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# Dual *vs.* triple antithrombotic treatment after percutaneous coronary intervention in patients with non-valvular atrial fibrillation: a meta-analysis on current evidence

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**Abstract. – OBJECTIVE: Combination and duration of antithrombotic therapy in order to prevent both stent thrombosis and thromboembolic complications after coronary artery stenting (PCI) in non-valvular atrial fibrillation (AF) is still debated. This uncertainty can be attributed mainly to the fact that the reference trials were open-label and not adequately powered in order to reach a definitive conclusion on ischemic endpoints (i.e., stent thrombosis). On these grounds, data from real-life studies could support evidence on dual antithrombotic treatment (DAT) safety (bleeding risk) and efficacy (stent thrombosis prevention). The aim of the meta-analysis is to investigate in both randomized controlled trials (RCTs) and observational studies (Obs) the risks and/or benefits related to DAT *vs.* triple antithrombotic treatment (TAT) regimens in patients affected by AF undergoing PCI.**

**MATERIALS AND METHODS: RCTs and Obs were retrieved through PubMed database. The risk ratio with 95% confidence interval was used to compare the primary and the safety endpoints.**

**RESULTS: Meta-analysis demonstrated no significant differences between DAT *vs.* TAT for mortality. However, a two-fold higher mortality rate was registered in Obs than in RCTs. The Obs did not confirm the expected significant reduction in bleeding risk shown by the RCTs; however, the bleeding rates in Obs were more than three-fold those of RCTs. In Obs, a significant greater risk for stent thrombosis was observed in DAT than in TAT.**

**CONCLUSIONS: The safety and efficacy outcomes observed in RCTs are unrealistic with respect to the current clinical practice. So, more evidence is needed to have more exhaustive guidelines based on RCTs with homogeneous designs and protocols that should mimic real-life population and practice.**

*Key Words:*
DAT, TAT, FA, PCI, Meta-analysis.

## Introduction

Dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor and aspirin is the recommended standard treatment after coronary artery stenting (PCI) to prevent stent thrombosis[1]. Additional oral anticoagulation (OAC) is also required when PCI is performed in patients affected by non-valvular atrial fibrillation (AF) to prevent stroke or systemic embolism[2,3]. In these patients European Society of Cardiology (ESC) 2017 guidelines recommended as standard care a triple antithrombotic treatment (TAT) regimen by prescribing DAPT plus OAC in order to prevent both stent thrombosis and thromboembolic complications[1,4].

Since ESC 2017 guidelines, in non-valvular AF, oral anticoagulation with novel oral anticoagulants (NOAC) is the preferred choice over vitamin K antagonists (VKA)[5,6]. Indeed, PIONER AF-PCI[7], RE-DUAL PCI[8], AUGUSTUS[9] and ENTRUST-PCI[10] trials have confirmed at least the non-inferiority of NOAC compared with VKA in patients with PCI and non-valvular AF. However, adding anticoagulants to DAPT increases the risk of bleeding[11].

Moreover, on the basis of the results of the above-mentioned trials[7-10], an early reversion of DAPT in favor of single platelet inhibition therapy together with NOAC (dual antithrombotic therapy, DAT), is recommended when the risk of stent thrombosis is low or if the risk of bleeding is high[12-15].



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Nowadays, the optimal combination and duration of antithrombotic combination therapy is still debated[16-20].

This uncertainty can be attributed mainly to the fact that the reference trials were: i) open-label (and thus information bias could be introduced) and ii) not adequately powered in order to reach a definitive conclusion on ischemic endpoints (i.e., stent thrombosis)[7-10,21-23].

On these grounds, data from real-life studies could support evidence on DAT safety (bleeding risk) and efficacy (stent thrombosis prevention).

The aim of the present meta-analysis is to investigate in both randomized controlled trials (RCTs) and observational studies (Obs) the risks and/or benefits related to DAT *vs.* TAT regimens in patients affected by non-valvular AF undergoing PCI.

## Materials and Methods

The meta-analysis was performed following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[24]. The articles (from January 1, 2013 to June 20, 2023) were selected from a literature search of the PubMed computerized database using the terms "AF" and "PCI", "DAT", "TAT". Additional manual literature searches through the reference lists of retrieved articles and reviews were also performed.

Two investigators independently examined the designs, patient populations, and interventions of the selected articles, with the aim to include study designed to test the effect of DAT *vs.* TAT in patients affected by non-valvular chronic AF undergoing PCI. Either RCTs or Obs were selected to evaluate if the outcomes from controlled interventions, as in RCTs, correspond to the clinical practice results from real-life studies, as in Obs.

Exclusion criteria were: articles retrieved by the search but unrelated to the topic, articles not in English, case reports, letters to the editor, duplicate studies and articles not providing sufficient data for risk estimation or patients followed for less or more than 6-12 (±2) months of follow-up. Any disagreements between the two investigators were resolved by consulting a third investigator.

DAT therapy could include an OAC in combination with a single antiplatelet agent, either acetylsalicylic acid (ASA), or a $P2Y_{12}$ receptor inhibitor (Clopidogrel, Prasugrel or Ticagrelor).

TAT included an OAC associated with double antiplatelet therapy. To reduce confounding in the comparison between DAT and TAT groups, we selected patients receiving the same antiplatelet therapy, when possible. Warfarin, a vitamin K antagonist anticoagulant, or NOAC, were the commonly used oral anticoagulants (OAC).

### Study Outcomes

Primary endpoints were cardiac and any cause of death at 6-12 months of follow-up (±2 months).

Secondary endpoints were the rate of all major bleedings, intracranial hemorrhage, stent thrombosis, and stroke at 6-12 months of follow-up. Bleeding criteria of the reviewed studies are reported in **Supplementary Table I** (RCTs) and **Supplementary Table II** (Obs). For all RCTs, the meta-analysis referred to the TIMI bleeding criterion.

