REVIEW

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Dual antiplatelet therapy of clopidogrel plus aspirin versus aspirin monotherapy in patients with Coronary Artery Disease (CAD): a systematic review and meta-analysis

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ABSTRACT

Background: Aspirin is the most commonly used for treatment in patients with coronary artery disease (CAD). However, there are many evidences from several trials suggested that dual antiplatelet therapy (DAPT) might exhibit a better outcome and more effective than aspirin monotherapy. Thus, we aimed to assess the effect of DAPT versus aspirin monotherapy in patients with CAD.

Methods: Electronic databases were performed in PubMed, EMBASE, and Cohrane from Januari 2005 until March 2021. We searched for randomized control trials comparing DAPT versus aspirin monotherapy in patients with CAD. Pooled effects estimates were reported as an odds ratio (OR) with 95% confidence intervals (CI) and calculated using random effects model. RevMan 5.4 software was used for data analysis.

Results: Five randomized control trials with a total of 8,203 participants met the inclusion critera. DAPT was found to have an association in reducing the risk of major adverse cardiovascular events (OR 0.72; 95% CI 0.57-0.90; $p = 0.003$; $I^2 = 17\%$) and death events (OR 0.62; 95% CI 0.49-0.79; $p < 0.0001$; $I^2 = 0\%$) compared with aspirin monotherapy. Yet, there were no significant difference in myocardial infarction events (OR 0.78; 95% CI 0.57-1.07; $p = 0.13$; $I^2 = 28\%$) and bleeding events (OR 1.65; 95% CI 0.97-2.81; $p = 0.06$; $I^2 = 0\%$) between two groups.

Conclusions: DAPT treatment has a significant effect in reducing the risk of major cardiovascular and death events without a significant effect in myocardial infarction and bleeding events compared with aspirin monotherapy.

Keywords: aspirin, coronary artery disease, dual antiplatelet therapy, meta-analysis.
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INTRODUCTION

Coronarycarterybdisease (CAD) is the most prevalent cardiovascularadisease and the number one cause of death with a total of 17.9 million people died each year and an estimates 31% of all deaths globally.[1] A total of seven million patients were diagnosed with acute myocardial infarction globally with 20% suffering a cardiovascular event for the second time in the first year.[2] Aspirin has been well known for treatment in patients with CAD. Many health-related agencies suggested aspirin use for the primary and secondary prevention of CAD particularly in adults.[3-6] Clopidogrel was found to have a promising agent as antiplatelet therapy in CAD patients and had a superior effect than aspirin. The ClopidogrelvversusgAspirin inuPatients at Risk of Ischemic Events (CAPRIE) trial showed that aspirin monotherapy had an inferior effect than clopidogel monotherapy in preventing cardiovascular events in CAD patientshwith highhrisks.[7] Yet, in many cases, clopidogrel or aspirin monotherapy is notnsufficient to prevent cardiovascular events in CAD patients especially those who have high risks.[8]

Several trials were investigating aspirin plus clopidogrel or dual antiplatelet therapy (DAPT) to know whether this DAPT has beneficial effects or not compared to aspirin or clopidogrel monotherapy. Several trials had reported conflicting results.[9-12] Some reported beneficial effects while others reported no effects. The outcomes that most trials reported were cardiovascular events, myocardial infarction, bleeding, and death. These results may lead to uncertainty regarding the effects of DAPT in patients with CAD although DAPT is prescribed in CAD patients and often indicated after undergoing surgical procedures to decrease and prevent infarction, thrombosis, and even stroke.[4]

Therefore, we conducted a meta-analysis from randomized controlled trials to assess the effect of DAPT versus aspirin monotherapy in patients with CAD. Findings from this meta-analysis will guide clinicians to be more accurate in the selection of DAPT and aspirin use for treatment and preventing the worst outcomes in patients with CAD based on the evidence in this study.

METHODS

Search strategy

This meta-analysis followed PRISMA 2009 guideline. All searches were performed

in Cochrane, PubMed, and EMBASE databases for relevant studies published until March, 2021. The search terms used were "aspirin and clopidogrel", "aspirin plus clopidogrel", "aspirin", "aspirin monotherapy", "acute coronary syndrome", "coronary artery disease" and "trial".

