Antiplatelet Resistance in Coronary Artery Bypass Grafting: A Systematic Review

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Abstract

Introduction: Aspirin and clopidogrel are the most commonly used antiplatelet agents, either alone or as dual therapy, in patients undergoing CABG surgery to reduce organ ischaemia and mortality. The systematic review aims to explore the resistance to the antiplatelet agents, how to assess it, and the effect of resistance on the outcomes in CABG surgery. **Materials & methods**: A systematic search is carried out on MEDLINE via Ovid, PubMed, Embase, the Cochrane Library Database and Google Scholar until November 2021 to look for studies evaluating the antiplatelet resistance in patients undergoing both on-pump and off-pump CABG surgery. Only high-quality studies were included after the risk of bias assessment. **Results**: A total of 17 studies, of which 3 randomised controlled trials and 14 observational studies were included after inclusion criteria is applied. The incidence of aspirin resistance ranges from 11-51.5%, whereas, clopidogrel resistance is 22%. A wide variety of different assessment methods for antiplatelets are reported. Antiplatelet resistance is a predictor of vein graft occlusion, with up to 13 fold increase in occlusion rate. There is no overall effect of aspirin resistance on mortality, stroke or myocardial infarction, however, clopidogrel resistance leads to higher mortality, MI and target vessel revascularisations. The effect of cardiopulmonary bypass on antiplatelet resistance is not clear. **Conclusion**: There is no uniform definition of antiplatelet resistance. Assessment methods differ greatly and their results are not interchangeable. Antiplatelet resistance is associated with a higher rate of graft occlusion in CABG patients. Aspirin resistance does not influence overall adverse outcomes, however, clopidogrel resistance leads to worse outcomes.

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Conclusion : There is no uniform definition of antiplatelet resistance. Assessment methods differ greatly and their results are not interchangeable. Antiplatelet resistance is associated with a higher rate of graft occlusion in CABG patients. Aspirin resistance does not influence overall adverse outcomes, however, clopidogrel resistance leads to worse outcomes.

Keywords : Antiplatelet resistance, Aspirin, Clopidogrel, CABG, Coronary artery bypass grafting

ABBREVIATIONS:

ACS: Acute coronary syndrome

ADP: Adenosine diphosphate

ARU: Aspirin reaction unit

AUC: Arbitrary area under the curve

BMI: Body mass index

CABG: Coronary artery bypass grafting

CADP: Collagen/ADP coated apertured cartridges

CEPI: Collagen/epinephrine coated apertured cartridges

CPB: Cardiopulmonary bypass

MA: Maximum amplitude

MEA: Multiple electrode aggregometry

MI: Myocardial infarction

NOS: Newcastle-Ottawa Scale

PFA: Platelet function assay

PRISMA: Preferred Reporting Items for Systematic Reviews And Meta-Analyses

PRP: Platelet-rich plasma

PRU: P2Y12 reaction unit

TEG: Thromboelastogram

TxA2: Thromboxane A2

TxB2: Thromboxane B2

1. INTRODUCTION

Aspirin and clopidogrel are the two most commonly used antiplatelets in patients undergoing coronary artery bypass grafting (CABG) surgery. Aspirin is administered early after CABG to reduce the risk of death and organ ischaemia of the heart, brain, kidneys and gastrointestinal tract.[1] The early administration of aspirin after CABG surgery also has significantly improved the patency of vein grafts without increasing the risk of bleeding.[2] Aspirin inhibits the transformation of arachidonic acid into thromboxane A2 (TxA2) by irreversibly acetylating the platelet cyclooxygenase (COX) enzyme. Due to its chemical instability, TxA2 is then converted to stable and inactive thromboxane B2 (TxB2), and its metabolite 11-dehydroTxB2, which can be detected in the urine.