### Statistical Analysis

The meta-analysis was performed using Review Manager [RevMan] Version 5.3 (Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration 2014)[25]. The selected studies were analyzed taking into account RCTs and Obs subgroups in order to investigate the pooled effects size derived from "controlled" and "real life" practice and the homogeneity/heterogeneity of the reported effect.

The risk ratio (RR) with 95% Confidence Interval (CI) was computed using the Mantel-Haenszel random-effect model to correct the effect estimate in case of heterogeneity among individual studies more than that expected from chance.

The results were presented graphically in the Forest plot reporting i) the effect estimate for individual studies together with ii) the effect estimate for RCTs and Obs separately considered as well as iii) the overall measure of the effect. The Cochran's Q test and $I^2$ statistics were computed in order to quantify the homogeneity/dishomogeneity i) among the individual studies, ii) within each subgroup as iii) in the overall estimate[26]. The test for differences between the RCTs and Obs subgroups was also computed to measure the homogeneity/dishomogeneity between the risk estimated in RCTs and the risk estimates from real clinical practice Obs.

Bidirectional alpha error $<0.05$ was considered statistically significant.

## Results

Of the 1,583 articles identified at the initial screening, after detailed review, 16 articles[7-10,21,27-37] referring to 14 studies[7-10,21,29-37] (6 RCTs[7-10,21,27-29], 8 Obs[30-37]) were selected (Figure 1). The main characteristics of the studies included in the meta-analysis are reported in Table I (RCTs) and in Table II (Obs). More details are included in **Supplementary Table I** (RCTs) and **Supplementary Table II** (Obs).

### Primary Endpoints

#### All-cause death

The analysis on all-cause death included 15,425 patients. The results showed that the overall risk estimate of all-cause death of RCTs and Obs was increased in DAT, not significantly, when comparing DAT *vs.* TAT (RR: 1.03, $p$=0.82; Figure 2). These results came from the comparison of homogeneous patient populations (test for subgroup differences: $I^2$=0%, $p$=0.80).

The all-cause mortality was identical in RCTs when comparing patients treated with DAT *vs.* TAT (RR: 1.00, $p$=0.98; $I^2$=35%, Figure 2), while in Obs subgroup, the same comparison showed higher mortality, although non-significantly, in DAT regimen (RR: 1.06, $p$=0.76, $I^2$=59%; Figure 2).

#### Cardiovascular mortality

The analysis of overall cardiovascular mortality included 15,518 patients (11,795 patients in RCTs, 3,723 patients in Obs; Figure 3). The overall risk estimate was higher, although not significantly, in DAT regimen (overall estimate: RR=1.17, $p$=0.12; RCTs: RR=1.06, $p$=0.61; Obs: RR=1.31, $p$=0.21). The comparisons were performed on a homogeneous patient population between two subgroups ($I^2$=5%) and in RCTs ($I^2$=0%). While a slight heterogeneity was observed in the Obs subgroup ($I^2$=37). The homogeneity of the subgroups was also confirmed by the results of the test for subgroup differences ($I^2$=0%, $p$=0.40; Figure 3).

### Secondary Endpoints

#### Major bleeding

The analysis included 16,218 patients (11,743 patients in RCTs, 4,475 patients in Obs; Figure 4). In the overall analysis, there was homogeneity between the two subgroups ($I^2$=0.0%, $p$=0.32; Figure 4) and in Obs ($I^2$=0%), while we found a mild heterogeneity in RCTs ($I^2$=37%). The results of the analysis showed that the risk of major bleeding was significantly reduced in patients receiving DAT *vs.* TAT (RR: 0.68, $p$=0.0001). However, while in the RCTs, major bleeding was significantly reduced in patients receiving DAT (RR: 0.63, $p$=0.006), in Obs the reduction was not statistically significant (RR: 0.78, $p$=0.07).

#### Intracranial hemorrhage

The analysis included 15,122 patients (11,743 patients in RCTs, 3,379 patients in Obs; Figure 5). There was homogeneity in the comparisons between RCTs and Obs subgroups ($I^2$=0%), in the overall analysis and in Obs ($I^2$=0%), while a low heterogeneity was observed in RCTs ($I^2$=28%, Figure 5). The comparison showed a reduction in the risk for intracranial hemorrhage in DAT *vs.* TAT, although not statistically significant, both in the overall analysis (RR: 0.69, $p$=0.09) and in RCTs subgroup (RR: 0.62, $p$=0.14). No difference was observed in the Obs subgroup (RR: 0.85, $p$=0.65). The incidence rate of intracranial hemorrhage is very low in RCTs (respectively: DAT 0.4%, TAT 0.7%) and low in Obs (respectively: DAT 0.9%, TAT 1.3%).

#### Stroke

The analysis on stroke incidence was performed on 17,051 patients (11,501 patients in RCTs, 5,550 patients in Obs; Figure 6). The stroke incidence was similar in DAT and TAT in the overall analysis (RR: 0.97, $p$=0.83), in RCTs (RR: 0.91, $p$=0.61) and in Obs (RR: 1.14, $p$=0.65). There was homogeneity in the comparisons between RCTs and Obs subgroups ($I^2$=0%), in the overall analysis and in RCTs ($I^2$=0%), and mild heterogeneity in Obs subgroup ($I^2$=29%; Figure 6).

