TIA) or stroke.

The secondary outcome is major bleeding, defined as transfusion of 4 units of packed red blood cells (PRBCs) and/or a need for re-exploration. Other bleeding outcomes include non-life-threatening bleeding, defined as transfusion of 2 units but <4 units of PRBCs.

Types of studies

Eligible studies are randomized control trials assessing the efficacy and safety of bridging anticoagulation therapy in patients undergoing CABG.

Search Strategy

The electronic database of Ovid/MEDLINE, PubMed/MEDLINE, and Cochrane Library (Wiley) were searched from inception to April 2020. The search strategy combines relevant medical subject headings (MeSH) and keywords. The MeSH and keywords contain “coronary artery bypass”, antithrombotic, anticoagulant, vitamin K antagonist, individual names of anticoagulants (warfarin, heparin, low molecular weight heparin i.e. enoxaparin, dalteparin, tinzaparin) including their brand names if relevant, and randomized controlled trial.

Study selection

Non-English language and non-published studies will be excluded from the selection. Results obtained from the electronic databases will be narrowed down using limiters in accordance with the aforementioned criteria.

All identified records will be entered into a reference manager, EndNote X7 in which duplicate articles will be removed. Screening of titles, abstracts and full texts according to inclusion and exclusion criteria were conducted by the first and second authors, Wardati Mazlan Kepli and Chuah Sim Mei. Any disagreements on whether a study should be included or excluded were resolved through consensus.

Data extraction

Data will be extracted from eligible studies based on the template developed by the Cochrane Collaboration. PRISMA flow diagram for the systematic review will be produced. Data will include study and publication details, participants and intervention characteristics as well as outcomes of interest. Two reviewers will independently perform data extraction. Corresponding authors will be contacted for key information when data are ambiguous or missing from the published study.

Data synthesis

For quantitative data, odds ratio and their 95% confidence intervals will be calculated from the data generated by each included randomised controlled trial. Heterogeneity between combined studies will be assessed using

the I^2 index. Results from selected literatures will be pooled into statistical meta-analysis using Review Manager Software from the Cochrane Collaboration.

Risk of bias assessment

Risk of bias will be assessed using the approach outlined by the Cochrane Collaboration Risk of Bias Tool (RoB V.2.0), which consists of five domains of bias that are relevant to the quality of RCTs. The five domains include bias due to the randomisation process, deviation from intended intervention, incomplete outcome data, measurement of the outcome, and selective reporting. Any disagreements will be recorded and resolved through consensus.

Ethics and dissemination

Due to the nature of the study, there are no ethical concerns nor informed consent required. We will disseminate the results of our systematic review through a peer-reviewed journal.

Appendix Table 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement [24]

Section and topic	Item No	Checklist item	Section and topic
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, paragraphs 1, 2 and 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, paragraph 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods (Search strategy and selection criteria)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods (Search strategy and selection criteria)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods (Search strategy and selection criteria)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix Table 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods (Search strategy and selection criteria)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods (Data identification and extraction)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods (Data identification and extraction)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods (Risk of bias and certainty assessment)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods (Statistical analyses)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not done

Section and topic	Item No	Checklist item	Section and topic
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not done
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods (Statistical analyses)
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. `	Figure, Appendix Table 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Not done
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Not done
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not done
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not done
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not done
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not done
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Funding section

Appendix Table 2. Systematic Review Searching Record

Literature search details

Language Restriction: English language only

Databases	Citations
Medline	540
Pubmed	669
Cochrane Library [Wiley]	479

Individual strategies

Pubmed [1977 to April Week 1 2020]

The search strategy combines relevant medical subject headings (MeSH) and keywords. The MeSH and keywords contain "coronary artery bypass", antithrombotic, anticoagulant, vitamin K antagonist, individual names of anticoagulant (warfarin, heparin, low molecular weight heparin i.e. enoxaparin, dalteparin, tinzaparin) and synonymous words.