Eligibility criteria

This meta-analysis included the studies if they were: (1) RCT studies (2) compared DAPT (aspirin and clopidogrel) and aspirin alone (3) reported relevant outcomes. We excluded the studies if they were: (1) The participants were not diagnosed with CAD (2) the outcomes were out of the scope. Trials includedkinpthis study should report majorhadverse cardiovascular events (MACE), myocardial infarction, bleeding, and mortality.

DatabExtractionkand Quality Assessment

The data extraction was done by two reviewers (HAH and T) independently. We screened all titles and abstracts. If they reach the inclusion criteria then we reviewed the full text to assess the eligibility. These are the following data extracted in the study: (1) Number of participants in DAPT and aspirin group (2) characteristic of participants and (3) the outcomes. The reviewers (HAH and T) assessed the quality of all trials independently using Cochrane Collaboration for the randomized controlled trials.[13] Every disaggrement were resolved through consesus.

Statistical Analysis

We used RevMan 5.3 software to analyze the data statistically. The meta-analysis was conducted for each outcome using random-effects models. Heterogeneity of all trials was assessed by I^2. The results of I^2 are between 0% and 100%. The value above 50% indicates substantial heterogeneity.[14] The pooled RR with 95% CI was reported for each outcome in the study. We used a forest plot to present the effects in each trial.

RESULTS

Search Results and Characteristic of The Study

The study identified 1,492 articles published from January 2005 to March 2021. A total of 1,451 articles were excluded based on abstract and title screening. 33 articles were assessed with full-text reviewed for eligibility. Of these, 5 trials met the inclusion criteria and were included in the study (**Figure 1**). A total of 8,213 participants were enrolled. **Table 1** summarizes the characteristic of the trial and the participants of each trial. Five trials committed 1 year follow-up, but one trial committed 1 month follow-up. Most of the participants were male and their mean age was slightly above 60 years old. The MACE outcomes were found in 3 trials, myocardial infarction in 4 trials, all-cause death in 4 trials, and bleeding in 3 trials.