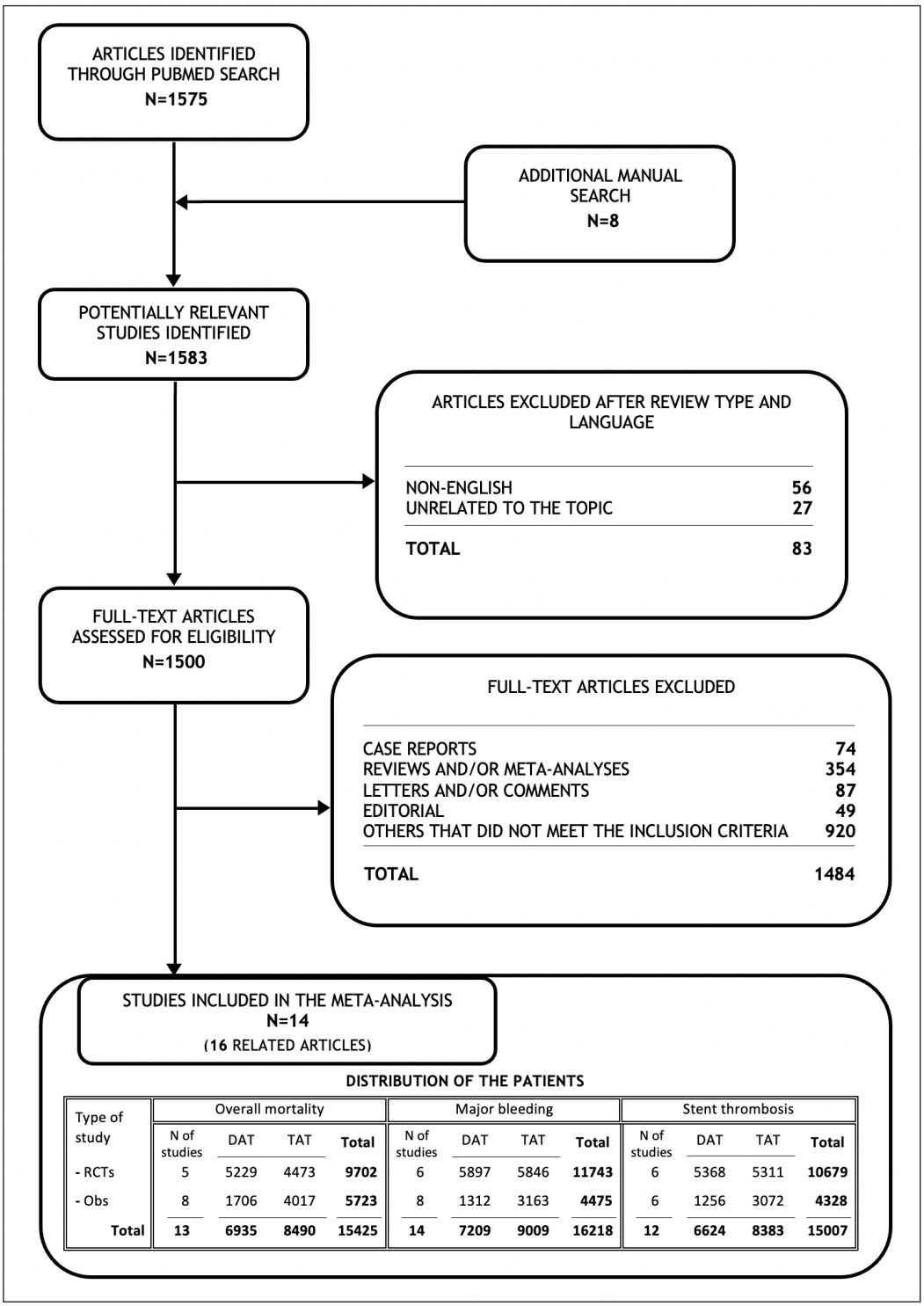
#### Stent thrombosis

The analysis on stent thrombosis was performed in 15,007 patients (10,679 patients in RCTs, 4,328 patients in Obs; Figure 7). There was homogeneity between RCTs and Obs subgroups ($I^2$=2.6%), in the overall analysis ($I^2$=0%), in RCTs ($I^2$=2%), and in Obs ($I^2$=0%; Figure 7). The overall analysis, performed on all 15,007 patients, showed a significantly greater risk for stent thrombosis in patients treated with DAT than in TAT (RR=1.42; $p$=0.05). This detrimental effect of DAT regimen was also observed in the Obs

**Table I.** Characteristics of the included randomized controlled trials.

| Study NCT*registry number | Regimen | | $P2Y_{12}$ inhibitor (%) | Patients included in the meta-analysis (n) | Critical appraisal† |
|---|---|---|---|---|---|
| | DAT (OAC+SAPT) | TAT (OAC+DAPT) | | | |
| WOEST<br>Dewilde et al[21], 2013<br>*NCT00769938* | - VKA+Clopidogrel: n = 284 | - VKA+Clopidogrel+ASA: n = 289 | - Clopidogrel: 100 | 573 | Underpowered for secondary endpoints[21] |
| PIONER AF-PCI<br>Gibson et al[7], 2016<br>*NCT01830543* | - NOAC+$P2Y_{12}$ inhibitor: n = 709<br>*NOAC: Rivaroxaban* | - NOAC+$P2Y_{12}$ inhibitor+ASA: n = 709<br>- VKA+$P2Y_{12}$ inhibitor+ASA: n = 706<br>*NOAC: Rivaroxaban* | - Clopidogrel: 94.4<br>- Ticagrelor: 4.3<br>- Prasugrel: 1.3 | 2,124 | Underpowered for efficacy endpoints[7] |
| RE-DUAL PCI<br>Cannon et al[8], 2017<br>Oldgren et al[27], 2021<br>*NCT02164864* | - NOAC+$P2Y_{12}$ inhibitor: n = 1,744<br>*NOAC: Dabigatran* | - VKA+$P2Y_{12}$ inhibitor+ASA: n = 981 | - Clopidogrel: 88.0<br>- Ticagrelor: 12.0 | 2,725 | Underpowered for efficacy endpoints[8] |
| AUGUSTUS<br>Lopes et al, 2019[9]<br>Lopes et al, 2020[28]<br>*NCT02415400* | - VKA+$P2Y_{12}$ inhibitor: n = 1,126 (in PCI subgroup: n = 876)<br>- NOAC+$P2Y_{12}$ inhibitor: n = 1,143 (in PCI subgroup: n = 876)<br>*NOAC: Apixaban* | - VKA+$P2Y_{12}$ inhibitor+ASA: n = 1,123 (in PCI subgroup: n = 872)<br>- NOAC+$P2Y_{12}$ inhibitor+ASA: n = 1,145 (in PCI subgroup: n = 874)<br>*NOAC: Apixaban* | - Clopidogrel: 92.6<br>- Ticagrelor: 6.2<br>- Prasugrel: 1.1 | 4,614 | Not adequately powered to draw a definitive conclusion on ischaemic endpoints[22] |
| ENTRUST-AF PCI<br>Vranckx et al[10], 2019<br>*NCT02866175* | - NOAC+$P2Y_{12}$ inhibitor: n = 751<br>*NOAC: Edoxaban* | - VKA+$P2Y_{12}$ inhibitor + ASA: n = 755 | - Clopidogrel: 92.4<br>- Prasugrel: 0.5<br>- Ticagrelor: 7.1 | 1,506 | "…underpowered to detect small but potentially clinically meaningful differences among less frequent ischaemic outcomes."[10] |
| MANJUSRI<br>Lu et al[29], 2021<br>*NCT02206815* | - VKA+Ticagrelor: n = 148 | - VKA+Clopidogrel+ASA: n = 146 | - Ticagrelor: 50.3<br>- Clopidogrel: 49.7 | 294 | Underpowered to detect differences between the two groups[29] |

