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Anti-thrombotic therapy strategies with long-term anticoagulation after percutaneous coronary intervention – a systematic review and meta-analysis

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ABSTRACT

Background: Long-term oral anticoagulants (OAC) increases bleeding risk after the percutaneous coronary intervention (PCI) with dual antiplatelet therapy (DAPT) with Aspirin and $P2Y_{12}$ inhibitors. We hypothesize that dual anti-thrombotic therapy (DATT) reduces bleeding without increased cardiovascular events.

Objectives: DATT does not increase adverse cardiovascular events compared to triple anti-thrombotic therapy (TATT).

Method: We searched MEDLINE, PUBMED, Google Scholar, Cochrane and EMBASE from inception to 6 April 2019 for randomized control trials (RCTs) comparing DATT to TATT after PCI.

Results: We identified 641 citations (411 after excluding duplicates). Four RCTs with 5,317 patients (3,039 on DATT vs 2,278 on TATT) were included. DATT arm showed significantly reduced *[total bleeding, 731 vs. 784, odds ratio [OR] = 0.51, Confidence Interval [CI] = 0.39–0.67, $p < 0.00001$, $I^2 = 71\%$ ($I^2 = 0\%$ without WOEST study)], [TIIMI major bleeding 60 vs. 80, OR = 0.56, CI = 0.4–0.79, $p = 0.0009$, $I^2 = 0\%$], and [TIIMI minor bleeding, 70 vs 126, OR = 0.43, CI = 0.32–0.59, $p < 0.00001$, $I^2 = 0\%$]. There was no difference in subsequent strokes, myocardial infarction, stent thrombosis, and mortality. A trend towards decreased non-cardiac deaths with DATT was observed, 14 vs 26, OR = 0.55, CI = 0.27–1.10, $p = 0.09$, $I^2 = 6\%$.*

Conclusions: DATT is associated with significantly reduced bleeding and a trend towards reduced non-cardiac death with no difference in adverse cardiovascular outcomes.

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Oral anticoagulation; atrial fibrillation; bleeding; triple anti-thrombotic therapy; dual-anti thrombotic therapy

1. Introduction

Dual antiplatelet therapy (DAPT) using Aspirin and $P2Y_{12}$ inhibitors is the standard of care after the percutaneous coronary intervention (PCI) and stent placement. It is superior in the prevention of stent thrombosis post PCI as compared to oral anticoagulant (OAC) alone [1,2]. On the other hand, OAC is preferred in reducing the risk of thromboembolic events as compared to DAPT in patients with mechanical heart valves [3], and atrial fibrillation [4]. Patients undergoing PCI with a concomitant indication for long-term anticoagulation are treated with triple antithrombotic therapy (TATT). This strategy consists of the combined use of DAPT and OAC [5–7]. One-fourth of elderly patients with atrial fibrillation and myocardial infarction also requires TATT [8]. However, this strategy is associated with an increase in bleeding complications with rates of 2.2% within the first month and increasing to 4% to 12% within the first year of treatment and more than three folds compared to Warfarin alone [9,10]. Patients receiving TATT are also more likely to be admitted to the hospital [11].

These findings have led to studies considering new therapeutic approaches to reduce the risk of bleeding in patients on both OAC and DAPT. There is an increasing interest in utilizing non-vitamin K antagonist OAC as studies have shown novel oral anticoagulants may provide an advantage over vitamin K antagonist (VKA) [12]. Dewilde et al. in their randomized controlled trial (RCT) showed that dual therapy with Clopidogrel and Warfarin might be considered as an alternative to initial triple treatment in selected patients [13]. Other studies have demonstrated the use of low dose Rivaroxaban along with $P2Y_{12}$ inhibitor was associated with reduced bleeding rates compared to triple therapy [14–16].

We have conducted a comprehensive systemic review and meta-analysis combining all previous RCT

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comparing triple antithrombotic therapy (TATT) (dual antiplatelet therapy plus oral anticoagulant with either warfarin or non-vitamin K antagonist) vs. dual antithrombotic therapy (DATT) (an antiplatelet agent plus an oral anticoagulant with either warfarin or non-vitamin K antagonist). We performed this analysis to elucidate the clinical outcomes, and adverse events associated with the DATT in patients who are undergoing PCI and simultaneously require long-term OAC.