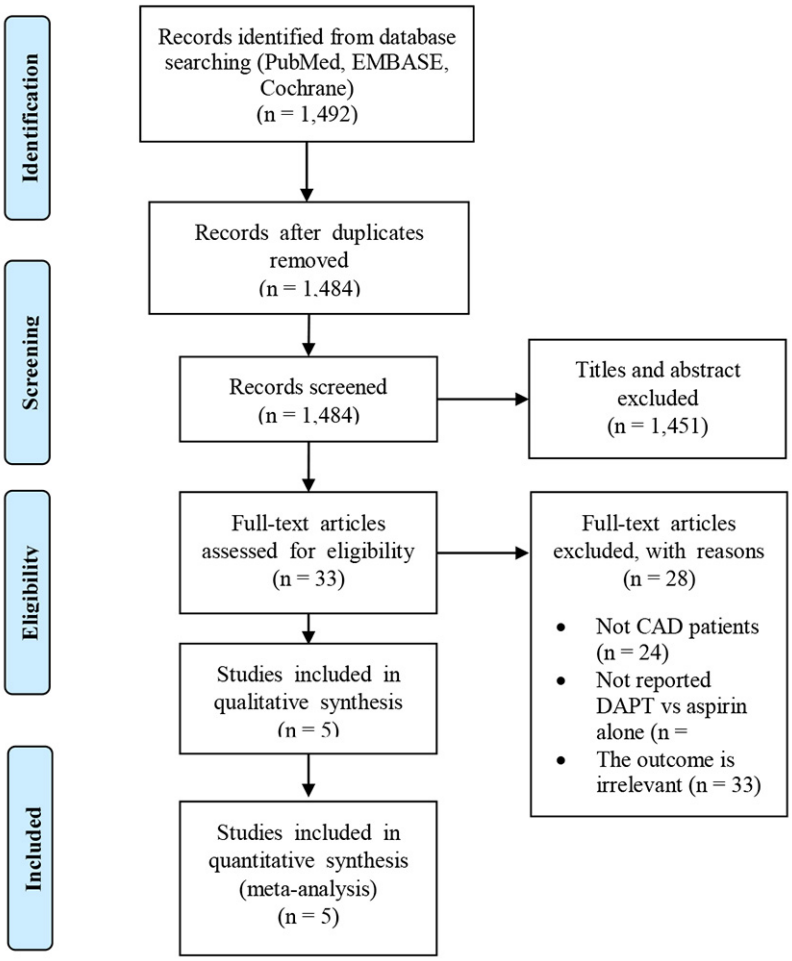

Figure 1. Flow diagram of study selection

The Effects of DAPT versus Aspirin

Three trials showed the effect of DAPT compared aspirin monotherapy on MACE outcome with a total of 4,890 participants and 1,234 reported MACE events. DAPT administration was associated with reduced risk of MACE significantly (OR 0.72; 95% CI 0.57-0.90; $p = 0.003$). The heterogeneity was found low for this outcome ($I^2 = 17\%$) (**Figure 2.a**).

The death outcomes were found in 4 trials with a total of 6,415 participants and 331 reported death events. DAPT was found in reducing the risk of death compared to aspirin alone significantly (OR 0.62; 95% CI 0.49-0.79; $p < 0.0001$). There was no heterogeneity for all-cause death significantly ($I^2 = 0\%$) (**Figure 2.b**).

The effect of DAPT compared to aspirin alone on myocardial infarction were reported in 4 trials with a total of 6,356 participants and 376 reported myocardial infarction events. Low heterogeneity ($I^2 = 28\%$) was found and there was no significant difference for myocardial

Tabel 1. Characteristic of the included study and participants

Study	Location	Total Participants		Mean age (years)		Sex (male)		Intervention	Follow-up duration (months)
		DAPT	Aspirin	DAPT	Aspirin	DAPT	Aspirin		
Ibrahim 2019[24]	Arabian Gulf (Bahrain, Kuwait, Oman, and United Arab Emirates)	2,634	925	60	60	1,829 (69.0%)	544 (59.0%)	DAPT (Aspirin 81/100 mg and clopidogrel 75 mg) and Aspirin 81/100 mg alone	12
Ebrahimi 2018[16]	United States of America	511	1014	62.4	62.7	507 (99.2%)	1008 (99.4%)	DAPT (Aspirin and clopidogrel) and aspirin 81-325 mg alone	12
Benedetto 2017[17]	Australia, Austria, Brazil, India, Italy, Poland, United Kingdom	609	2308	62.9	62.9	536 (88.0%)	1.977 (85.7%)	DAPT and aspirin	12
Kulik 2010[18]	Canada	56	57	64.9	68.1	51 (91.1%)	50 (87.7%)	DAPT (Aspirin 100 mg and clopidogrel 75 mg) and aspirin 75-162 mg	12
Sun 2010[15]	Canada	49	50	66.0	64.5	46 (93.9%)	43 (86.0%)	DAPT (Aspirin 325 mg and clopidogrel 300 mg and aspirin 81 mg	1