*NCT: National Clinical Trial (https://www.clinicaltrials.gov). ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; DAT: dual antithrombotic therapy; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulation; SAPT: single antiplatelet therapy; TAT: triple antithrombotic therapy; VKA: vitamin K antagonist. †References refer to papers containing critical appraisal of the studies.




| Type of study | Overall mortality | | | | Major bleeding | | | | Stent thrombosis | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N of studies | DAT | TAT | Total | N of studies | DAT | TAT | Total | N of studies | DAT | TAT | Total |
| - RCTs | 5 | 5229 | 4473 | **9702** | 6 | 5897 | 5846 | **11743** | 6 | 5368 | 5311 | **10679** |
| - Obs | 8 | 1706 | 4017 | **5723** | 8 | 1312 | 3163 | **4475** | 6 | 1256 | 3072 | **4328** |
| **Total** | **13** | **6935** | **8490** | **15425** | **14** | **7209** | **9009** | **16218** | **12** | **6624** | **8383** | **15007** |

**Figure 1.** Flowchart of the study selection process. RCTs: Randomized controlled trials, Obs: observational studies.

subgroup (RR: 1.85, $p$=0.05), while in RCTs, it was milder and not statistically significant (RR: 1.26, $p$=0.28). However, we found that the incidence rate of stent thrombosis in patients treated with DAT of the RCTs subgroup was quite lower than that observed in the Obs subgroup (1.1% *vs.* 1.8%), making it more difficult to highlight a protective effect of TAT regimen.

**Table II.** Characteristics of the included observational studies.

| Study<br>NCT*registry number | Regimen | | $P2Y_{12}$ inhibitor (%) | Patients included in the meta-analysis (n) |
|---|---|---|---|---|
| | DAT (OAC+SAPT) | TAT (OAC+DAPT) | | |
| Lamberts et al[30], 2013 | - VKA+Clopidogrel: n = 548 | - VKA+Clopidogrel+ASA: n = 1,896 | - Clopidogrel: 100 | 2,444 |
| AFCAS Registry<br>Rubboli et al[31], 2013<br>*NCT00596570* | - VKA+Clopidogrel: n = 73 | - VKA+Clopidogrel+ASA: n = 679 | - Clopidogrel: 100 | 752 |
| Wustrow et al[32], 2018 | - VKA+$P2Y_{12}$ inhibitor: n = 60<br>- NOAC+$P2Y_{12}$ inhibitor: n = 29<br>*NOAC: Dabigatran, Rivaroxaban* | - VKA+$P2Y_{12}$ inhibitor +ASA: n = 139<br>- NOAC+$P2Y_{12}$ inhibitor +ASA: n = 9<br>*NOAC: Dabigatran, Rivaroxaban* | - Clopidogrel: 95.4<br>- Ticagrelor/Prasugrel: 4.6 | 237 |
| WEST 2 Registry<br>Bor et al[33], 2022<br>*NCT02635230* | - VKA+$P2Y_{12}$ inhibitor: n = 314<br>- NOAC+$P2Y_{12}$ inhibitor: n = 331<br>*NOAC: Apixaban, Dabigatran, Edoxaban, Rivaroxaban* | - VKA+$P2Y_{12}$ inhibitor+ASA: n = 182<br>- NOAC+$P2Y_{12}$ inhibitor +ASA: n = 232<br>*NOAC: Apixaban, Dabigatran, Edoxaban, Rivaroxaban* | - Clopidogrel: 93.9<br>- Prasugrel: 5.6<br>-Ticagrelor: 0.5 | 1,059 |
| PACO-PCI Registry<br>De La Torre Hernandez et al[34], 2021 | - VKA+$P2Y_{12}$ inhibitor: n = 67<br>- NOAC+$P2Y_{12}$ inhibitor: n = 161<br>*NOAC: Apixaban, Dabigatran, Edoxaban, Rivaroxaban* | - VKA+$P2Y_{12}$ inhibitor+ASA: n = 527<br>- NOAC+$P2Y_{12}$ inhibitor+ASA: n = 494<br>*NOAC: Apixaban, Dabigatran, Edoxaban, Rivaroxaban* | - Clopidogrel: 99.4<br>- Ticagrelor: 0.6 | 1,249 |
| AVIATOR 2 Registry<br>Chandrasekhar et al[35], 2022<br>*NCT02362659* | - VKA+SAPT: n = 18<br>- NOAC+SAPT: n = 47<br>*SAPT: ASA: n = 2, $P2Y_{12}$ inhibitor n = 63* | - VKA+$P2Y_{12}$ inhibitor+ASA: n = 155<br>- NOAC+$P2Y_{12}$ inhibitor+ASA: n = 183 | - Clopidogrel: 95.1<br>- Ticagrelor: 3.2<br>- Prasugrel: 1.2 | 403 |
| Berteotti et al[36], 2023 | - VKA+SAPT: n = 9<br>- NOAC+SAPT: n = 47<br>*SAPT: ASA: n = 1, $P2Y_{12}$ inhibitor: n = 55* | - VKA+$P2Y_{12}$ inhibitor+ASA: n = 38<br>- NOAC+$P2Y_{12}$ inhibitor+ASA: n = 53 | - Clopidogrel: 93.9<br>- Ticagrelor: 5.4 | 147 |
| CHIBA AF-PCI Registry<br>Kitahara et al[37], 2023 | - OAC+Clopidogrel: n = 157 | - OAC+Clopidogrel+ASA: n = 471 | - Clopidogrel: 100 | 628 |

*NCT: National Clinical Trial (https://www.clinicaltrials.gov). ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; DAT: dual antithrombotic therapy; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulation; SAPT: single antiplatelet therapy; TAT: triple antithrombotic therapy; VKA: vitamin K antagonist.

