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Research paper

Safety and efficacy of double vs. triple antithrombotic therapy in patients with atrial fibrillation with or without acute coronary syndrome undergoing percutaneous coronary intervention： a systematic review and meta-analysis of vitamin k antagonist and/or non-vitamin k antagonist oral anticoagulant-based randomized clinical trials

Phav Sophearith *

Department of Cardiology, Zhongnan Hospital of Wuhan University, Wuhan, 430071 Mentor: Professor Wan Jing, MD-Phd
**Corresponding author E-mail:*

Abstract

Objective: To compare the safety and efficacy of double therapy (DT) (no aspirin) versus triple therapy (TT) (with aspirin) antithrombotic drugs in patients with atrial fibrillation and acute coronary syndrome or underwent percutaneous coronary intervention (PCI).
Methods: We searched PubMed, Cochrane, Scopus, and Web of Science for relevant articles from inception to December 2020. We conducted the analysis of dichotomous outcomes using risk ratio (RR) and relative 95% confidence interval (CI), while the continuous outcomes were analyzed using mean difference (MD) and relative 95% CI. Heterogeneous outcomes were analyzed with random-effects model, and homogeneous data were analyzed with fixed-effects model. We assessed the risk of bias among the included studies by using Cochrane's risk of bias tool.
Results: A total of five studies were included. Regarding Major or Minor Bleeding, the overall risk ratio was significantly lower with DT group compared with TT group (RR=0.60 [0.45, 0.81], (P = 0.07)). For the safety endpoint (TIMI major or minor bleeding, TIMI major bleeding) favored DT group over TT group, respectively (RR=0.60 [0.45, 0.81], (P = 0.07)); (RR= 0.55 [0.43, 0.70], (P < 0.01)). Intracranial hemorrhage did not differ between both groups (RR=0.62 [0.37, 1.05], (P = 0.07)). The efficacy endpoint, all-cause death showed no significant difference between both groups (RR=1.08 [0.89, 1.31], (P = 0.42)). There were no significant differences between two groups in cardiovascular death, stent thrombosis, myocardial infarction and stroke, respectively (RR=1.10 [0.86, 1.41], (P = 0.43); (RR=1.40 [0.92, 2.12], (P = 0.11); (RR=1.20 [0.98, 1.49], (P = 0.08); (RR=0.95 [0.66, 1.37], (P = 0.79).; respectively).
Conclusion: Compared with triple antithrombotic therapy, double antithrombotic therapy is associated with lower bleeding risks, including minor and major bleeding, but the incidence of efficacy endpoints was similar between both groups.

Keywords: *Acute Coronary Syndrome; Atrial Fibrillation; Percutaneous Coronary Intervention; Double and Triple Antithrombic Therapy.*

1. Introduction

High percentage of ischemic cardiac patients require percutaneous coronary intervention (1, 2). In patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI), confusion exists about optimal antithrombotic treatment. The cornerstone in prevention of thrombosis in these patients is oral anticoagulants with or without aspirin. However, random use of antithrombotic can cause high risk of bleeding leading to bad prognostic outcome in AF patients (3, 4). Since in patients undergoing PCI with stent implantation, combined antiplatelet treatment with a P2Y12 receptor antagonist and aspirin is recommended to avoid cardiac complications, particularly stent thrombosis (5).
American and European guidelines have recommended using aspirin plus vitamin K antagonist in addition to P2Y12 inhibitor as a triple antithrombotic strategy for these patients (6, 7). However, bleeding complications are of high risk (8, 9). In order to reduce the risk of bleeding among patients both oral anticoagulants and antiplatelet therapy are indicated, two new models have emerged. The first method is the use of oral anticoagulants that are non-vitamin K antagonists and dabigatran. Giving two doses can reduce stroke risk among pa-

