Stent Thrombosis With Dual Antithrombotic Therapy in Atrial Fibrillation–ACS/PCI Trials

There are now 6 randomized controlled trials (RCTs) comparing dual (DAT) versus triple antithrombotic therapy (TAT) in patients with atrial fibrillation (AF) and acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI) (1). The first 2 trials, WOEST (What is the Optimal antiplatElet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary StenTing) and ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation), used a vitamin K antagonist (VKA) in both the DAT and TAT arms, whereas the 4 most recent trials (PIONEER AF-PCI [An Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention], RE-DUAL PCI [Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting], AUGUSTUS [The Open-Label, 2 × 2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention], and ENTRUST-AF-PCI [Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention]) used a direct oral anticoagulant (DOAC) in the DAT arm and a VKA in the TAT arm (with an exception made in AUGUSTUS for one-quarter of the patients randomly assigned to DOAC-TAT and one-quarter randomly assigned to VKA-DAT) (2,3).

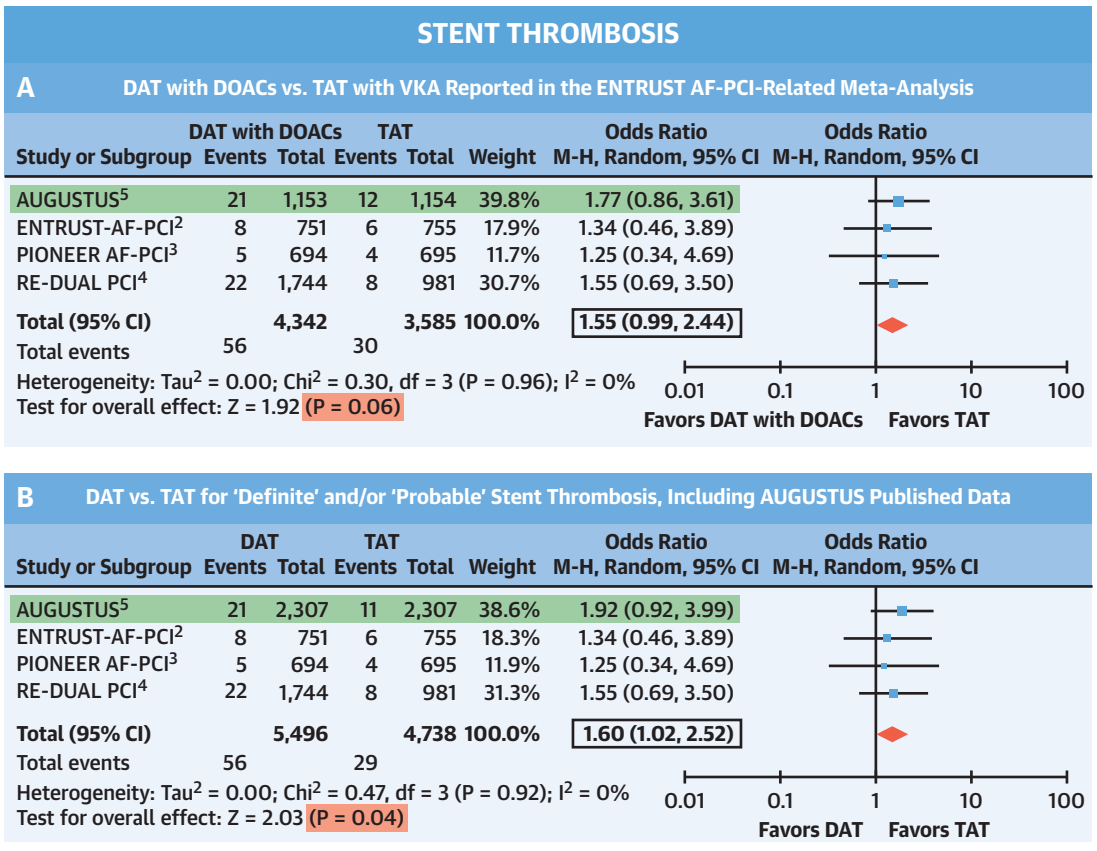
DOACs have been shown to be safer than VKA-based therapy (2,4). Thus, attention should focus on the 4 RCTs testing DOAC-DAT versus TAT. With the exception of ENTRUST-AF-PCI (1), these trials showed significantly reduced rates of trial-defined primary safety outcomes, as well as major and minor bleeding, for DOAC-DAT compared with TAT, without significant differences in ischemic outcomes, including rates of stent thrombosis (ST) (1,3). None of these trials, however, was powered to assess differences between treatment arms in ischemic events; meta-analyses—as long as they are reliable, reproducible, and methodologically sound—may help overcome this limitation.