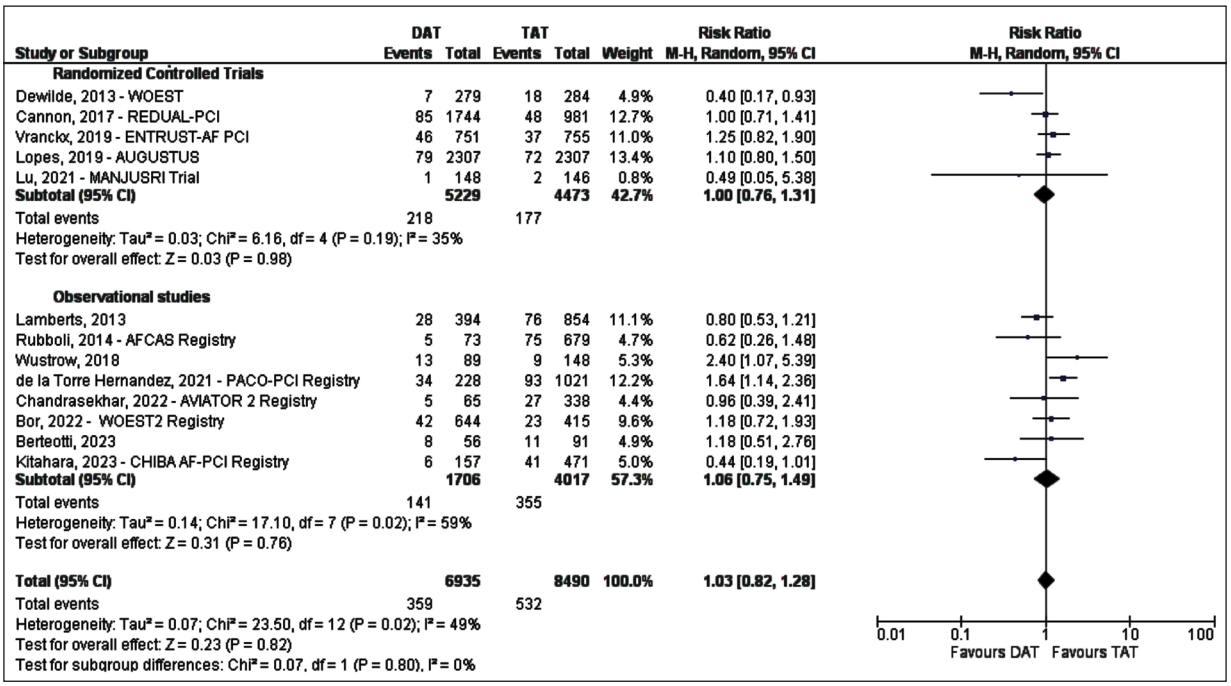



**Figure 2.** Meta-analysis on risk ratio of all-cause mortality between patients with DAT *vs*. those with TAT. DAT: dual antithrombotic therapy, TAT: triple antithrombotic therapy.

## Discussion

The prevalence of AF in patients undergoing PCI varied between studies with an increased trend due to population aging. Moreover, incident AF can occur after the procedure[38-40]. These patients have a higher risk of morbidity and mortality both during in-hospital stay and follow-up[39].