Dual antiplatelet therapy with aspirin and clopidogrel is associated with a reduced risk of thrombotic complications following acute coronary syndrome (ACS).[3] Clopidogrel is adenosine diphosphate (ADP) receptor antagonist that irreversibly inhibits by binding to the platelet P2Y12 receptor. Dual antiplatelet therapy leads to reduced all-cause mortality and improved vein graft patency, and their effects are more significant in patients with ACS undergoing CABG surgery.[4,5]

Antiplatelet resistance in some patients has been linked to early graft failure and identified to be due to the poor responsiveness of these groups of patients to the administered antiplatelet agents.[6] A variety of tests are available for the assessment of antiplatelet resistance, however, these tests are neither equally precise nor correlate among themselves.[7] The systematic review aims to explore the current practice, application of assessment methods and the effects of antiplatelet resistance in patients undergoing CABG surgery.

2. MATERIALS AND METHODS

This systematic review is conducted following the Preferred Reporting Items for Systematic Reviews And Meta-Analyses (PRISMA) statement.[8] No ethical approval or patient consent was sought for the review, which is based on all previously published studies.

2.1 Search Strategy

A systematic search was carried out across major databases of MEDLINE via Ovid, PubMed, Embase, the Cochrane Library Database and Google Scholar until August 2022 to identify eligible studies using Boolean operators to achieve maximum sensitivity. The terms used are “CABG”, “Coronary artery bypass grafting”, “Cardiac surgery”, “Antiplatelet”, “Aspirin”, “Clopidogrel”, “Antithrombotic”, “Mortality”, “Morbidity”, “Graft patency”, “Survival”, “Resistance”, and “Platelet mapping”. Bibliographies of relevant studies were also screened manually to identify additional suitable studies.

2.2 Study Selection & Data Extraction

The inclusion criteria include human studies with patients undergoing CABG surgery who are on antiplatelet, and the studies must report at least one outcome in patients with antiplatelet resistance such as vein graft failure, mortality or morbidity. Animal studies, case reports and case series, review articles and non-English articles are excluded.

Two authors independently searched the databases, reviewed the potentially relevant articles, extracted data and evaluated the quality and risk of bias of the included studies. Any discrepancies were resolved by consensus or by escalating to the third author.

2.3 Risk of Bias Assessment

The quality of observational cohort studies was evaluated using the Newcastle-Ottawa Scale (NOS) with scores greater than 6 regarded as high-quality studies.[9] The 2015 Updated Method Guidelines for Systematic Reviews in the Cochrane Back and Neck Group was used for quality assessment of randomised controlled trials, and studies are deemed the low risk of bias if they meet at least 6 criteria.[10]

3. RESULTS

3.1 Characteristics of the studies

A total of 200 articles were identified by the systematic search (Figure 1), of which 3 randomised controlled trials and 15 observational cohort studies were included in the systematic review. The details of the included studies are summarised in Table 1. All 15 observational studies had a score of more than 6 with NOS, and therefore, are determined as high-quality observational studies. Three randomised controlled trials met at least 6 of the 12 criteria set in the 2015 Updated Method Guidelines for Systematic Reviews in the Cochrane Back and Neck Group[10], and they are recognised as high-quality studies.

3.2 Assessment of antiplatelet resistance

The assessment of antiplatelet resistance widely varies using several different platelet function tests and by using downstream arachidonic acid breakdown products such as serum TxB2 or its metabolite in the urine, 11-dehydroTxB2, reflecting the effect of aspirin on platelets.

3.2.1 Light transmission aggregometry:

Platelet-rich plasma (PRP) is prepared by centrifuging the 5ml of anticoagulated blood sample at 150g for 10 minutes at room temperature. PRP is then adjusted to a platelet count of a minimum of 150 000 - 300 000 µl. The samples are then assayed using light transmission aggregometry by adding 0.05 ml of arachidonic acid. However, it can also be performed without adjustment of platelet count, and type I collagen and ADP could also be used instead of arachidonic acid.[11] The aggregation was plotted against time and reported as total aggregation % at 5 minutes.[12,13]

3.2.2 Impedance platelet aggregometry :

It measures platelet aggregation by continuously monitoring electrical impedance changes due to activation of platelets and adhesion to the metal sensor electrodes in 3-5 separate channels in multiple electrode aggregometry (MEA).[14–21] Whole blood sample is used in each channel with the addition of arachidonic acid to assess the effect of aspirin (*ASPItest*), ADP for platelet P2Y12 inhibitor effect (*ADPtest*) or thrombin receptor agonist peptide to measure glycoprotein IIb/IIIa inhibitor effect (*TRAPtest*).[14,19–21] Collagen can also be used as a substitute for arachidonic acid to assess the effect of aspirin.[17] The aggregation result is obtained as an arbitrary area under the curve (AUC) or presented as an aggregation unit against time (AU x min).