2. Methods

2.1. Study selection protocol

We included only those studies for final analysis which met our predefined inclusion criteria.

Inclusion Criteria – ***1)*** *Prospective RCT's,* ***2)*** *Comparing only DATT to TATT in patients undergoing PCI and also require long-term anti-thrombotic therapy,* ***3)*** *Adult patients (age ≥ 18 years),* ***4)*** *All of the following outcomes were addressed:* ***I*** *– Any bleeding (including major and minor),* ***II*** *– thromboembolic events (including ischemic stroke, stent thrombosis or MI), and* ***III*** *– death (cardiac and non-cardiac).*

2.2. Information sources and search strategy

We completed our systematic review per the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines [17]. A comprehensive review of PubMed, MEDLINE, Google Scholar, Cochrane and EMBASE databases was completed from inception until 6 April 2019, for the studies comparing DATT to TATT after PCI in patients who require long-term anticoagulation. We used the MeSH terms and keywords for our search. We used following search strategy ('percutaneous coronary intervention' OR PCI) AND (antiplatelet OR aspirin OR clopidogrel OR prasugrel OR ticagrelor) AND (NOAC OR DOAC OR anticoagulation OR anticoagulant OR antithrombotic OR warfarin OR dabigatran OR apixaban OR rivaroxaban OR edoxaban). We combined search themes using the Boolean operator 'AND' and 'OR.' Our initial search was not limited by language or publication year, but it was limited to RCTs.

2.3. Study selection

The initial search yielded a total of 649 articles, after excluding the duplicates, they reduced to 411. We excluded 394 studies based on titles and abstracts which included cohort studies, non-randomized trials, post hoc analysis of original trials, review articles, editorials, and retrospective studies. We read full texts of 17 studies, of which 13 were excluded. Only four studies met our inclusion criteria which we included in our analysis [13,15,18,19]. Out of 13 excluded studies, five studies were the sub-studies of original RCTs; eight were the trial designs. We searched the clinicaltrials.gov for the study designs of three trials whose completed trials did not appear in our search and were published before 2017 [20–22]. When we contacted the corresponding authors, we did not receive any response from them. One study's design was published in 2017, and this study is currently underway [23]. The included trials compared DATT to TATT post PCI in patients requiring long-term anticoagulation. We then searched through the references of individual papers, but we did not come across any additional RCTs meeting our inclusion criteria.

2.4. Data collection process

Three independent reviewers (W.J.S, M.S.R., and M. Y.K.) selected the studies. Two reviewers (W.J.S. and C.A.) extracted the data using the pre-defined data fields. W.J.S. cross-checked all the entered data. We resolved any discrepancies within the data entry after mutual discussion and understanding. ***Figure 1*** shows the study flow diagram.

2.5. Risk of bias in individual studies

We assessed the quality of the individual study using the Cochrane collaboration's tool for determining the risk of bias in randomized trials [24]. These are summarized in Table 1 and Supplementary Figure 1.

2.6. Data synthesis and analysis

The PIONEER AF-PCI trial used two different doses of Rivaroxaban (10/15mg vs. 2.5 mg) in the TATT arm. We only used outcomes from the group which used a higher dose (10/15mg) for our analysis. Also, to mention that ISAR-TRIPLE trial used Warfarin, Clopidogrel, and Aspirin in the trial. It was primarily designed to evaluate short duration (six weeks) vs. long duration (six months) of TATT where Clopidogrel was used only for the first six weeks in the short duration arm and after that aspirin was continued with warfarin. We only assessed events after the initial six-week period between 6 weeks and nine months when the real comparison of DATT vs. TATT was made. The censored events from the first six weeks of the trial and the events used in our analysis between the six weeks and six months are summarized in supplementary appendix Table 1. The two older trials, the WOEST trial, and the ISAR-TRIPLE trial used Warfarin for the anticoagulation [13,19] as compared to the two newer trials, the PIONEER AF-PCI and the RE-DUAL PCI trial which used Rivaroxaban and Dabigatran, respectively, [15,18].

We assessed the following endpoints.