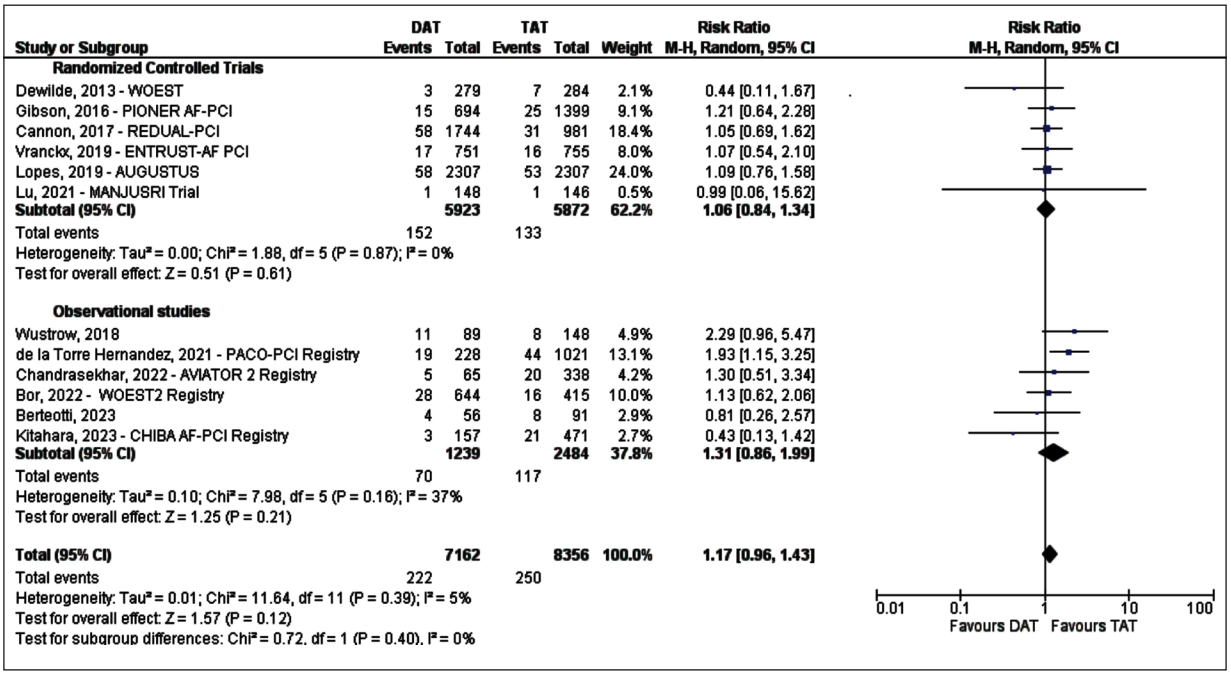



**Figure 3.** Meta-analysis on risk ratio of cardiac mortality between patients with DAT *vs*. those with TAT. DAT: dual antithrombotic therapy, TAT: triple antithrombotic therapy.

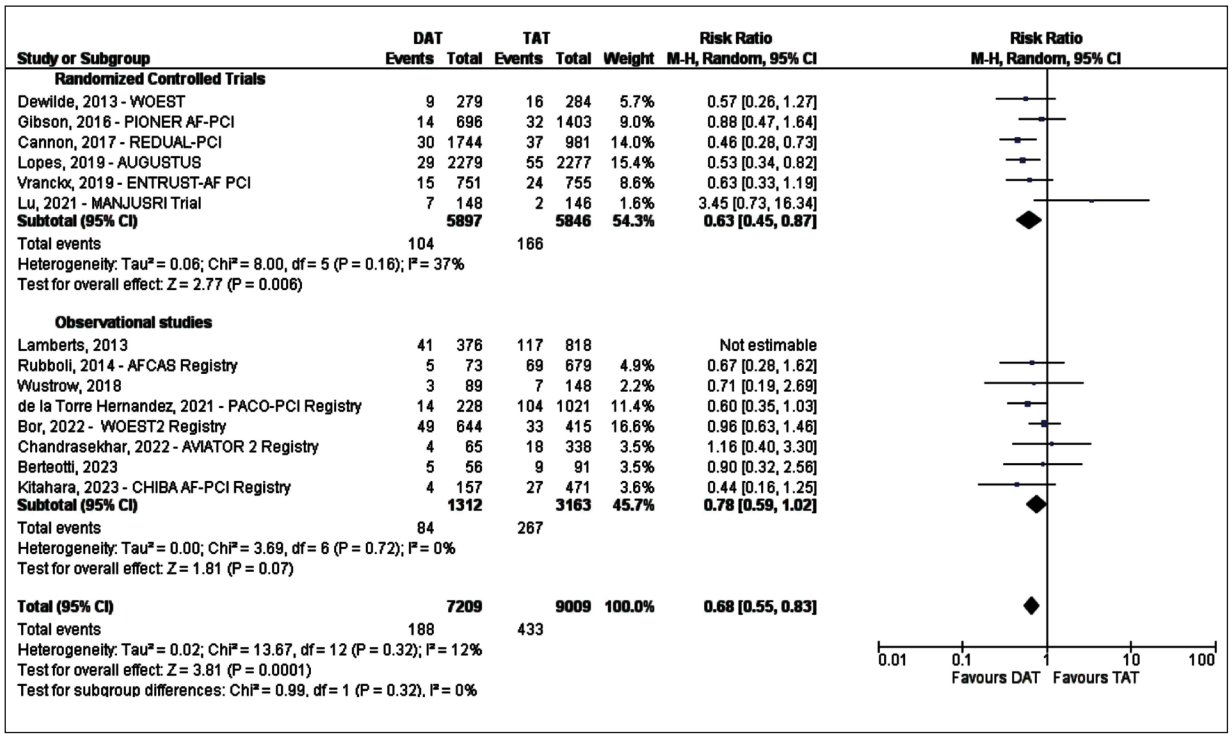



**Figure 4.** Meta-analysis on risk ratio of major bleeding between patients with DAT *vs*. those with TAT. DAT: dual antithrombotic therapy, TAT: triple antithrombotic therapy.