Date Run: 08/04/2020

No.	Searches	Results
1.	coronary artery bypass[MeSH Terms]	52,381
2.	coronary artery bypass[Text Word]	64,821
3.	coronary artery bypass[Title/Abstract]	40,720
4.	((coronary artery bypass[MeSH Terms]) OR (coronary artery bypass[Text Word])) OR (coronary artery bypass[Title/Abstract])	65,673
5.	(antithrombotic[Text Word]) OR (anti-thrombotic[Text Word])	18,967

No.	Searches	Results
6.	(((anticoagula*[MeSH Terms]) OR (anticoagula*[Text Word])) OR (anti-coagula*[Text Word])) OR ((anticoagula*[Title/Abstract]) OR (anti-coagula*[Title/Abstract]))	132,777
7.	((vitamin K antagonist*[MeSH Terms]) OR (vitamin K block*[MeSH Terms])) OR (vitamin K inhibit*[MeSH Terms])	49,371
8.	(warfarin[Text Word]) OR (coumadin[Text Word])	30,341
9.	heparin[Text Word]	96,070
10.	(((enoxaparin[Text Word]) OR (clexane[Text Word])) OR (lovenox[Text Word])) OR (Xaparin[Text Word])	5,295
11.	(dalteparin[Text Word]) OR (Fragmin[Text Word])	1,528
12.	(tinzaparin[Text Word]) OR (innohep[Text Word])	478
13.	(((((((((antithrombotic[Text Word]) OR (anti-thrombotic[Text Word])) ((antithrombotic[Text Word]) OR (anti-thrombotic[Text Word]))) OR ((((anticoagula*[MeSH Terms]) OR (anticoagula*[Text Word])) OR (anti-coagula*[Text Word])) OR ((anticoagula*[Title/Abstract]) OR (anti-coagula*[Title/Abstract])))) OR (((vitamin K antagonist*[MeSH Terms]) OR (vitamin K block*[MeSH Terms])) OR (vitamin K inhibit*[MeSH Terms]))) OR ((warfarin[Text Word]) OR (coumadin[Text Word]))) OR (heparin[Text Word])) OR ((((enoxaparin[Text Word]) OR (clexane[Text Word])) OR (lovenox[Text Word])) OR (Xaparin[Text Word]))) OR ((dalteparin[Text Word]) OR (Fragmin[Text Word]))) OR ((tinzaparin[Text Word]) OR (innohep[Text Word]))	214,479
14.	((randomized controlled trial[Publication Type]) OR (randomized controlled trial[MeSH Terms])) OR (randomized controlled trial[Title/Abstract])	653,090
15.	controlled clinical trial[Publication Type]	592,693
16.	(randomized[Title/Abstract]) OR (randomised[Title/Abstract])	612,235
17.	placebo[Title/Abstract]	212,002
18.	random*[Title/Abstract]	1,118,823
19.	trial[Title]	215,308
20.	(((((((randomized controlled trial[Publication Type]) OR (randomized controlled trial[MeSH Terms])) OR (randomized controlled trial[Title/Abstract])) OR (controlled clinical trial[Publication Type])) OR ((randomized[Title/Abstract]) OR (randomised[Title/Abstract]))) OR (placebo[Title/Abstract])) OR (random*[Title/Abstract])) OR (trial[Title])	1,470,192
21.	((((coronary artery bypass[MeSH Terms]) OR (coronary artery bypass[Text Word])) OR (coronary artery bypass[Title/Abstract])) AND ((((((((((antithrombotic[Text Word]) OR (anti-thrombotic[Text Word])) ((antithrombotic[Text Word]) OR (anti-thrombotic[Text Word]))) OR ((((anticoagula*[MeSH Terms]) OR (anticoagula*[Text Word])) OR (anti-coagula*[Text Word])) OR ((anticoagula*[Title/Abstract]) OR (anti-coagula*[Title/Abstract])))) OR (((vitamin K antagonist*[MeSH Terms]) OR (vitamin K block*[MeSH Terms])) OR (vitamin K inhibit*[MeSH Terms]))) OR ((warfarin[Text Word]) OR (coumadin[Text Word]))) OR (heparin[Text Word])) OR ((((enoxaparin[Text Word]) OR (clexane[Text Word])) OR (lovenox[Text Word])) OR (Xaparin[Text Word]))) OR ((dalteparin[Text Word]) OR (Fragmin[Text Word]))) OR ((tinzaparin[Text Word]) OR (innohep[Text Word])))) AND ((((((((randomized controlled trial[Publication Type]) OR (randomized controlled trial[MeSH Terms])) OR (randomized controlled trial[Title/Abstract])) OR (controlled clinical trial[Publication Type])) OR ((randomized[Title/Abstract]) OR (randomised[Title/Abstract]))) OR (placebo[Title/Abstract])) OR (random*[Title/Abstract])) OR (trial[Title]))	669