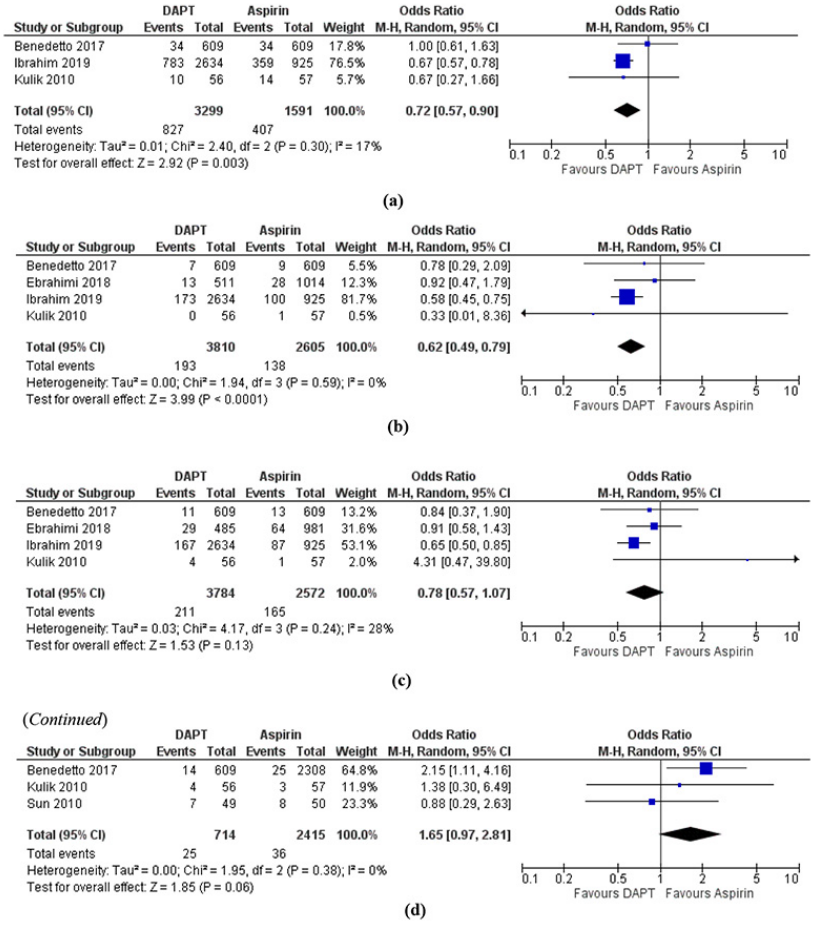

Figure 2. Summary odds ratio of (a) the major adverse cardiovascular events (b) myocardial infarction (c) death and (d) bleeding between two groups. DAPT = dual antiplatelet therapy.

infarction (OR 0.78; 95% CI 0.57-1.07; p = 0.13) (**Figure 2.c**).

The last outcome was bleeding. Bleeding implies drug safety. In this study, bleeding outcomes were reported in 3 trials with a total of 3,129 participants and 61 reported bleeding events. No significant difference was found in bleeding outcome (OR 1.65; 95% CI 0.97-2.81; p = 0.06) with no significant heterogeneity (I^2 = 0%) (**Figure 2.d**).

DISCUSSION

The results of this study were vary based on the analysis of each outcome. The analysis of 5 trials suggests that DAPT administration was associated with reduced risk of MACE and death compared to aspirin monotherapy use significantly. However, no significant differences were found in myocardial infarction and bleeding events. In this study, the definition of MACE is a composite outcome including myocardial infarction, mortality, and cerebrovascular accident. Only one trial in the study from Sun et al., reported short-term follow up which was a month. This trial yielded no difference between DAPT andaaspirin groups in the outcomes of bleeding, myocardial infarction, and death, significantly.[15] Another trial that reported

one-year follow-up showed vary results. The ROOBY trial conducted by Ebrahimi et al., revealed no significant effect on death and myocardial infarction.[16] The ART trial carried out by Benedetto et al., has a similar result that DAPT and aspirin groups were not associated with a risk reduction on MACE after one-year follow-up.[17] The CASCADE trial also reported no significant effect in MACE and bleeding between 2 groups.[18]

This might be due to less postdischarge DAPT adherence from all participants. There was no adherence monitoring carried out in the ROOBY trial. Thus, the duration of therapy and adherence were unknown. The ART trial also committed a similar issue. Only 31% participants prescribed on DAPTccompletedc1cyearcofctreatment. There were no data avalaible on duration and participants who discontinued the treatment. Thus, the results were underpowered. In CASCADE study, the sample size was small so the study could not summarize conclusively. Yet, other trial carried out by Ibrahim et al., showed a beneficial effect on DAPT use compared with aspirin alone after one year follow up. In this trial, DAPT was associated to reduce the risk of MACE and death significantly. The sample size in this trial was larger than others trial included in the study.[19] Therefore, this trial had a huge impact to make the analysis of the study yielded significant results in MACE and death.

This study has a linear result with previous meta-analysis. Previous meta-analysis on this topic revealed that DAPT (aspirin and P2Y12 inhibitor) administration showed to be associated with a reduction on MACE and death compared to aspirin alone and not associated with myocardial infarction. This meta-analysis analyzed 17 studies and specifically included those who undergoing CABG as a participant.[9] Although there is a different on antiplatelet agent, the result appears linear. Another meta-analysis by Deo et al., reported conflicting result. In this meta-analysis, DAPT (clopidogrel and aspirin) appears to be associated with an increasing of bleeding risk and reducing myocardial infarction event in patients undergoing CABG with a short-term follow-up (30 days). The findings on both outcomes were not in line with the current study.[10]