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tients with atrial fibrillation either receiving single or dual antiplatelet therapy (10,11). The second scenario is to exclude aspirin and to use a single inhibitor of P2Y12 in conjunction with oral anticoagulant treatment (12).
If aspirin is omitted, this could be useful to minimize the risk of bleeding in coronary artery disease (CAD) patients. Two major randomized studies revealed that oral anticoagulants alone were associated with lower levels of re-infarction and stroke compared with aspirin addition following myocardial infarction, while the risk of bleeding was also increased (13). The risk of bleeding in patients with atrial fibrillation that had underwent PCI was smaller among those obtaining dual dabigatran and P2Y12 inhibitor therapy than among those receiving triple warfarin, P2Y12 inhibitor and aspirin therapy but prevention of thromboembolism was the opposite in randomized multicenter trial (14).
In a nationwide cohort study of AF patients after PCI follow up, they concluded that using conventional triple antithrombotic drugs including vitamin k antagonist clopidogrel, aspirin increased bleeding risk with no ultimate safety according to patients follow up (3). New trials with opposite results to the usual practice in this critical point necessitate reevaluation of efficacy of triple therapy treatment strategy. As risk of bleeding competes with getting the best protection against thrombosis in AF patients following PCI, we did this study trying to reach the most accurate recommendations regarding using double versus triple antithrombotic drugs.

2. Methods

In this systematic review and meta-analysis, we strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (15). All steps of this study were conducted according to Cochrane's handbook of systematic reviews of interventions (16).

2.1. Literature search

We searched four databases: PubMed, SCOPUS, Cochrane CENTRAL, and Web of Science, without any restrictions on time or languages. We performed our search using the following search strategy: ("Percutaneous coronary intervention" OR PCI OR "coronary stenting" OR "acute coronary syndrome" OR ACS) AND ("atrial fibrillation" OR AF) AND ("vitamin k antagonist" OR warfarin'OR Phenprocoumon OR "oral anticoagulation" OR "oral anticoagulants" OR "dual antithrombotic therapy" OR "dual therapy" OR "triple therapy" OR "triple antithrombotic therapy" OR "dual antiplatelet therapy" OR clopidogrel OR aspirin)

2.2. Eligibility criteria

Results from searching the literature were marked as included if they have met the following eligibility criteria: (I) Population: patients with atrial fibrillation undergoing percutaneous coronary intervention or acute coronary syndrome, (ii) Intervention: double therapy, (iii) Comparator: triple therapy, (IV) Outcomes: TIMI (Thrombolysis in Myocardial Infarction) Major or Minor Bleeding, TIMI major bleeding, intracranial hemorrhage, all-cause death, cardiovascular death, stent thrombosis, myocardial infarction, and stroke and (V) Study design: we included only randomized clinical trials (RCTs). Our exclusion criteria were: (1) non-randomized controlled clinical trials, (2) studies that did not report data or measures for our selected outcomes (3) single-armed trials, or (4) that with no available full-text.

2.3. Screening of results

After retrieving the search results, we exported the data into Endnote X8.0.1 (Build 1044), with the automatic removal of any duplicates. We screened the included articles manually through two steps, the first step was the title and abstract screening, and the second step was full-text screening. Two independent authors (Rit and Kia) conducted the screening steps and obtained the full-text files for all included studies based on our criteria for eligibility criteria. A third author solved any discrepancies.

2.4. Data extraction and analysis

After the screening process has completed, we performed the data extraction step. We extracted the data into two main categories:

1) Baseline and demographic data of patients in each study, including age, body mass index, number of current smokers, number of diabetics, number of hypertensive patients, and number of patients suffering from dyslipidemia.
2) Data for analysis that consisted mainly of our included outcomes:

Safety endpoint: TIMI major or minor bleeding, TIMI major bleeding, intracranial hemorrhage
Efficacy endpoint: all-cause death, cardiovascular death, stent thrombosis, myocardial infarction, and stroke.
We also extracted the data about the seven domains assessing the risk of bias according to Cochrane's risk of bias.