3.2.3 Platelet function assay (PFA):

PFA-100 (Dade Behring, Germany) is a commercially available point-of-care platelet function assay, which assesses platelet activation under high shear stress through aspiration of whole blood through collagen/epinephrine coated apertured cartridges (CEPI) or collagen/ADP coated apertured cartridges (CADP).[11,22]The assessment is reported as aperture closure time (CT), the time taken for subsequent activation of platelets to obstruct the apertures in the CEPI and CADP cartridges.

3.2.4 VerifyNow assay :

VerifyNow system (Accumetrics, San Diego, CA, USA) is a cartridge-based rapid assay system, which assesses the effect of aspirin on platelet reactivity in VerifyNow Aspirin Test using arachidonic acid as an agonist and VerifyNow P2Y12 Test measures the direct inhibition of clopidogrel on the P2Y12 receptors.[23,24] Aspirin test results are expressed as aspirin reaction units (ARU) and P2Y12 test results as P2Y12 reaction units (PRUs).

3.2.5 Thromboelastogram (TEG):

Heparinised whole blood is used in the TEG assay (Haemoscope Corp, Niles, IL, USA) to evaluate the platelet function in terms of clot maximum amplitude with added arachidonic acid (MA_{AA}) or without a platelet agonist (MA_0), which is compared with kaolin-activated TEG assay (MA_{KH}) to derive percent of platelet aggregation using the formula: $\%MA_{AA} = [(MA_{AA} - MA_0) / (MA_{KH} - MA_0)] \times 100\%$.[17] The result is reported as a percent aggregation of platelets.

3.2.6 Whole-blood flow cytometry:

The antiplatelet resistance can be measured by incubating blood with or without arachidonic acid (1.0 mmol/L) for 2 minutes, adding radiolabeled antibodies to CD41a or CD62P receptors on platelets, fixing the samples with 1% paraformaldehyde and analysing with a fluorescent cell sorter (Becton-Dickinson FACScan; BD Immunocytometry Systems, San Jose, CA, USA).[17] The result is described as the percent increase in the expression of the CD62P receptor after activation.

3.2.7 Thromboxane B2 (TxB2):

The urinary 11-dehydroTxB2 is the excretory form of TxB2 and its concentration is usually measured using enzyme immunoassay kits (Cayman Chemical, MI, USA).[11–13] The results are normalised for urinary creatinine concentration. Serum TxB2 level reflects cyclooxygenase-2-dependent thromboxane biosynthesis, and the level is measured in the plasma after whole blood is cultured at 37 °C for 24 hours and centrifuged at 700 x g for 15 minutes.[11]Serum TxB2 level can also be measured by using immunoassay[18] (Neogen, Lexington, KY, USA) or radioimmunoassay.[25] Alternatively, centrifuged plasma could be used to measure serum 11-dehydroTxB2 level with an enzyme immunoassay kit (Assay Designs Inc, Ann Arbor, MI, USA).[17]

3.3 Definition of antiplatelet resistance

There is no uniform definition of antiplatelet resistance in literature, and it varies hugely with each method of assessment. Light transmission aggregometry-derived platelet aggregation of [?]20% with arachidonic acid is regarded as aspirin resistant,[13] and in some studies, it is an aggregation of >30%.[26,27] Aspirin resistance is determined by impedance aggregometry if AUC [?]30 units[15,16,21,28] or AUC_{ASPI}>300 units (APSItest value >75 percentile).[17,18,20]

Using the VerifyNow system, ARU >550 and PRU >230 are considered aspirin resistance and clopidogrel resistance respectively,[23,29] although, PRU cut-off point could be as low as 188 for clopidogrel to be resistant.[24] Aspirin resistance is determined as having a collagen and/or epinephrine (CEPI) closure time <193 seconds in the PFA-100.[22]