OVID-Medline [1946 to April Week 1 2020]

No.	Searches	Results
1.	exp Coronary Artery Bypass/	52375
2.	coronary artery bypass.mp.	60789
3.	exp Coronary Artery Bypass/ or coronary artery bypass.mp.	61644
6.	antithrombotic.mp. or anti-thrombotic.mp.	16959
9.	exp Anticoagulants/ or anticoagula*.mp.	248617

No.	Searches	Results
6.	vitamin k antagonist*.mp. or vitamin k block*.mp. or vitamin k inhibit*.mp.	4921
7.	warfarin.mp. or exp Warfarin/	26938
8.	coumadin.mp.	954
9.	warfarin.mp. or exp Warfarin/ or coumadin.mp.	27323
10.	heparin.mp. or exp Heparin/	94314
11.	enoxaparin.mp. or exp Enoxaparin/	4676
12	enoxaparin.mp. or exp Enoxaparin/ or clexane.mp. or lovenox.mp.	4720
13.	dalteparin.mp. or exp Dalteparin/	1225
14.	dalteparin.mp. or exp Dalteparin/ or Fragmin.mp.	1424
15.	tinzaparin.mp. or exp Tinzaparin/	437
16.	tinzaparin.mp. or exp Tinzaparin/ or innohep.mp.	440
17.	antithrombotic.mp. or anti-thrombotic.mp. or exp Anticoagulants/ or anticoagula*.mp. or vitamin k antagonist*.mp. or vitamin k block*.mp. or vitamin k inhibit*.mp. or warfarin.mp. or exp Warfarin/ or coumadin.mp. or heparin.mp. or exp Heparin/ or enoxaparin.mp. or exp Enoxaparin/ or clexane.mp. or lovenox.mp. or dalteparin.mp. or exp Dalteparin/ or Fragmin.mp. or tinzaparin.mp. or exp Tinzaparin/ or innohep.mp.	281822
18.	randomized controlled trial.mp. or exp Randomized Controlled Trial/	517158
19.	controlled clinical trial.m_titl.	4643
20.	randomized.m_titl. or randomised.m_titl.	164590
21.	placebo.m_titl.	31956
22.	"random*".m_titl.	181449
23.	trial.m_titl.	184997
24.	randomized controlled trial.mp. or exp Randomized Controlled Trial/ or controlled clinical trial.m_titl. or randomized.m_titl. or randomised.m_titl. or placebo.m_titl. or "random*".m_titl. or trial.m_titl.	619197
25.	[exp Coronary Artery Bypass/ or coronary artery bypass.mp.] AND [antithrombotic.mp. or anti-thrombotic.mp. or exp Anticoagulants/ or anticoagula*.mp. or vitamin k antagonist*.mp. or vitamin k block*.mp. or vitamin k inhibit*.mp. or warfarin.mp. or exp Warfarin/ or coumadin.mp. or heparin.mp. or exp Heparin/ or enoxaparin.mp. or exp Enoxaparin/ or clexane.mp. or lovenox.mp. or dalteparin.mp. or exp Dalteparin/ or Fragmin.mp. or tinzaparin.mp. or exp Tinzaparin/ or innohep.mp.] AND [randomized controlled trial.mp. or exp Randomized Controlled Trial/ or controlled clinical trial.m_titl. or randomized.m_titl. or randomised.m_titl. or placebo.m_titl. or "random*".m_titl. or trial.m_titl.]	540