2.5. Data analysis

We performed our analysis using Review Manager Software (RevMan 5.4.1) under the Inverse variance method. Continuous data were expressed using mean difference (MD) and standard error, relative to 95 % confidence interval (CI), while dichotomous outcomes were expressed using percent and total. Two main tests indicate inconsistency among studies(17), the I-square test (I2) and the P-value of the Chi-square test. The outcomes with $I^2 > 50\%$, $P<0.1$ were considered heterogeneous, while outcomes with $I^2 < 50\%$, $P>0.1$ were considered homogeneous, according to the Cochrane Handbook(16). We performed the analysis of homogeneous data under a fixed-effects model, while heterogeneous data were analyzed under the random-effects model.

2.6. Quality assessment

We performed the quality assessment of this meta-analysis by using the guidelines of the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE). We included only the controlled trials and excluded the observational evidence. To assess the risk of bias among the included studies, we used Cochrane's risk of bias tool (18). The tool depends on the following domains for assessment of the risk of bias: 1) proper randomization, 2) blinding allocation of the included patients into each group, 3) blinding of patients only (single-blinding), blinding of both personnel and participants (double-blinding), or not blinding at all, 4) attrition bias, 5) se-

lection bias (outcomes reported matches with that of the protocol or not), 6) awareness of the outcome assessor (whether blinded or not) and 7) other bias. The total risk of bias for the studies has been assessed as well.

3. Results

3.1. Summary of included studies

The results of our literature search are illustrated in the PRISMA flow diagram (figure 1). We present the analysis of 11449 patients from five studies (12,14,19–21). A total of 5749 patients received double therapy (DT), while triple therapy (TT) was given to 5700 patients. The mean age of patients in the DT and TT group was 70.36 years and 69.76 years respectively. Table 1 shows a detailed summary of included patients and their demographic data, body mass index, number of current smokers, number of diabetics, number of hypertensive patients, and number of patients suffering from dyslipidemia.

3.2. Results of risk of bias assessment

We found an overall low risk of bias according to Cochrane's tool (10). Regarding randomization, all studies (12,14,19–21) reported adequate randomization thus they were categorized as low risk of bias. In regard to selection bias, all studies (12,14,19–21) reported no allocation concealment so they were put as high risk. The majority of studies (14,19–21) reported blinding of participant, personnel, and outcome assessment, therefore they were categorized as low risk of performance and detection bias respectively except for Dewilde et al (12) which did not report enough data about blinding of participant, personnel, and outcome assessment. Concerning detection bias, attrition bias, and other bias all studies (12,14,19–21) were categorized as "low risk". A detailed illustration of the risk of bias of included trials is summarized in figure 2.

4. Analysis of outcomes

4.1. TIMI major or minor bleeding

All studies reported TIMI major or minor bleeding outcome (12,14,19–21). The overall risk ratio favored DT group significantly (RR=0.60 [0.45, 0.81], (P = 0.07)). The analysis was heterogeneous (P = 0.01); I^2 = 77% as shown in figure 3a. We solved the heterogeneity by excluding Vranckx et al (21) (P = 0.20); I^2 = 35%. Homogeneous results still showed significant favoring of DT group (RR=0.53 [0.42, 0.65], (P < 0.01) as shown in figure 3b.

4.2. TIMI major bleeding

TIMI major bleeding outcome was reported by all studies (12,14,19–21). The combined effect estimate favored DT group over TT group (RR= 0.55 [0.43, 0.70], (P < 0.01)). Pooled analysis was homogeneous (P = 0.86); I^2 = 0% as shown in figure 4.

4.3. Intracranial hemorrhage

All studies reported intracranial hemorrhage (12,14,19–21). The overall analysis did not show any significant difference between both groups (RR=0.62 [0.37, 1.05], (P = 0.07)). Data was homogeneous (P = 0.36); I^2 = 8% as shown in figure 5.

4.4. All-cause death

All-cause death was reported by all studies (12,14,19–21). Analysis showed no significant favoring of any group over the other (RR=1.08 [0.89, 1.31], (P = 0.42)). Data was homogeneous (P = 0.20); I^2 = 33% as shown in figure 6.

4.5. Cardiovascular death

Cardiovascular death was reported by all studies (12,14,19–21). The combined risk ratio did not show any significant variation between both groups (RR=1.10 [0.86, 1.41], (P = 0.43)). Pooled analysis was homogeneous (P = 0.69); I^2 = 0% as shown in figure 7.