Serum TxB2 inhibition <90%[18] and increase in serum 11-dehydro TxB2 >25% from baseline,[17] urinary 11-dehydro TxB2 levels higher than 67.9ng/mmol of creatinine is illustrated as aspirin resistance.[12] Platelet aggregation >50% on TEG[30,31] and 25% increase in expression of CD62P receptor following simulation in whole-blood flow cytometry are other definitions of aspirin resistance.[17]

3.4 Antiplatelets used in the studies

All studies used aspirin as primary antiplatelet therapy, and clopidogrel is added to aspirin to constitute dual antiplatelet therapy in some studies.[13,18,24,28] While clopidogrel 75 mg is always used, the dosage for aspirin varies from 80-325 mg with 100 mg being the most commonly used dosage. A postoperative loading dose of intravenous aspirin 500 mg was used in one study.[27]

3.5 Incidence of antiplatelet resistance

The incidence of overall aspirin resistance ranged from 11-51.5%[13,15,17,20–23,26–28] and the incidence of clopidogrel resistance was reported as 22%.[23] 12.6% of patients on dual antiplatelet therapy were found to be resistant to both aspirin and clopidogrel, however, it was reduced to 10.6% after 30-day treatment.[23] Preoperative aspirin resistance was found to be 13-29%[20,26,27].

In terms of TxB2 measurements, inhibition >90% was not achieved until postoperative day 5 and only 34% of patients reached the effective platelet inhibition by then.[12,18]Insufficient inhibition of TxB2 is observed with aspirin 100mg, but not with a higher dose of 325mg.[11]

The aspirin resistance had disappeared in all previously perioperative resistant patients when retested at 6-month[13] and 12-month follow-ups.[26,27]

3.6 Effect of Cardiopulmonary Bypass (CPB)

The effect of CPB on aspirin resistance is not clear. Platelet aggregation and thromboxane are significantly inhibited after off-pump CABG, but not after the on-pump CABG.[25] The cardiopulmonary bypass time is described as an independent predictor of an ASA non-response in one study.[21] Nonetheless, it was also demonstrated that CPB has no significant effect on aspirin resistance in other studies.[26,27]

3.7 Outcomes

3.7.1 Vein graft occlusion

Antiplatelet resistance is a predictor of graft occlusion.[23] Aspirin resistance, together with compromised endothelial integrity in vein grafts, leads to graft thrombosis and failure within a few days after CABG.[17]Moreover, the risk of late occlusion of vein grafts is increased by 13 folds (odds ratio) in patients with aspirin resistance.[22] Dual antiplatelet therapy with aspirin and clopidogrel is a strong predictor of vein graft patency and is associated with the reduced vein graft occlusion rate.[23]

3.7.2 Mortality, Myocardial Infarction (MI) and Stroke

There was no overall difference in mortality, MI or stroke in patients with aspirin resistance and those without it at 6-month and 12-month follow-up.[20,21,28] Whereas, all patients who died during the follow-up period exhibited aspirin resistance previously.[26,27]

The addition of clopidogrel to aspirin does not reduce adverse outcomes or increase bleeding episodes. However, dual antiplatelet therapy leads to a lower rate of adverse events in younger (age <65 years) obese patients with body mass index (BMI) >30.[28] In patients with clopidogrel resistance undergoing off-pump CABG, high residual platelet reactivity is associated with higher mortality, MI and target vessel revascularisations.[24]

3.7.3 Postoperative immediate blood loss

Postoperative 12-hour blood loss was higher in preoperative aspirin-sensitive patients compared to the patients with preoperative aspirin resistance (mean volume of 555 ml vs 406ml).[29]Although the chest drain output was comparable within the first hour after surgery, the aspirin-sensitive group had more blood loss at 6 and 12 hours. In addition, they are more likely to require allogenic blood transfusion postoperatively.[14]

4. DISCUSSION

A true resistance to inhibition of thromboxane A2, i.e. the resistance to the biochemical effects of aspirin is rare. On the other hand, thrombotic events and poor clinical outcomes despite the use of aspirin in patients could secondary to multiple mechanisms, but not limited to the inhibition of the COX-1 enzyme.[32] Hence, the term "anitplatelet resistance" is not uniformly defined in the literature. However, antiplatelet resistance demonstrated with in-vitro platelet assays has been linked to adverse clinical outcomes in patients on antiplatelet therapy.[33–36]