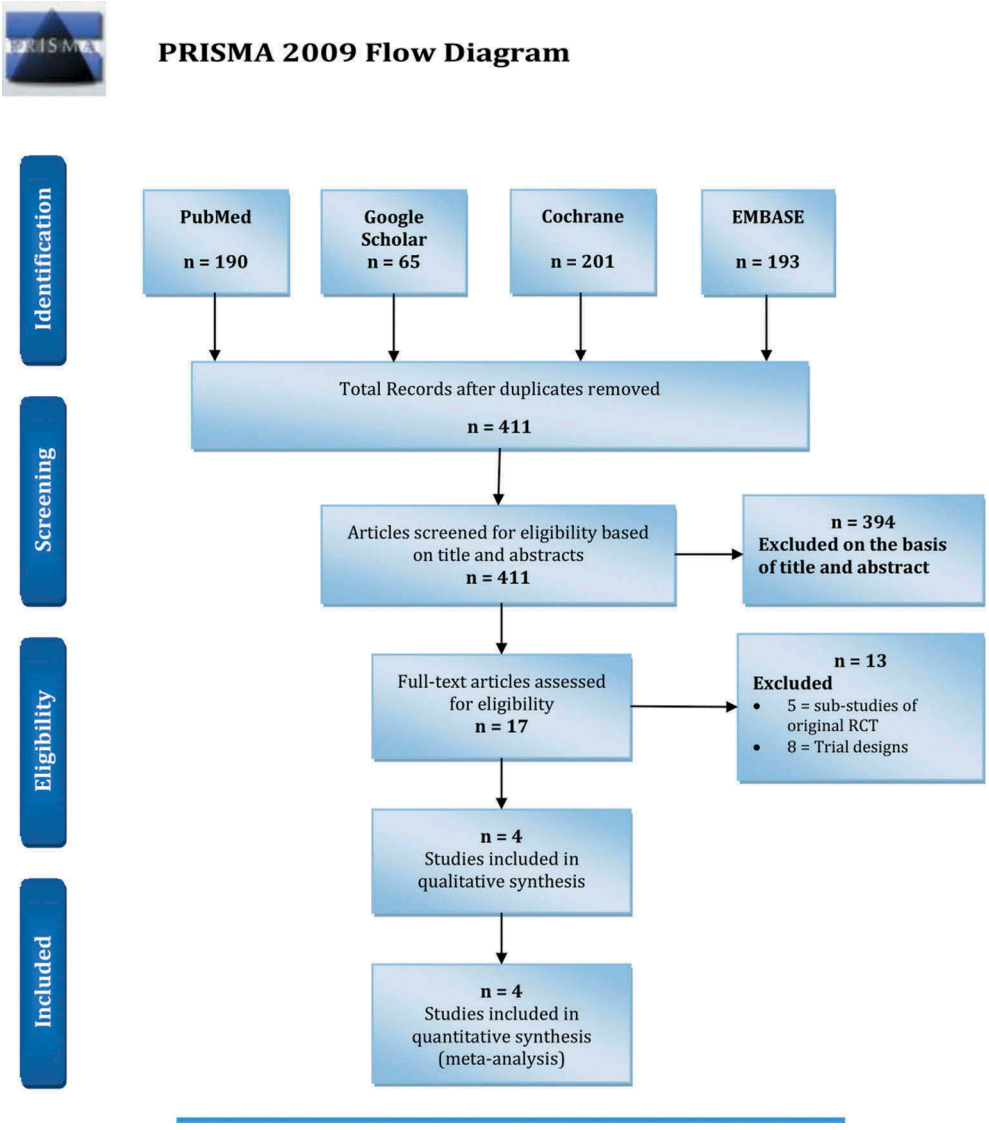

Figure 1. Showing the PRISMA 2009 Study Flow Diagram.