4.6. Stent thrombosis

All studies reported stent thrombosis outcome (12,14,19–21). Pooled analysis did not show any difference between both groups (RR=1.40 [0.92, 2.12], (P = 0.11)). Data was homogeneous (P = 0.31); I^2 = 16% as shown in figure 8.

4.7. Myocardial infarction

All studies reported myocardial infarction outcome (12,14,19–21). The overall risk ratio did not show any significant difference between both groups (RR=1.20 [0.98, 1.49], (P = 0.08)). Data was homogeneous (P = 0.49); I^2 = 0% as shown in figure 9.

4.8. Stroke

Stroke outcome was reported by all studies (12,14,19–21). The combined effect estimate showed no significant variation between both groups (RR=0.95 [0.66, 1.37], (P = 0.79)). Pooled analysis was homogeneous (P = 0.59); I^2 = 0% as shown in figure 10.

5. Discussion

In our meta-analysis, we examined the role of triple antithrombotic therapy (TAT) and that of double antithrombotic therapy (DAT) in 5027 patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI). We found that DAT significantly reduced The Thrombolysis in Myocardial Infarction Score (TIMI) major or minor bleeding and TIMI major bleeding. The DAT was non-inferior for intracranial hemorrhage, all causes of death, stent thrombosis, and stroke compared with TAT.

TIMI score estimates the mortality following ST-elevated myocardial infarction. Vranckx et al (21) and Cannon et al (14) found that TIMI major bleeding was significantly lower in DAT groups than in the TAT group. Dewilde et al (12) showed that dual-therapy was associated with lower episodes, but there was no significant difference between both groups.

A randomized, open-label trial ENTRUST-AF PCI (21) was the first trial estimating the effect of edoxaban-based DAT versus a vitamin k antagonist TAT in patients with AF. The ENTRUST-AF PCI (21) showed that edoxaban-based DAT had plus a P2Y12 inhibitor had similar results to vitamin k antagonist TAT regarding the risks of major and minor bleeding. Also, no significant difference was observed regarding cardiovascular death, stroke, and myocardial infarction, which is consistent with our result.

The RE-DUAL PCI (14) trial, a multicenter, randomized trial of 2725 patients with AF, showed that a DAT of dabigatran with P2Y12 inhibitor resulted in a significantly lower risk of major and nonmajor bleeding events compared with TAT with warfarin. Besides, DAT showed similar results regarding composite efficacy and thromboembolic events.

In the PIONEER AF-PCI (19), a multicenter, randomized, open-label study, the rivaroxaban-based dual therapy was superior to warfarin-based therapy. Two different doses of Rivaroxaban resulted in a significantly lower risk of major and minor bleeding compared with warfarin. No significant difference in results regarding ischemic outcomes.

The WOEST trial showed that the use of clopidogrel alone as a part of DAT in patients, who required PCI, was associated with a significantly lower rate of bleeding complications than the use of aspirin. Aspirin irreversibly inhibits thromboxane A_2, which is an important factor promoting platelet aggregation. This may explain the increased frequency of gastrointestinal bleeding episodes in the aspirin group (23).

A meta-analysis by Gargiulo et al showed that new oral anti-coagulant based (NOAC) dual therapy significantly reduced the risk of major and minor bleeding, compared with TAT. DAT was also associated with similar rates of cardiovascular death and stroke. On the other hand, DAT was associated with an increased risk of ischemic complications such as myocardial infarction. Our meta-analysis compares the effects of DAT with that of TAT in patients with atrial fibrillation undergoing PCI or acute coronary syndrom. We only included randomized clinical trials, which ensures the highest evidence according to GRADE. All the included studies were at low risk of bias in general, which is another strength point, and we also conducted the analysis on a large sample size (5027 patients). We solved the heterogeneity among studies using appropriate methodologies reported by Cochrane's handbook (22).

6. Limitations

The main limitation of our meta-analysis is the heterogeneity in some outcomes. However, we managed to elicit the attributing factors and overcome this inconsistency among the studies.