Studies reporting the antiplatelet resistance in cardiac surgery patients have different cut-off values for measurement; even when they used the same assessment method, let alone different measurement methods. For example, using light aggregometry, aspirin resistance is determined at platelet aggregation [?]20% in one study[13] but defined as >30% in other studies.[26,27]

Different assessment methods also mean different results in assessing antiplatelet resistance, making it non-interchangeable between studies.[11] A patient deemed antiplatelet resistant in one study may not be equivalent to being antiplatelet resistant in another study using a different assessment method. In addition, different doses of aspirin used in individual studies might have had an impact on aspirin resistance.

Furthermore, studies assessing antiplatelet resistance focused heavily on the assessment of aspirin resistance, but scanty information is available on the resistance of other antiplatelets, such as clopidogrel. Most of the assessment methods offer the ability to test clopidogrel resistance using ADP instead of arachidonic acid as a substrate, yet it is not widely employed. Despite clopidogrel being used in many studies[15,16,23,24,28], only one study examined and reported clopidogrel resistance.[23]

Previous studies in the non-cardiac surgery cohort demonstrated that antiplatelet resistance is associated with higher rates of cardiovascular thrombotic events and mortality.[35,37,38] Although there are a few randomised controlled trials and observational studies which reported no significant difference in adverse outcomes in patients undergoing cardiac surgery, including mortality, stroke and myocardial infarction, they did not investigate graft patency or patient symptoms.[20,21,28] No difference in adverse outcomes may be because aspirin resistance could be transient in nature.[13,26,27] Aspirin resistance is associated with less blood loss in the immediate postoperative period,[29] which could be loosely translated into a pro-thrombotic feature when compared with the aspirin-sensitive population.

The clinical outcomes were improved in a subset of younger (<65 years) and obese patients with aspirin resistance when dual antiplatelet therapy with clopidogrel is used.[28]Besides, all patients who died during the follow-up period were found to have perioperative aspirin resistance initially.[26,27]Youn et al reported worse outcomes in patients undergoing cardiac surgery with clopidogrel resistance.[24] Assessment of this patient cohort could be improved by using follow-up coronary angiogram and/or computed tomography coronary angiography.

This systematic review is not without limitations. Most of the studies included are observational cohort studies rather than randomised controlled trials. Due to the applications of various assessment methods for antiplatelet resistance and their diverse results, it is not possible to carry out a meta-analysis. There is also a lack of uniformity in the definition of Antiplatelet resistance using different methods. Future research should aim to generate adequately powered randomised controlled trials to demonstrate standardised results of antiplatelet resistance, single agent or in combinations, including the resistance of other antiplatelet agents,

rather than being limited to aspirin. The clinical relevance of resistance to antiplatelet medication requires more imaging investigation by taking into consideration the quality of the grafted coronary artery.

5. CONCLUSION

There is no uniform definition of antiplatelet resistance in the current literature. Assessment methods of antiplatelet resistance differ greatly, and so are the results without being interchangeable between them. Studies are excessively focused on aspirin resistance, yet little information is available for other antiplatelets such as clopidogrel and ticagrelor. Antiplatelet resistance in CABG patients is associated with a higher rate of vein graft occlusion. Aspirin resistance does not influence overall adverse outcomes, however, clopidogrel resistance leads to worse outcomes in patients undergoing CABG surgery.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Myat Soe Thet: Concept/design, Data collection, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article

Amir Khosravi: Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article

Samson Egbulonu: Concept/design, Data collection, Data analysis/interpretation, Drafting article, Approval of article

Aung Ye Oo: Concept/design, Critical revision of article, Approval of article, Supervision