Several studies reported that DAPT used was associated with reducing cardiovascular event, myocardial infarction, and mortality compared to other antiplatelet agent alone such as aspirin or clopidogrel.[20-22] Aspirin plus clopidogrel combination was found to have a beneficial effects of MACE with a short-term period (30 days).[21] Another study reported that the addition of clopidogrel to aspirin significantly reduces cardiovascularrrisk.[22] At the same time, DAPT can cause an increasing risk of bleeding and also life-threatening events. Nevertheless, the results in bleeding events were debatable as many studies reported conflicting results. A meta-analysis by Agarwal et al., reported that the analysis did not report any significant difference in major bleeding between DAPT and aspirin monotherapy groups in patients undergoing CABG.[9] Previous meta-analysis also reported that the administration of aspirin or clopidogrel alone did not show any significant difference in mortality and bleeding events.[12] Another study revealed different results which reported that a combination of aspirin and clopidogrel yielded in a relative increased in bleeding events.[11] A study carried out by Squizatto et al., also reported that there is an increase in major bleeding in participant treated with clopidogrel plus aspirin. The risk of having major bleeding was 44% higher compared with aspirin monotherapy.[23] Thus, there is a huge challenge in balancing the benefit and the harm of DAPT use for short-term and long-term treatment.

To our knowledge, this is the first meta-analysis that reported the effect of DAPT and aspirin monotherapy treatment in CAD patients that comes from accross the world because all participants spread in every continents. Hence, the result of this study could represent in every region.

Study Limitations

The current study has several limitations. The follow-up period of all 5 trials included were not similar. Only one trial carried out short-term follow-up (30 days). The findings in bleeding events showed no significant effect in two groups. This might be due to a lack of data with only 3 trials reported the bleeding outcome. Two of them have small sample size. Besides, there were only 5 trials included in the study. Therefore, the number of sample size was small and not sufficient to summarize conclusively.

CONCLUSIONS

The current study found that DAPT has a significant effect in reducing the risk of major cardiovascular event and death compared to aspirin monotherapy. No significant effect were found in myocardial infarction and bleeding events. In order to reach more significant conclusion, further large randomized-trial are required to verify the findings of the current study.

FUNDING

No funding was received for the study

CONFLICTS OF INTEREST

The authors have no conflicts of interest

AUTHOR CONTRIBUTIONS

HAH and T conceptualized the study and were involved in the acquisition and interpretation of the data. T performed the statistical analysis. All authors contributed to critical revision of the manuscript and approved the final version of the manuscript.

REFERENCES

1. WHO. Cardiovascular disease (CVDs) [Internet]. World Health Organization. 2017 [cited 2021 Apr 10]. p. 1. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
2. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients : nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J. 2015;36:1163–70.
3. Pearson T a., Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. Circulation. 2002;106(3):388–91.
4. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF / AHA / SCAI Guideline for Percutaneous Coronary

