Efficacy and Safety of Ticagrelor Monotherapy Versus Dual-Antiplatelet Therapy After Percutaneous Coronary Intervention With Drug-Eluting Stent in Patients With Diabetes Mellitus: A Systematic Review and Meta-analysis

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Abstract

BACKGROUND: Dual-antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor is the standard for the prevention of thrombotic events in patients undergoing percutaneous coronary intervention (PCI). Type 2 diabetes mellitus (DM) patients are a subgroup with a higher risk of bleeding and thrombotic events after PCI.

OBJECTIVES: This meta-analysis aimed to determine whether ticagrelor monotherapy after an initial short-course DAPT is an effective and safe option in preventing thrombotic events among DM patients undergoing PC.

METHODS: A systematic review and meta-analysis was done on randomized controlled trials (RCT) comparing ticagrelor monotherapy following short-course DAPT versus conventional DAPT in T2DM patients who underwent PCI. Outcome measures for major bleeding, myocardial infarction, and all-cause mortality were extracted and analyzed using a random-effects model via RevMan version 5.3.

RESULTS: A total of three RCTs, with 7482 patients, were analyzed. There were no significant differences in major bleeding ($P = 0.26$) and myocardial infarction ($P = 0.66$) events between the ticagrelor and DAPT groups. However, there was a higher rate of all-cause mortality in the DAPT group, which was statistically significant (risk ratio, 0.76; 95% confidence interval, 0.59–0.98; $P = 0.03$).

CONCLUSION: Ticagrelor monotherapy following short-course DAPT and conventional DAPT have similar rates of major bleeding and myocardial infarction among DM patients undergoing PCI with DES. However, conventional DAPT has a higher incidence of all-cause mortality, which suggests that ticagrelor monotherapy after short-course DAPT may be a preferable antiplatelet strategy in DM patients undergoing PCI.

KEYWORDS: bleeding, diabetes mellitus, dual-antiplatelet therapy, percutaneous coronary intervention, thrombosis, ticagrelor

INTRODUCTION

The definitive treatment of patients who underwent percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) is dual-antiplatelet therapy (DAPT) using an irreversible nonselective cyclooxygenase inhibitor (aspirin) and a P2Y12 inhibitor (eg, clopidogrel and ticagrelor). In the most recent American College of Cardiology/American Heart Association guidelines, continuing DAPT for at least 12 months after an acute coronary syndrome (ACS) is a class 1 recommendation.[1] Patients with diabetes mellitus (DM) are at increased risk of atherothrombotic events.[2] DM is one of the major risk factors of chronic kidney disease. These observations underscore the importance of antiplatelet therapy for the secondary prevention of atherothrombotic recurrences in these high-risk patients.[3] Patients with DM treated with clopidogrel have increased rates of recurrent atherothrombotic events, which may be in part due to the reduced platelet inhibitory effects of clopidogrel consistently observed in these patients.[4] The ischemic benefit occurs at the expense of risk of bleeding; therefore, balance is needed wherein bleeding risk is reduced but antithrombotic effects are maintained.[5] In line with this, there are emerging studies on antiplatelet monotherapy after short-course DAPT. In a recent study, the Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) trial showed that among high-risk PCI patients, after 3 months of DAPT, P2Y12 inhibitor monotherapy with ticagrelor reduced bleeding without increasing ischemic harm.[6] As such, there is considerable thought in understanding the benefit of this strategy in DM patients who are at high risk of bleeding events.

This meta-analysis aimed to determine the efficacy and safety of ticagrelor monotherapy after short-course DAPT versus conventional DAPT after PCI using DES in patients with DM.

MATERIALS AND METHODS

Eligibility Criteria

Studies were included if (1) the study was a prospective randomized controlled trial (RCT); (2) patients had type 2 DM; (3) patients underwent PCI using a DES; (4) the study compared ticagrelor monotherapy after short-course DAPT vs conventional DAPT; and (5) bleeding events (using Bleeding Academic Research Consortium [BARC]) and all-cause mortality were reported. Studies were excluded if (1) studies were nonhuman, nonrandomized, nonprospective, and/or observational studies; (2) there was absence of both of the aforementioned clinical outcomes; and (3) they were duplicate studies. There was no restriction on language of reporting or on time period. Published and unpublished RCTs were included whether it was single-blinded, double-blinded, or unblinded.

Outcomes

The primary outcome measure in this study was major bleeding, which was defined in the included trials as BARC-defined bleeding type 3 or 5. Secondary outcome measures included all-cause mortality and rate of myocardial infarction (MI).

Search Methods for Identification of Studies

Three independent reviewers (B.J.D., A.N.T., and J.D.T.) conducted a systematic search and evaluation of studies from inception up to May 2021, in the following search engines: PubMed, Cochrane Library, Lancet, ScienceDirect, and TRIP Clinical Trials. This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Figure 1). The following search terms were used: "percutaneous coronary intervention," "ticagrelor," "dual antiplatelet therapy," AND "type 2 diabetes mellitus." The authors also sought unpublished trials and ongoing studies in national and international trial registers (ISRCTN Register, EU Clinical Trials Register, and WHO ICTRP), dissertation and thesis databases, conference abstracts, and other gray literature sources in the relevant search. The comprehensive search was not restricted by any language or publication date filter.

Selection of Studies

Three authors (BJD, ANT and JDT) independently performed a systematic process for selecting studies for inclusion in the review, wherein any duplicate records of the same report were removed. Abstracts and manuscript titles were examined to include only those that met the criteria for assessment. Studies were included if there was an agreement between the three reviewers. During the study selection process, any discrepancies were resolved accordingly and consulted with a fourth expert investigator (FRG).