The primary endpoints were *1) all-cause bleeding, 2) Thrombolysis in Myocardial Infarction (TIMI) major bleeding and 3) TIMI minor bleeding.*

The secondary endpoints were *1) all strokes, 2) ischemic strokes, 3) hemorrhagic strokes, 4) myocardial infarction, 5) stent thrombosis, 6) all-cause death, 7) cardiovascular cause of death and 8) non-cardiac death.*

2.7. Statistical method

We used the random effects model for our statistical analysis in RevMan Version 5.3 Copenhagen. We used the Mantel-Haenszel method for the statistical analysis of dichotomous data to calculate the odds ratio. We used the effect estimate to report our results. 95% confidence interval, with 2-sided p-value of <0.05 was considered statistically significant. Baseline characteristics and differences of individual studies are summarized in Supplementary Table 2 and Table 2, respectively.

2.8. Heterogeneity

We used Chi^2 and I^2 statistics for calculating the heterogeneity with *RevMan Version 5.3 Copenhagen*. We estimated the percentage of variability present between studies (inter-study variability) compared to the variability present in individual studies (intra-study) with the I^2 statistic. An I^2 value of >50% was classified as the substantial existence of heterogeneity as explained by the Cochrane Handbook for Systematic Reviews for Interventions, Version 5.1.0, Part 2: General Methods for Cochrane Reviews [25]. We performed a sensitivity analysis on outcomes where substantial heterogeneity was present.

3. Results

We found 649 articles, which were reduced to 411 after removing duplicated. After screening based on title and abstract, we excluded 394 studies which included cohort studies, non-randomized studies,

Table 1. Cochrane risk of bias for quality assessment.

Name	RE – DUAL PCI Cannon et al	PIONEER AF-PCI Gibson et al	ISAR-TRIPLE Fiedler et al	WOEST Dewilde et el
Random Sequence	Permuted Blocks **Low Risk**	Interactive voice/Web response system on day 1 in Permuted Blocks **Low Risk**	Computer-generated sequence (ISA Research Centre, Munich) for German patients Computer-generated web-based system (Aarhus University Hospital, Aarhus) for the Danish patients **Low Risk**	Computer generated at St Antonius Hospital (blocked randomization per center) **Low Risk**
Allocation Concealment	Not reported **Unclear**	Not reported **Unclear**	1:1 by means of sealed opaque envelopes **Low Risk**	1:1 ratio in sequentially numbered sealed envelopes **Low Risk**
Blinding of Participants and Personnel	No Open Label **High Risk**	No Open Label **High Risk**	No Open Label **High Risk**	No Open Label **High Risk**
Blinding of Outcome Assessment	Independent committee **Low Risk**	Independently by PERFUSE study group **Low Risk**	Not Reported **Unclear**	Not Reported **Unclear**
Incomplete Outcome Data	No **Low Risk**	No **Low Risk**	No **Low Risk**	No **Low Risk**
Reporting Bias	Open Label Study **Low to intermediate Risk**	Open Label Study **Low to intermediate Risk**	Open Label Study **Low to intermediate Risk**	Open Label Study **Low to intermediate Risk**

RCT = Randomized Control Trial, NEJM = New England Journal of Medicine, JACC = Journal of American College of Cardiology, NVAF = Non-Valvular Atrial Fibrillation, SAPT = Clopidogrel or Ticagrelor, DAPT = Clopidogrel or Ticagrelor + Aspirin, LD = Low Dose, VLD = Very Low Dose

post hoc analysis of original trials, review articles, editorials, and retrospective studies. We read full texts of 17 studies, of which 13 were excluded. Five were sub-studies of the original trials included in the analysis and eight were the study designs. Only four studies met our inclusion criteria which we included in our analysis [13,15,18,19]. We searched the clinicaltrials.gov for the study designs of three trials whose completed trials did not appear in our search and were published before 2017 [20–22]. We included four RCT's with 5,317 patients for our analysis. There were a total of 3,039 patients in DATT group compared to 2,278 in TATT arm.

3.1. Primary outcomes

There was significantly decreased number of bleeding episodes in DATT group compared to TATT group, **731 vs 786 *(odds ratio [OR] = 0.51, Confidence Interval [CI] = 0.39– 0.67, p < 0.00001, I^2 = 71%),*** (Figure 2a). Since ***I^2 was 71%*** which suggested substantial heterogeneity, on running the sensitivity analysis without WOEST study, (9) ***I^2 decreased to 0%*** with results still significantly favoring DATT over TATT. On assessing the TIIMI major bleeding, there were a total of 60 episodes in DATT group which was significantly lower compared to 80 in TATT group, ***(OR = 0.56, CI = 0.4– 0.79, p = 0.0009, I^2 = 0%),*** (Figure 2b). Similarly, on assessing the On TIIMI minor bleeding, there were significantly decreased episodes in the DATT vs TATT group, **(70 vs 126, OR = 0.43, CI = 0.32– 0.59, p < 0.00001, I^2 = 0%)** (Figure 2c).