Cochrane Library [Wiley]
Date Run: 08/04/2020

No.	Searches	Results
#1	(coronary artery bypass):ti,ab,kw (Word variations have been searched)	12264
#2	MeSH descriptor: [Coronary Artery Bypass] explode all trees	5362
#3	#1 or #2	12275
#4	(antithrombotic*):ti,ab,kw (Word variations have been searched)	2560
#5	MeSH descriptor: [Anticoagulants] explode all trees	4520
#6	(vitamin K antagonist*):ti,ab,kw (Word variations have been searched)	992
#7	(vitamin K inhibit*):ti,ab,kw	577
#8	(vitamin K block*):ti,ab,kw	79
#9	MeSH descriptor: [Warfarin] explode all trees	1670
#10	("Warfarin"):ti,ab,kw	4737
#11	("Coumadin"):ti,ab,kw	176
#12	MeSH descriptor: [Heparin] explode all trees	4739
#13	(heparin):ti,ab,kw	11324
#14	(enoxaparin):ti,ab,kw	2139
#15	MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees	1930
#16	("Clexane"):ti,ab,kw	100
#17	("Lovenox"):ti,ab,kw	59
#18	(dalteparin):ti,ab,kw	735

#19	(fragmin):ti,ab,kw	223
#20	(tinzaparin):ti,ab,kw	234
#21	("Innohep"):ti,ab,kw	33
#22	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21	14463
#23	(randomi*):ti,ab,kw	850204
#24	(placebo):ti,ab,kw	292412
#25	(randomly):ti,ab,kw	231728
#26	(clinical trial):ti,ab,kw	534359
#27	[or #23-#26]	1078065
#28	#3 and #22 and #27	479

Appendix Table 3. List of excluded studies along with reasons for exclusion

Study	Reason for exclusion
Aldea 1996	Compared different anticoagulation protocols in patients on heparin-bonded or non-heparin-bonded cardiopulmonary bypass circuits during cardiopulmonary bypass (CPB)
Aldea 1998	Compared full or lower anticoagulation protocol in patients on heparin-bonded cardiopulmonary bypass circuits during CPB
Baufreton 2002	Not a RCT but a retrospective pilot study that compared different anticoagulation protocols in patients on heparin-bonded or standard cardiopulmonary bypass circuits during cardiopulmonary bypass (CPB)
Boldt 1994	Four groups on different doses of heparin with or without aprotinin before or during bypass were studied
Boldt 1995	Paper was retracted
Brinks 2001	Not a RCT but a clinical pilot study
Carrier 2003	Compared perioperative heparin and danaparoid
Chakravarthy 2017	Compared different doses of heparin during off-pump coronary artery bypass (OPCAB)
Chen 2006	Conducted in patients undergoing percutaneous coronary angiography (PCI). Compared enoxaparin with unfractionated heparin given pre-procedure
Chew 2008	Not a RCT, compared patients undergoing coronary artery bypass graft (CABG) with PCI or medical treatment
Gargiulo 2018	Compared bivalirudin and unfractionated heparin with or without glycoprotein IIb/IIIa inhibitor (GPIIb/IIIa)in patients undergoing PCI
Grima 2003	Compared different prebypass doses of heparin
Hashimoto 1999	Compared aprotinin at different doses with no aprotinin
Hoenicka 2015	Compared individualized heparin management with activated clotting time-based protocol during CABG
Kao 2006	Not a RCT but a post hoc analysis that compared heparin in addition to GP IIb/IIIa inhibitors with bivalirudin with or without GP IIb/IIIa inhibitors in patients undergoing CABG or PCI
Kincaid 2003	Not a RCT but a retrospective review. Compared preoperative enoxaparin and unfractionated heparin
Kolluri 2016	Compared postoperative fondaparinux and placebo
Koster 2007	Not a RCT, patients treated with bivalirudin during CPB were compared with a historical group of patients treated with alternative anticoagulation strategies
Kozek-Langenecker 1998	Compared prostaglandin E1 versus placebo during CPB
Lax 2020	Compared different doses of heparin during CPB
Medalion 2003	Not a RCT but a prospective study. Compared preoperative enoxaparin and unfractionated heparin
Meesters 2016	Compared low versus high protamine-to-heparin dosing ratios after CPB
Merry 2004	Compared bivalirudin with unfractionated heparin during OPCAB
Merry et al 2004	Compared bivalirudin or heparin with protamine reversal during OPCAB
Mirhosseini 2013	Compared aspirin plus heparin versus heparin alone given from admission to discharge in patients undergoing OPCAB
Mirow 2008	Compared uncoated and heparin-coated extracorporeal circulation (ECC) with