7. Conclusion

We found that DAT (Included NOAC and/or vitamin k antagonist plus P2Y12 receptor inhibitors without aspirin) significantly reduced the safety endpoint (TIMI score for major or minor bleeding, TIMI major). However, there was no significant difference in intracranial hemorrhage. We also found that DAT, compared with TAT, was associated with similar risks of the efficacy endpoint for all-cause death, cardiovascular death, myocardial infarction, stent thrombosis, and stroke.

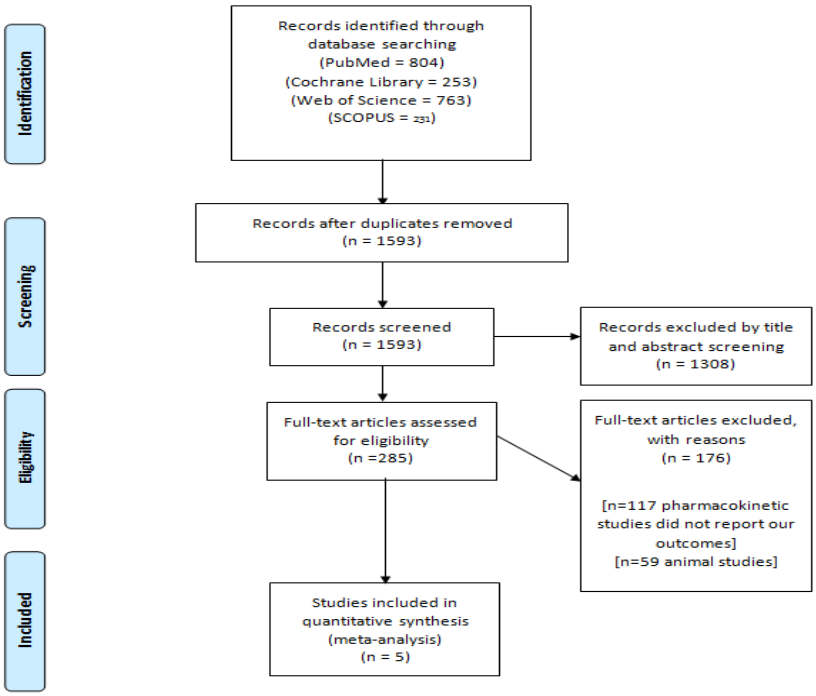
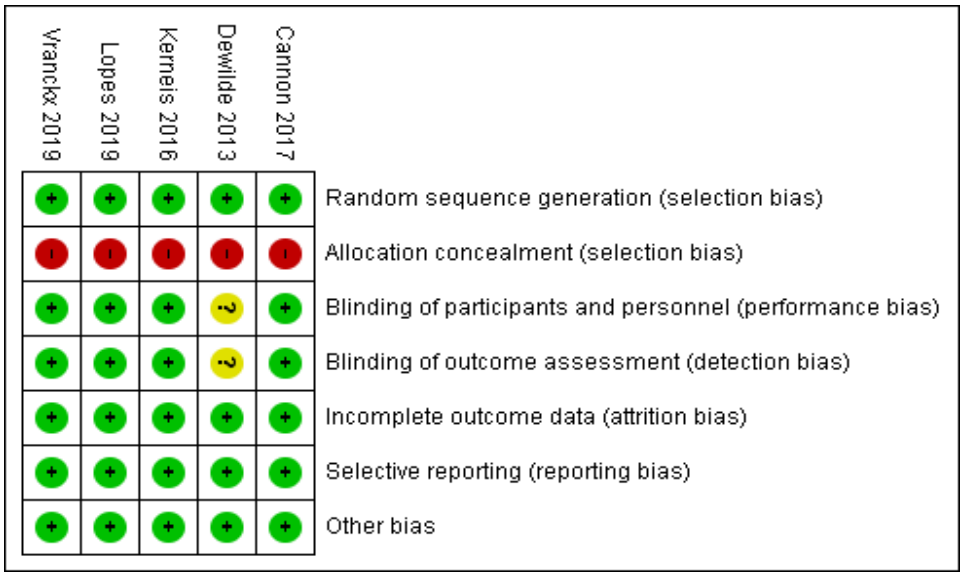


Fig. 2: Risk of Bias Assessment.