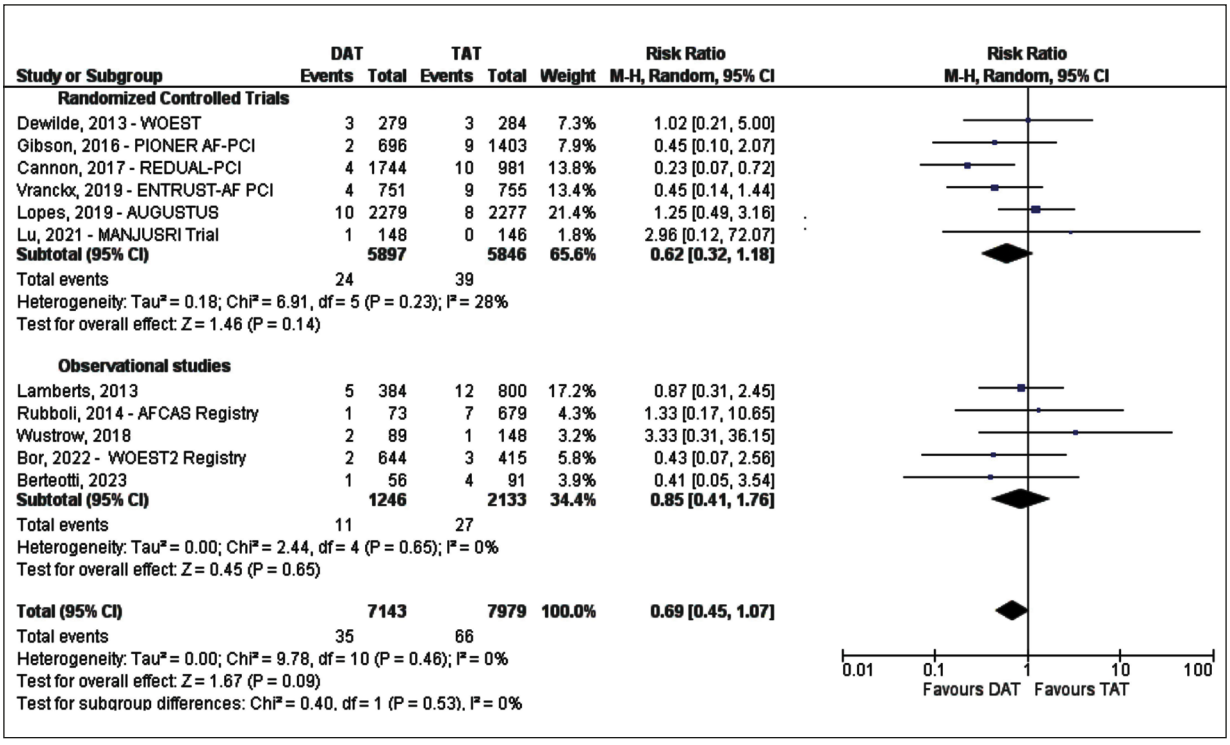



**Figure 5.** Meta-analysis on risk ratio of intracranial hemorrhage between patients with DAT *vs*. those with TAT. DAT: dual antithrombotic therapy, TAT: triple antithrombotic therapy.

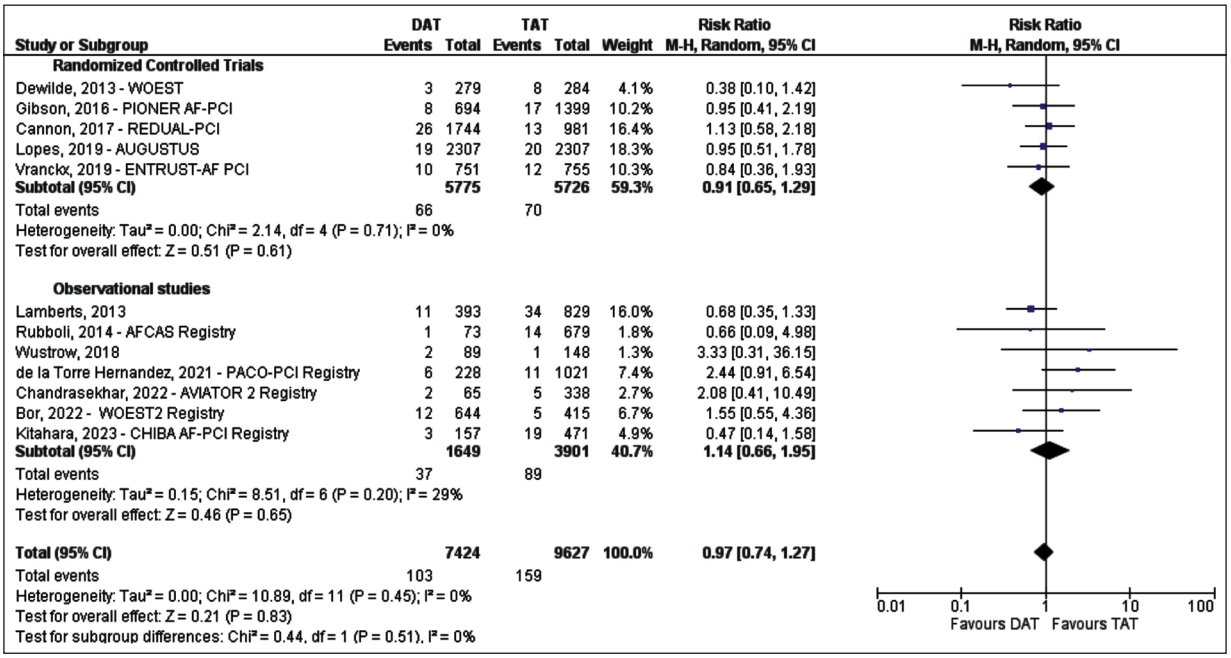



***Figure 6.*** Meta-analysis on risk ratio of stroke between patients with DAT *vs*. those with TAT. DAT: dual antithrombotic therapy, TAT: triple antithrombotic therapy.

In this condition, patients should be currently treated with an OAC and dual antiplatelet therapy (DAPT) (aspirin in association with a $P2Y_{12}$ inhibitor) to prevent thrombotic recurrences. However, choosing the optimal antithrombotic regimen for these patients is still subject of debate[16-20]. Current American and European Guidelines recommend short-term TAT (1 week-1 month) both in acute and