Intervention. JAC [Internet]. 2011;58(24):e44–122. Available from: http://dx.doi.org/10.1016/j.jacc.2011.08.007
5. Vandvik PO, Lincoff a. M, Gore JM, Gutterman DD, Sonnenberg F a., Alonso-Coello P, et al. Primary and secondary prevention of cardiovascular disease: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of chest physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 SUPPL.):e637S – e668S.
6. Graham MM, Sessler DI, Parlow JL, Biccard BM, Guyatt G, Leslie K, et al. Aspirin in Patients With Previous Percutaneous Coronary Intervention Undergoing Noncardiac Surgery. Ann Intern Med. 2018 Feb;168(4):237–44.
7. Committee CS. A randomised , blinded , trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996;348(9038):1329–39.
8. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. EFFECTS OF CLOPIDOGREL IN ADDITION TO ASPIRIN IN PATIENTS WITH ACUTE CORONARY SYNDROMES WITHOUT ST-SEGMENT ELEVATION. N Engl J Med. 2001;345(7):494–502.
9. Agarwal N, Mahmoud AN, Patel NK, Jain A, Garg J, Mojadidi MK, et al. Meta-Analysis of Aspirin Versus Dual Antiplatelet Therapy Following Coronary Artery Bypass Grafting. Am J Cardiol [Internet]. 2017;121(1):32–40. Available from: https://doi.org/10.1016/j.amjcard.2017.09.022
10. Deo S V, Dunlay SM, Shah IK, Altarabsheh SE, Erwin PJ, Boilson BA, et al. Dual Antiplatelet Therapy After Coronary Artery Bypass Grafting : Is There Any Benefit ? A Systematic Review and Meta-Analysis. J Card Surg. 2013;28:109–16.
11. Zhou Y, Wei X, Lu J, Ye X, Wu M, Xu J, et al. Effects of Combined Aspirin and Clopidogrel Therapy on Cardiovascular Outcomes : A Systematic Review and Meta-analysis. PLoS One. 2012;7(2).
12. Yuan J, Xu GM, Ding J. Aspirin Versus Clopidogrel Monotherapy for the Treatment of Patients with Stable Coronary Artery Disease : A Systematic Review and Meta-Analysis. Adv Ther [Internet]. 2019;36(8):2062–71. Available from: https://doi.org/10.1007/s12325-019-01004-6
13. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD. The Cochrane Collaboration ' s tool for assessing risk of bias in randomised trials. BMJ. 2011;343:1–9.
14. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58.
15. Sun JCJ, Teoh KHT, Lamy A, Sheth T, Ellins M Lou, Jung H, et al. Randomized trial of aspirin and clopidogrel versus aspirin alone for the prevention of coronary artery bypass graft occlusion: the Preoperative Aspirin and Postoperative Antiplatelets in Coronary Artery Bypass Grafting study. Am Heart J. 2010 Dec;160(6):1178–84.
16. Ebrahimi R, Gupta S, Carr BM, Collins J, Grover FL, Quin JA, et al. Comparison of Outcomes and Costs Associated With Aspirin ± Clopidogrel After Coronary Artery Bypass. Am J Cardiol [Internet]. 2018;121(6):709–14. Available from: https://doi.org/10.1016/j.amjcard.2017.12.010
17. Benedetto U, Altman DG, Gerry S, Gray A, Lees B, Flather M, et al. Impact of dual antiplatelet therapy after coronary artery bypass surgery on 1-year outcomes in the Arterial Revascularization Trial. Eur J cardio-thoracic Surg Off J Eur Assoc Cardio-thoracic Surg. 2017 Sep;52(3):456–61.
18. Kulik A, Le May MR, Voisine P, Tardif J-C, Delarochelliere R, Naidoo S, et al. Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the clopidogrel after surgery for coronary artery disease (CASCADE) Trial. Circulation. 2010 Dec;122(25):2680–7.
19. Al-zakwani I, Alawi A. Impact of Dual versus Single Antiplatelet Therapy on Major Cardiovascular Outcomes in Patients with Acute Coronary Syndrome in the Arabian Gulf. Med Princ Pract. 2020;29:181–7.
20. Khan SU, Talluri S, Rahman H, Lekkala M, Khan MS, Riaz H, et al. Meta-analysis of efficacy and safety of dual antiplatelet therapy versus aspirin monotherapy after coronary artery bypass grafting. Eur J Prev Cardiol. 2018;1–4.
21. Bhatt DL, Bertrand ME, Berger PB, Allier PLL, Moussa I, Moses JW, et al. Meta-Analysis of Randomized and Registry Comparisons of Ticlopidine With Clopidogrel After Stenting. J Am Coll Cardiol [Internet]. 2002;39(1):9–14. Available from: http://dx.doi.org/10.1016/S0735-1097(01)01713-2
22. Liang L-R, Ma Q, Feng L, Qiu Q, Zheng W, Xie W-X. Long-term effect of clopidogrel in patients with and without diabetes: A systematic review and meta-analysis of randomized controlled trials. World J Diabetes. 2020;11(4):137–49.
23. Squizzato A, Bellesini M, Takeda A, Middeldorp S, Mp D. Clopidogrel plus aspirin versus aspirin alone for preventing cardiovascular events (Review). Cochrane Database Syst Rev. 2017;(12).
24. Ibrahim A, Al-Lawati J, Alsheikh-Ali AA, Almahmeed W, Rashed W, Al-Mulla A, et al. Impact of Dual versus Single Antiplatelet Therapy on Major Cardiovascular Outcomes in Patients with Acute Coronary Syndrome in the Arabian Gulf. Med Princ Pract. 2020;29(2):181-187.