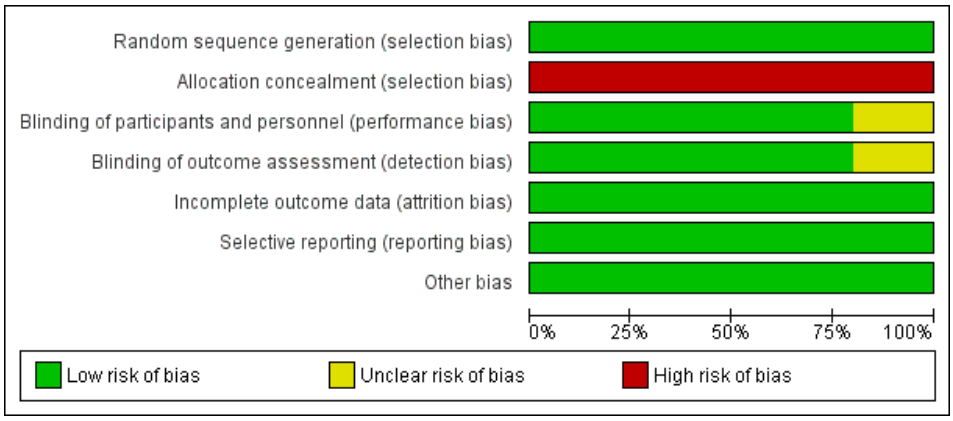


Table 1: Summary of Included Patients

Study ID	Sample size		Follow-up	Age (mean)		Female sex		BMI (mean)		Current smoker		Diabetes	
	Double G N	Triple G N	Duration, months	Double G mean	Triple G mean	Double G %	Triple G %	Double G mean	Triple G mean	Double G %	Triple G %	Double G %	Triple G %
Lopes 2019	2307	2307	6	70.6	70.8	27.8	30.2					36.2	36.5
Vranckx 2019	751	755	12	69	70	25.8	25.4	28.5	28.9	15.6	14.6	34.5	34.2
Gibson 2016	709	706	12	70.4	69.9	25.5	26.6	28.6	29	5.2	6.8	28.8	31.3
Cannon 2017	981	981	14	71.5	68.6	25.8	23.5					36.9	37.9
Dewilde 2013	279	284	12	70.3	69.5	23	18	27.5	28.6	22	5.2	24	28.8

Data are represented as Mean and SD, n (%) unless proved otherwise.

Study ID	Hypertension		Prior MI		Prior PCI		Prior stroke		Prior bleeding		Creatinine clearance	
	Double G %	Triple G %	Double G %	Triple G %	Double G %	Triple G %	Double G %	Triple G %	Double G %	Triple G %	Double G ml/min	Triple G ml/min
Lopes 2019	88.5	88					14.7	13			79.7	78.6
Vranckx 2019	89.7	91	25	23.4	26.5	25.8	12.9	12.2	7.5	6.5	71.8	71.7
Gibson 2016	73.3	75.4	19.8	22.2					1	0.7	78.3	80.7
Cannon 2017			24.2	27.3	33.2	35.4	7.5	10.2			76.3	75.4
Dewilde 2013	69	73.3	34	35	31	36	18	18	14	14		

Data are represented as Mean and SD, n (%) unless proved otherwise.

Study ID	Creatinine clearance <30 ml/min		ACS		Stable CAD		Type of AF		
	Double G	Triple G	Double G	Triple G	Double G	Triple G	Paroxismal	Persistent	Permanent

	%	%	%	%	%	%	Double G %	Triple G %	Double G %	Triple G %	Double G %	Triple G %
Lopes 2019			61.7	60.7	38.3	39.3						
Vranckx 2019	1.9	1.8	51.7	51.5	48.3	48.5	53.5	47.5	18.6	19.4	27.8	33.2
Gibson 2016	1.2	0.3	39.6	36.4	60.4	63.6	42.4	44.4	20.6	21.1	37	34.5
Cannon 2017	16	19.2	51.9	48.4	48.1	51.6	49.6	49.4	17.7	18.2	32.6	32.4
Dewilde 2013												

Data are represented as Mean and SD, n (%) unless proved otherwise.