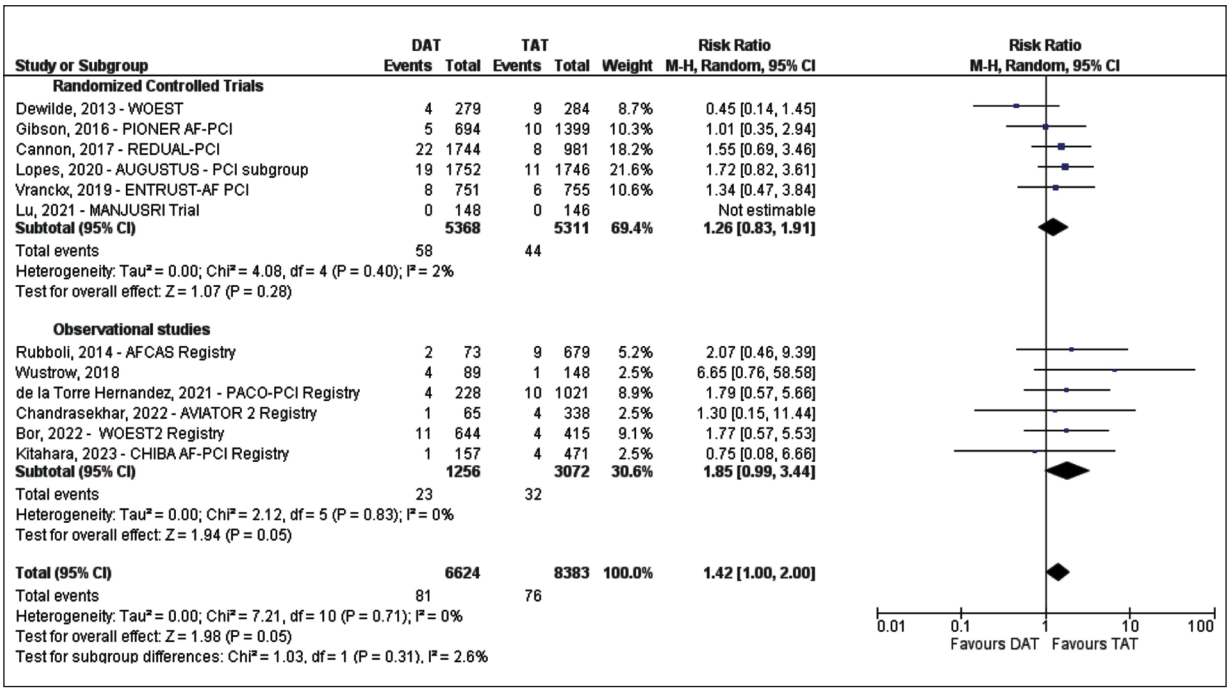



***Figure 7.*** Meta-analysis on risk ratio of stent thrombosis between patients with DAT *vs*. those with TAT. DAT: dual antithrombotic therapy, TAT: triple antithrombotic therapy.

chronic coronary syndromes and long-term DAT of 1 year and more in acute coronary syndromes or 6 months in chronic coronary syndromes[12-14]. On the other hand, Obs show that in real-life clinical practice, the recommended duration for antithrombotic treatment varies considerably[41]. Our meta-analysis demonstrated no significant differences between DAT *vs.* TAT for mortality. However, a two-fold higher mortality rate was registered in Obs (all-cause: DAT 8.3%, TAT 8.8%; cardiac: DAT 5.6%, TAT 4.7%) than in RCTs (all-cause: DAT 4.2%, TAT 4.0%; cardiac: DAT 2.6%, TAT 2.3%). The Obs did not confirm the expected significant reduction in bleeding risk shown by the RCTs; however, the bleeding rates in Obs were more than three-fold those of RCTs (Obs: DAT 6.4%, TAT 8.4%; RCTs: DAT 1.8%, TAT 2.8%).

With respect to the treatment goal, i.e., the efficacy in the prevention of stent thrombosis, in our meta-analysis, the RCTs, as reported in current guidelines, were not able to detect significant differences, with similar event rate between DAT (1.1%) and TAT (0.8%). These studies, despite enclosing 10,679 patients, had the statistical power for detecting the safety outcomes but were underpowered to detect such a small difference for the efficacy endpoint[21-23]; in addition, incidence rates in RCTs were unrealistic compared to those observed in current clinical practice. On the contrary, the Obs including 4,328 patients, showed a significantly higher ($p$=0.05) stent thrombosis incidence in DAT (1.8%) than in TAT (1.0%). By accumulating evidence in the overall analysis, with 15,007 patients, the increased risk of stent thrombosis in DAT regimen could be clinically more relevant, confirming the statistical significance.

Differences between our results and the current guidelines are possibly due to the fact that the analyzed RCTs, even if considered as reference studies in international guidelines, lack external validity, and participants are unrepresentative of a wider population[42]. Possible causes are excessively selected population samples and/or much greater attention in the administration of therapies and in compliance of patients than can be done in current clinical practice. For these reasons, recent indications coming from the FDA support the use of real-world evidence in clinical decision-making[43,44].

Indeed, as reported by Metelli and Chaimani[45], "meta-analysis of observational data alone or in combination with RCTs (when possible) is often desirable": in many cardiovascular settings meta-analyses including Obs are increasingly available[46-50].

### Limitations

The possible limitations of our meta-analysis derive from the heterogeneity of the patients included and/or from poor adherence to the prescribed treatments. However, the test for differences between groups showed a substantial homogeneity between the two types of studies (RCTs and Obs), while the incidence rates observed in RCTs were unrealistic in comparison with real-life studies.

Another possible limitation could derive from a different size of the RCTs and Obs, which is able to affect the weight and the related effects in the meta-analysis. However, as reported in the Forest plots, the RCTs were larger (weight > 50%) of Obs in all the comparisons performed, with the only exception of all-cause mortality (weight: RCT 42.7%, Obs: 57.3%).

## Conclusions

Our data confirm the fundamental role of real-life clinical practice studies in the choice of antithrombotic treatment regimen after PCI in patients with non-valvular AF.

Due to the issues discussed above, the studied populations should be more representative of the general population in order to have more exhaustive guidelines. Two major problems, in our opinion, should be tackled: i) complexity and number of stented coronary lesions, ii) homogeneity of designs and protocols of the RCTs that should mimic real-life population and practice.

The role of observational studies is to confirm and complete with more robust evidence what is highlighted by the RCTs. In no case should the respective results be conflicting. Should this occur, the population of RCTs probably does not correspond to a larger population and, therefore, further studies are needed.

### Conflict of Interest

The authors declare that they have no conflict of interests.

### Funding

None.

### Ethics Approval and Informed Consent

Not applicable.

### Availability of Data and Materials

All data reported in this meta-analysis are extracted or derived from the selected studies and exhaustively reported in the Forest plots and/or in Table I and II; further inquiries can be directed to the corresponding author.

### Authors' Contribution

Maria Cristina Acconcia and Quintilio Caretta: contributed to the conception and design of the study, analyzed data and drafted the manuscript; Carlo Gaudio contributed to the conception and design of the study; Gaetano Tanzilli and Concetta Torromeo contributed to the acquisition and analysis of the data; Flavia Chiarotti and Giuseppe Pannarale contributed to drafting the text and preparing the figures.
All authors critically revised the manuscript, proofread and approved the final manuscript. The corresponding authors attest that all listed authors meet the authorship criteria and that no other individuals meeting the criteria have been omitted.

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