Study	Reason for exclusion
	different perioperative heparin doses
Mirow 2001	Unable to retrieve full text
Mullen 2002	Compared uncoated with heparin-coated bypass equipment with different heparin doses during bypass
Murase 1993	Non-English (Japanese)
Nenna 2016	Not a RCT but a cohort study comparing preoperative aspirin and enoxaparin
Nilsson 2012	Compared reduced systemic heparinization versus full heparin dose during bypass
Ovrum 1995	Compared heparin-coated circuit versus uncoated circuit with different heparin doses during bypass
Paparella 2005	Compared standard versus high heparin doses during and following CPB
Pfisterer 1989	Compared different anticoagulant and antiplatelet regimens started either pre or post-operatively
Pfisterer 1990	Compared different anticoagulant and antiplatelet regimens started either pre- or post-operatively
Pocock 2010	Compared heparin (either unfractionated heparin or enoxaparin at site discretion) plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone in patients who underwent PCI, CABG or conservative medical care
Pothula 2004	Not a RCT. Compared no preoperative treatment with preoperative with adenosine diphosphate (ADP) receptor antagonist and preoperative ADP receptor antagonist plus IV heparin
Radulovic 2015	Compared heparin and protamine dosing with Hepcon HMS Plus device to standard weight and activated clotting time-based dosing during bypass
Ranucci 2002	Compared different types of circuits and perioperative heparin doses. Outcome measured coagulation parameters
Renda 2007	Compared preoperative unfractionated heparin and enoxaparin
Riess 2007	Not a RCT but a pilot study comparing lepirudin with heparin during bypass
Shuhaibar 2004	Compared different doses of heparin during bypass
Smedira 2006	Compared heparin with protamine reversal to bivalirudin in patients undergoing OPCAB
Sun 2011	Compared fondaparinux and heparin given post-operatively
Tanaka 2007	Compared patients undergoing on-pump with off-pump coronary bypass
van der Meer 1993	Compared aspirin, aspirin plus dipyridamole, or oral anticoagulants before (dipyridamole, oral anticoagulants) or after (aspirin) bypass
von Segesser 1990	Not a RCT but a preliminary clinical result study of low versus full systemic heparinization during perfusion with heparin-coated equipment
von Segesser 1992	A clinical evaluation of heparin-coated perfusion equipment with low or full systemic heparinization in resection of descending thoracic aortic aneurysms, coronary artery revascularization, and rewarming in accidental deep hypothermia
von Segesser 1994	Compared low versus full systemic heparinization in open heart surgeries
Weber 1990	Compared aspirin (started before surgery) and anticoagulant post bypass
Weiss 1996	Compared low and high heparin dose for heparin-coated cardiopulmonary bypass equipment
Wilczynski 2014	Unable to retrieve full text
Yli-Mäyry 1992	Not a RCT, but a randomized consecutive series comparing preoperative anticoagulant with combination of dipyridamole (before surgery) and aspirin (after surgery)

RCT: randomized controlled trial; CPB: cardiopulmonary bypass; OPCAB: off-pump coronary artery bypass; CABG: coronary artery bypass graft; PCI: percutaneous coronary angiography; GPIIb/IIIa: glycoprotein IIb/IIIa inhibitor; ECC: extracorporeal circulation; ADP: adenosine diphosphate; IV: Intravenous.

Wardati Mazlan-Kepli. A, et. al. "Bridging anticoagulation therapy in patient undergoing coronary artery bypass graft: A systematic review." *IOSR Journal of Pharmacy (IOSRPHR)*, 11(11), 2021, pp. 14-25.