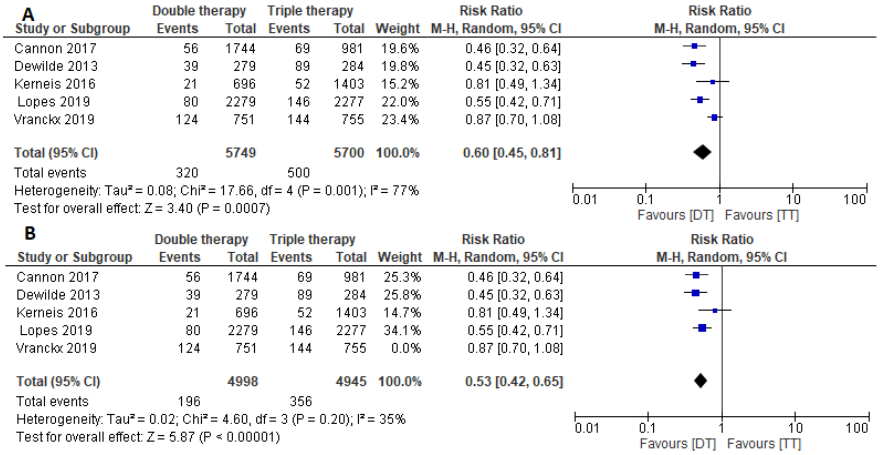


Fig. 3: TIMI Major or Minor Bleeding.

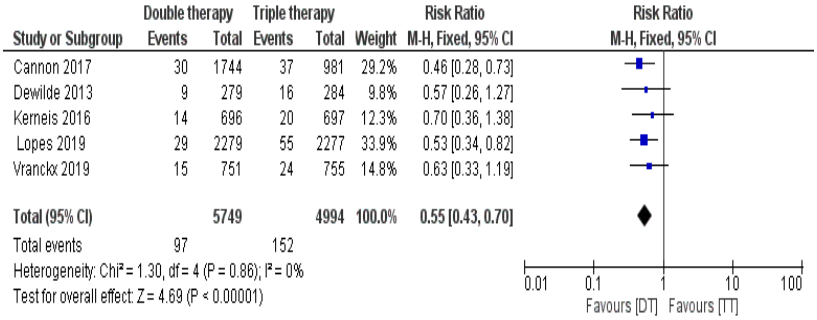


Fig. 4: TIMI Major Bleeding.

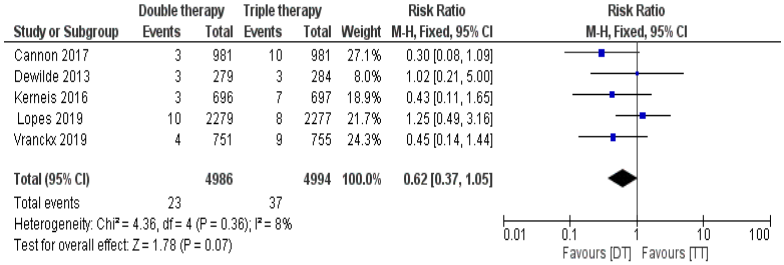


Fig. 5: Intracranial Hemorrhage.

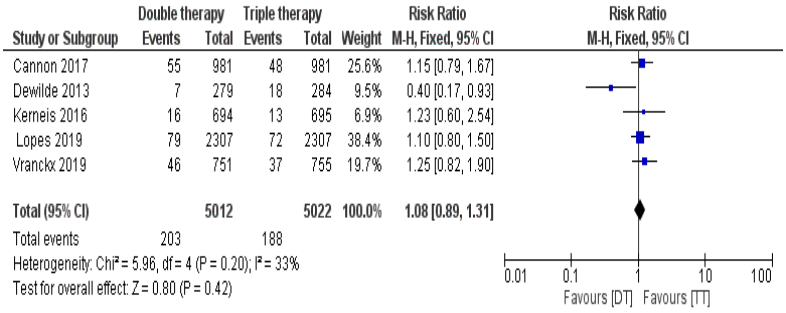


Fig. 6: All-Cause Death.