The ENTRUST-AF-PCI publication (1) included a meta-analysis of RCTs data on DOAC-DAT versus VKA-TAT, reporting that DAT versus TAT was associated with reduced bleeding and comparable ischemic outcomes, with a nonsignificant increase in ST rates (odds ratio [OR]: 1.55; 95% confidence interval [CI]: 0.99 to 2.44; p = 0.06; I^2 = 0) (**Figure 1A**). Given the 2 × 2 factorial design of AUGUSTUS (2), only 2 of the 4 treatment arms of this particular trial were included in the ENTRUST-AF-PCI-related meta-analysis (DOAC + $P2Y_{12}$ inhibitor vs. VKA + dual antiplatelet therapy), because the DOAC-TAT and VKA-DAT arms were beyond its scope (1). Surprisingly, although the ENTRUST AF-PCI-related meta-analysis (1) included only 2 of the 4 AUGUSTUS arms, the number of ST events reported for this trial was comparable to that described for the entire AUGUSTUS population (33 vs. 32) (**Figures 1A and 1B**) (1,2). The number 33 coincides with "any stent thromboses" reported in a recent network meta-analysis (i.e., including "possible" events in AUGUSTUS) (4). Of note, consideration of "possible" stent thrombosis is discouraged by the Academic Research Consortium 2, given its poor specificity, and it was not contemplated in any of the trials included in the analysis (ENTRUST-AF-PCI [1] and RE-DUAL PCI considered "definite" ST, PIONEER-AF did not provide a definition for ST, and AUGUSTUS [2] originally considered "definite" and "probable" ST).

To overcome these limitations, we performed a meta-analysis of the 4 DOAC trials, focusing on "definite" and "probable" ST and including all 4 arms of AUGUSTUS (for a total of 10,234 patients). The Mantel-Haenszel model with inverse variance weighting using RevMan software, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), yielded a significant 60% increase of ST with DAT versus TAT (OR: 1.60; 95% CI: 1.02 to 2.52; p = 0.04; I^2 = 0) (**Figure 1B**). This result was also consistent when a sensitivity analysis, using incidence risk ratios given differences in follow-up, was run (incidence risk ratio: 1.59; 95% CI: 1.01 to 2.51; p = 0.04; I^2 = 0). DAT regimens were associated with nonsignificant differences in all-cause mortality (OR: 1.11; 95% CI: 0.9 to 1.36) or cardiovascular death (OR: 1.10; 95% CI: 0.86 to 1.42) compared with TAT.

Given that all expected RCTs comparing DOAC-DAT versus TAT for patients with AF-ACS/PCI have now been published, we conclude that there is a significant 60% increase of "definite" and "probable" stent thrombosis with early DAT with DOACs versus TAT, which is in line with a previous meta-analysis that did not include ENTRUST-AF-PCI (5).

FIGURE 1 Meta-Analyses for the Outcome of Stent Thrombosis



(A) DAT versus TAT reported in the ENTRUST AF-PCI-related meta-analysis. **(B)** DAT with direct oral anticoagulants versus TAT with VKA for "definite" and/or "probable" stent thrombosis, including AUGUSTUS published data. AF = atrial fibrillation; CI = confidence interval; DAT = dual antithrombotic therapy; DOAC = direct oral anticoagulant; M-H = Mantel-Haenszel; PCI = percutaneous coronary intervention; TAT = triple antithrombotic therapy; VKA = vitamin K antagonist.

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REFERENCES

1. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet 2019;394:1335–43.

2. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med 2019;380:1509–24.

3. Capodanno D, Huber K, Mehran R, et al. Management of antithrombotic therapy in atrial fibrillation patients undergoing PCI: JACC state-of-the-art review. J Am Coll Cardiol 2019;74:83–99.

4. Lopes RD, Hong H, Harskamp RE, et al. Safety and efficacy of antithrombotic strategies in patients with atrial fibrillation undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials. JAMA Cardiol 2019;4:747–55.

5. Galli M, Andreotti F, D'Amario D, et al. Dual therapy with DOACs significantly increases the risk of stent thrombosis compared to triple therapy. Eur Heart J Cardiovasc Pharmacotherap 2019 Jul 16 [E-pub ahead of print].