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TABLE

Table 1: Characteristics of the included studies

Author	**Year**	**Study type**	**Sample size**	**Antiplatelets used**	**Measurements**
Bednar et al	2009	Prospective cohort	40	Aspirin	Platelet aggregation, 11
Bednar et al	2012	Prospective cohort	30	Aspirin + Clopidogrel	Platelet aggregation, 11
Bollinger et al	2016	Prospective cohort	304	Aspirin	Platelet aggregation
Brambilla et al	2010	Randomised controlled trial	56	Aspirin	Platelet aggregation, 11
Gasparovic et al	2014	Randomised controlled trial	219	Aspirin	Platelet aggregation
Hiyasat et al	2014	Prospective cohort	100	Aspirin	Platelet aggregation
Kempfert et al	2009	Prospective cohort	59	Aspirin	Platelet aggregation
Mannacio et al	2012	Randomised controlled trial	300	Aspirin	Platelet function assay
Nicola et al	2019	Prospective cohort	250	Aspirin	Platelet aggregation
Petricevic et al	2013	Prospective cohort	131	Aspirin + Clopidogrel	Platelet aggregation
Petricevic et al	2011	Prospective cohort	99	Aspirin	Platelet aggregation
Poston et al	2006	Prospective cohort	225	Aspirin	Platelet aggregation, 11
Wand et al	2017	Prospective cohort	400	Aspirin	Platelet aggregation
Wang et al	2012	Prospective cohort	333	Aspirin + Clopidogrel	Platelet aggregation, 11
Yilmaz et al	2005	Prospective cohort	28	Aspirin	Platelet function assay
Youn et al	2014	Prospective cohort	859	Aspirin + Clopidogrel	Platelet function assay
Willemsen et al	2021	Prospective cohort	128	Aspirin	Platelet function assay
Zimmermann et al	2005	Prospective cohort	29	Aspirin	Platelet aggregation

FIGURE

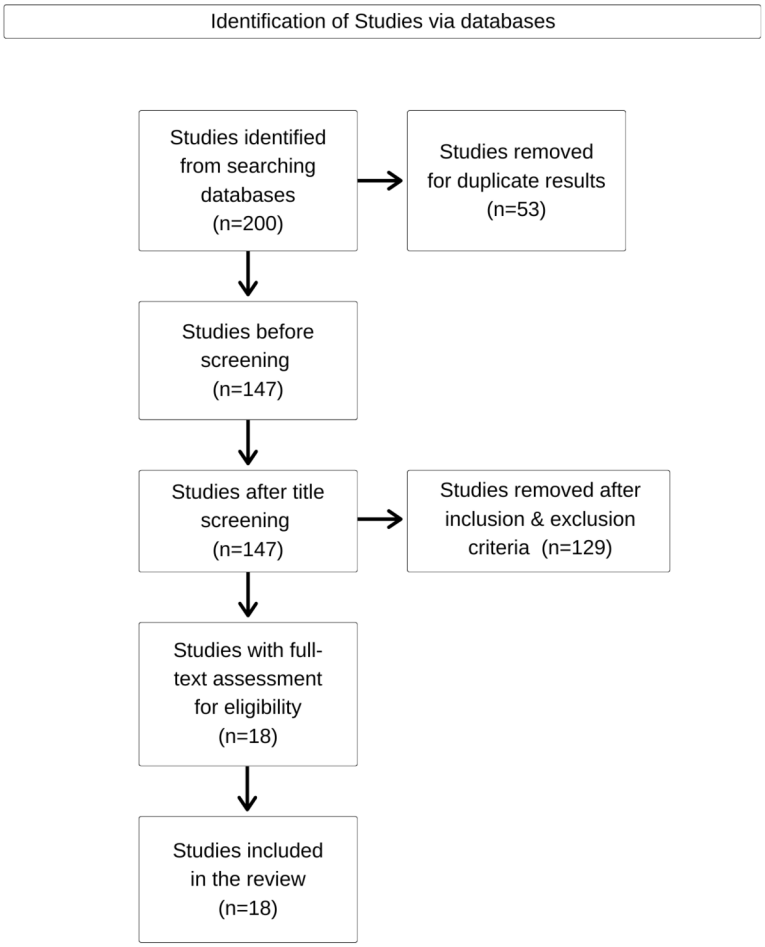

Figure 1: PRISMA flow diagram for study search and selection