3.2. Secondary outcomes

There was no significant difference in all strokes ***(43 vs 40 in DATT vs TATT, OR = 0.75, CI = 0.48– 1.17, p = 0.20, I^2 = 0%)***, ischemic strokes ***(36 vs 26 in DATT vs TATT, OR = 0.91, CI = 0.39– 2.14, p = 0.83, I^2 = 41%)*** and hemorrhagic strokes ***(7 vs 13 in DATT vs TATT, OR = 0.49, CI = 0.14– 1.73, p = 0.27, I^2 = 27%)*** Supplementary Figure 2. There was also no difference in the cardiac events including MI with 99 vs 63 in DATT and TATT arms, respectively, ***(OR = 1.12, CI = 0.80– 1.55, p = 0.52, I^2 = 0%).*** Number of in-stent thrombosis was also similar in both groups 31 vs 21 in DATT and TATT arms, respectively ***(OR = 1.03, CI = 0.48– 2.19, p = 0.94, I^2 = 32%)*** Supplementary Figure 3. On assessing the mortality, there was no statistical difference in all cause death, ***(120 in DATT and 100 in TATT arms, OR = 0.80, CI = 0.55– 1.16, p = 0.24, I^2 = 29%).*** CV cause of death was also similar in both groups, ***(21 in DATT vs 26 in TATT, OR = 0.70, CI = 0.28– 1.74, p = 0.44, I^2 = 49%).*** There was a trend towards decreased non-cardiac deaths in DATT patients compared to TATT arm ***(14 vs 26, OR = 0.55, CI = 0.27–1.10, p = 0.09, I^2 = 6%),*** Supplementary Figure 4.

Table 2. Characteristics and differences of RCT's.

Name	RE – DUAL PCI Cannon et al	PIONEER AF-PCI Gibson et al	ISAR-TRIPLE Fiedler et al	WOEST Dewilde et el
Design	Prospective, Multicenter, Open Label Blinded end point RCT	Prospective, Multicenter, Open Label Blinded end point RCT	Prospective, Multicenter, Open Label, RCT	Prospective, Multicenter, Open-label, RCT
Country	USA, Europe, Japan, other countries (41 countries)	Multiple Countries	Germany, Denmark	Netherlands and Belgium (15 sites)
Publication Year	**2017**	**2016**	**2015**	**2013**
Journal	NEJM	NEJM	JACC	Lancet
Enrollment	July 2014 – October 2016	Unknown	September 2008 – December 2013	November 2008 – November 2011
Population	NVAF patients > 18 years old s/p successful PCI with BMS or DES	NVAF patients > 18 years old s/p successful PCI with BMS or DES	Patients receiving OAC for ≥ 12 months + receiving DES for Stable Angina or ACS	Adults receiving OAC and Undergoing PCI
Indication of Anticoagulation	Atrial Fibrillation (100%)	Atrial Fibrillation (100%)	Atrial Fibrillation (84%), Mechanical Valve (7%) Other (9%)	Atrial Fibrillation (69%), Mechanical Valve (11%) Other (20%)
Intervention vs Comparison	Dabigatrin + SAPT **vs** Warfarin + DAPT	LD Rivaroxaban + $P2Y_{12}$ Inhibitors **vs** VLD Rivaroxaban + DAPT **vs** Warfarin + DAPT	Aspirin + Warfarin + 6-week of Clopidogrel **vs** Aspirin + Warfarin + 6-month of Clopidogrel	Warfarin + Clopidogrel (Double Therapy) **vs** Warfarin + Clopidogrel + Aspirin (Triple Therapy)
Primary Outcome	Major or clinically relevant nonmajor bleeding event during follow-up	Composite of major bleeding or minor bleeding according to TIMI criteria or bleeding requiring medical attention	Composite of death, MI, definite stent thrombosis, stroke, or TIMI major bleeding at 9 months	Any bleeding episode within 1 year of Percutaneous Intervention
F/u Duration	**14 months**	**12 months**	**9 months**	**12 months**