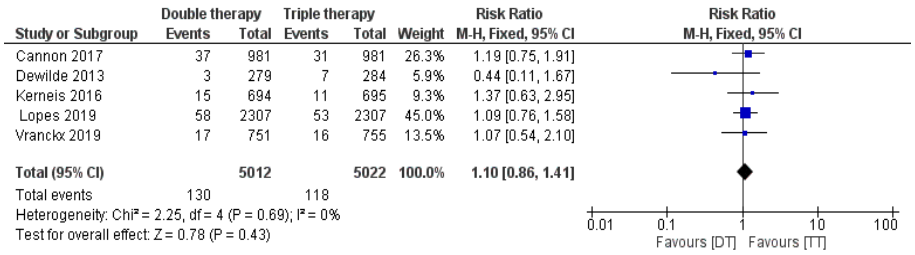


Fig. 7: Cardiovascular Death.

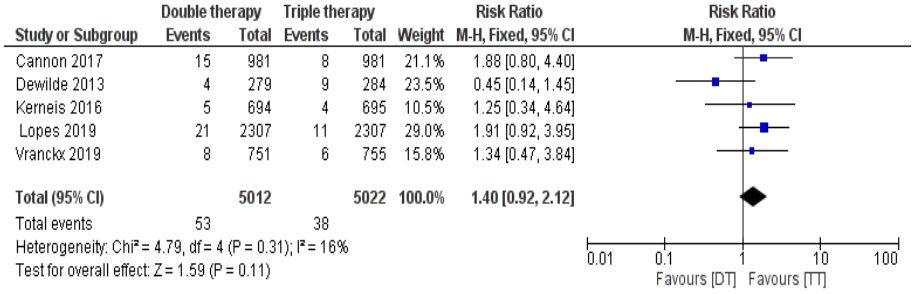


Fig. 8: Stent Thrombosis.

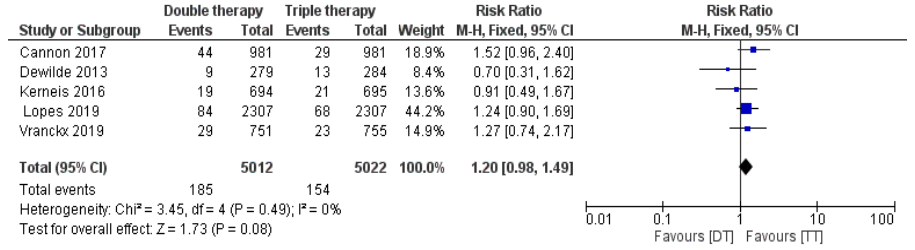


Fig. 9: Myocardial Infarction.

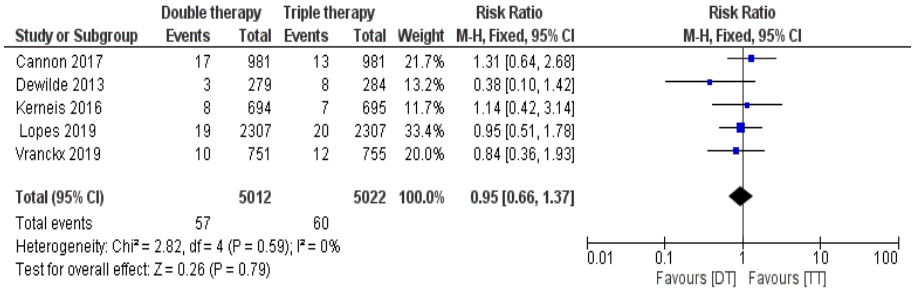


Fig. 10: Stroke.

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