RCT = Randomized Control Trial, NEJM = New England Journal of Medicine, JACC = Journal of American College of Cardiology, NVAF = Non-Valvular Atrial Fibrillation, OAC = Oral Anti-Coagulation, DES = Drug Eluting Stent, ACS = Acute Coronary Syndrome, SAPT = Single Anti-Platelet Therapy (Clopidogrel or Ticagrelor), DAPT = Dual Anti-Platelet Therapy (Clopidogrel or Ticagrelor + Aspirin), LD = Low Dose, VLD = Very Low Dose, TIMI = Thrombolysis in Myocardial Infarction, MI = Myocardial Infarction.

4. Discussion

The patients undergoing PCI who require long-term OAC most commonly secondary to atrial fibrillation, the choice, and duration of therapy presents a significant challenge to clinicians. It is a balance between the risk of stroke/emboli (CHA2DS2-VASc score), recurrent ischemic events, stent thrombosis, and major bleeding [5]. Most commonly used combinations are; i) triple antithrombotic therapy (TATT) with a DAPT (aspirin and $P2Y_{12}$ inhibitor) plus an oral VKA or a non-vitamin K oral anticoagulant (NOAC), or ii) oral anticoagulation plus aspirin or a $P2Y_{12}$ inhibitor [5]. As treatment with TATT confers almost a 2–3 fold increased risk in bleeding complications, recent guidelines have recommended that the duration of triple therapy should be as short as possible, followed by OAC plus a single antiplatelet therapy [7,26,27]. DATT with an OAC (either with NOAC or a VKA) and Clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients with CHA2DS2–VASc score ≥2 [7,26,28]. To date, there has been no systematic review and meta-analysis of only RCTs comparing DATT to TATT.

In our analysis, there was a significantly decreased incidence of all-cause bleeding, TIMI major bleeding and TIMI minor bleeding in the DATT group as compared to the TATT group. These results are consistent with the results of individual RCTs and endorse that DAPT is safe as compared to TATT in patients who need long-term anticoagulation and also require concomitant antiplatelet therapy [19]. One cohort study found that the risk of bleeding with TATT was greatest within 30 days post-PCI [29]. Several studies have suggested that bleeding after PCI is an independent risk factor for mortality. This risk is even higher in patients who need red blood cell transfusion [30–32]. The current antithrombotic recommendation in high-risk patients for bleeding with atrial fibrillation undergoing PCI is to use single antiplatelet therapy (SAPT) with either VKA or NOAC (preferably NOAC) post stent placement. This recommendation further suggests discontinuing SAPT after one year if the patient remains at low risk for the thrombotic event. Patients with a high risk of thrombotic events should be given DAPT for at least 3– 6 months after stent placement. The duration of DAPT depends on the type of stent used, with three months for a bare-metal stent and six months for drug-eluting stents. Subsequently, SAPT should be continued for life unless the patient is at low risk of thrombotic events when SAPT can be discontinued after 12 months [33,34]. Before initiating either TATT or DATT, bleeding and thromboembolic

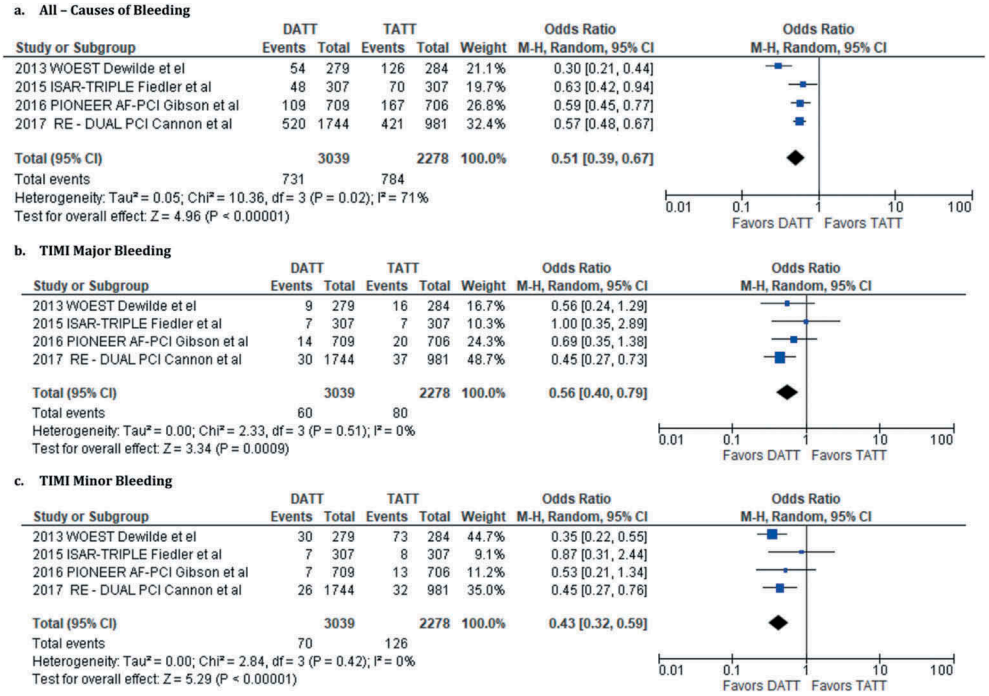

Figure 2. Primary Outcomes.

a. Showing the incidence of all-cause bleeding with Dual Anti-Thrombotic Therapy (DATT) vs. Triple Anti-Thrombotic Therapy (TATT)
b. Showing the incidence of TIMI major bleeding with Dual Anti-Thrombotic Therapy (DATT) vs. Triple Anti-Thrombotic Therapy (TATT)
c. Showing the incidence of TIMI minor with Dual Anti-Thrombotic Therapy (DATT) vs. Triple Anti-Thrombotic Therapy (TATT)

risks should be ascertained using the CHA2DS2-VASc and the HAS-BLED scores to individualize the treatment strategy.

Our meta-analysis did not reveal any significant difference in the cardiovascular events of strokes, MI and stent thrombosis between the two treatment arms of DATT and TATT. There was also no difference in the all-cause and cardiovascular cause of mortality. However, there was a trend towards decreased non-cardiac deaths in the DATT group compared to the TATT group. This reduced trend in non-cardiac deaths in the DATT group can likely be reflected by the significant decrease in bleeding events in the DATT group compared to the TATT group. Our findings differ from a previous meta-analysis by Briasoulis et al., which found a significant decrease in MI's in the TATT group compared to the DATT group. These results could have been affected by population selection bias which included five cohort studies [35].

Our meta-analysis has several limitations and should be carefully considered before inferring any additional conclusions. The first limitation is that two studies used warfarin and the other two studies used NOACs which creates a heterogeneity between the treatments arms since Warfarin is known to cause a higher incidence of bleeding episodes compared to the NOACs. Rivaroxaban has also been associated with a lower risk of stroke, and systemic embolism than VKA and it also associated with significantly lower rates of intracranial hemorrhage and fatal bleeding [12]. Therefore, it is possible that TATT with Rivaroxaban would has equally reduced adverse events without excess bleeding if it was compared to DATT with Rivaroxaban. The second limitation is that the treatments were un-blinded which could potentially lead to a bias. The third limitation was the indication for long-term OAC which was not uniform across the studies with two studies were purely done on patients with pre-existing atrial fibrillation, and other two studies had other indications of long-term OAC. The fourth limitation is the administration of TATT to both arms in the ISAR-TRIPLE trial for the initial six weeks which is the most sensitive time for adverse events. The last limitation was the lack of availability of the patient level data which does not allow the more critical analysis of different risk groups where longer and shorter duration of TATT may be of an advantage.

5. Conclusion

The results of our analysis show a significant decrease in the incidence of bleeding in patients who receive DATT over TATT without any significant rise in thromboembolic events or CV death. In the future, trials comparing different DATT with head-to-head comparison of oral anticoagulants to each other and standard of care with Warfarin are required with an extended follow-up time on a large and diverse population to elucidate the difference that exists between different oral anticoagulants.

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