Data Collection

Review authors planned the relevant data to be collected in this meta-analysis and systematic review. A data collection form was created, including the citation details, study design, total study duration, type and number of participants, study location, study inclusion and exclusion criteria, baseline patient characteristics, description of the intervention and control, and the relevant outcome of interest and results. This data collection form guaranteed some consistency in data abstraction and was deemed necessary in comparing data.

Data Extraction and Management

Four data extractors, an interventional-cardiology specialist, and three of the review authors (BJD, ANT and JDT).) independently extracted data using a data collection form created by the authors. Data in the studies were tabulated separately by the study authors.

Risk of Bias

Three independent reviewers (BJD, ANT and JDT) critically appraised each trial using the Cochrane Risk of Bias (RoB 2.0) tool for the randomized controlled trial. The domains in RoB 2.0 include bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in selecting the reported result. These were further subdivided into "low risk of bias," "some concerns," or "high risk of bias" (Figure 2).

Table 1. Characteristics of included studies

Study	Patients included	Method	Intervention Group	Control group	Outcome
TICO 2021[7]	ACS treated with PCI with DES N=835 with DM	Randomized, open-label trial	3-month DAPT + 9-month ticagrelor monotherapy	12-month ticagrelor-based DAPT	All-cause mortality, MI, major bleeding using BARC
TWILIGHT 2019[6,8]	PCI with DES, and high ischemic or bleeding risk N=2620 with DM	Randomized, double-blind trial	3-month DAPT + additional 12 months ticagrelor monotherapy	3-month DAPT + additional 12 months of continued DAPT	All-cause mortality, MI, major bleeding using BARC
GLOBAL LEADERS 2020[9]	Stable CAD or ACS PCI treated with DES N=4027 with DM	Randomized, open-label trial	1-month ticagrelor-based DAPT + 23-month ticagrelor monotherapy	Aspirin plus either clopidogrel (stable CAD) or ticagrelor (ACS) for 12 months, followed by 12-month aspirin monotherapy	All-cause mortality, MI, major bleeding using BARC

ACS=acute coronary syndrome; CAD=coronary artery disease; BARC=Bleeding Academic Research Consortium; DAPT=dual antiplatelet therapy; DES=drug-eluting stent; DM=diabetes mellitus; MI=myocardial infarction; PCI=percutaneous coronary intervention.

Data Synthesis and Analysis
Data synthesis and analysis were performed using RevMan 5.4 (The Cochrane Collaboration) for Mac OS windows. All *P* values were two-sided and determined as statistically significant. The effect measure of choice for the outcome was reported as risk ratio (RR) for dichotomous data at 95% confidence interval (CI). The Mantel-Haenszel method was used primarily in this study because it has small sample sizes and lower event rates.

The I^2 statistic was used to assess statistical heterogeneity across studies. An I^2 value of 30% to 60% was reconsidered moderate heterogeneity; 50% to 90%, substantial heterogeneity; and 75% to 100%, considerable heterogeneity. A fixed-effect estimate was utilized, but a random-effects analysis model was used if heterogeneity was noted. A subgroup analysis was not done because of lack of available articles that satisfy the inclusion criteria.

RESULTS

Characteristics of included studies
Of the 975 records identified through database searching, 323 duplicate records were removed, and 313 articles were excluded after screening the titles and abstracts. Ten full-text articles were assessed for eligibility with the final exclusion of seven articles, resulting in three included studies (Table 1). Across three RCTs, 7482 patients were included for the bleeding outcome (3779 patients from the ticagrelor arm and 3687 patients from the DAPT arm) and 7455 patients for the ischemic event (3768 patients for the ticagrelor group and 3687 for the DAPT group). The follow-up ranged from 1 month to 2 years.

Bleeding events
There were a total of 7482 patients included in this study wherein 206 (2.8%) had bleeding episodes (BARC 3 or 5). In the treatment arm, there were 90 bleeding events (2.4%) compared with the control arm showing 3.1% (n = 116) event rate. The pooled analysis (Figure 3) showed statistically significant benefit of using ticagrelor monotherapy after short-course DAPT versus conventional DAPT in bleeding episodes with an RR of 0.70 (95% CI, 0.37–1.32; $P = 0.26$). Using random-effects model, the studies had heterogeneity with an I^2 of 79%; this may be attributed to the time DAPT was shifted to ticagrelor monotherapy, and the risk of bleeding of each patient was specifically remarkable on the TWILIGHT trial, wherein many patients were initially at high risk of bleeding prior to the initiation of DAPT.

All-cause mortality
In the treatment arm, 104 patients died (2.8%) compared with the control arm (134 deaths, 3.6%). In the pooled analysis (Figure 4), there is a statistically significant benefit in using ticagrelor monotherapy after short-course DAPT compared with conventional DAPT in reducing all-cause mortality with an RR of 0.76 (95% CI, 0.59–0.98; $P = 0.03$). Using a random-effects model, the studies had minimal heterogeneity ($I^2 = 0\%$).

Myocardial infarction
For MI, 135 patients (3.6%) experienced the outcome compared with the control arm (139 patients, 3.7%). In the pooled analysis (Figure 5), there was no statistically significant benefit in using ticagrelor monotherapy after short-course DAT compared with conventional DAPT in reducing MI events with an RR of 0.95 (95% CI, 0.75–1.20; $P = 0.66$). Using a random-effects model, the studies had minimal heterogeneity ($I^2 = 0\%$).

DISCUSSION

This systematic review evaluated evidence from three studies. This meta-analysis determined that ticagrelor monotherapy and DAPT have similar rates of major bleeding and MI among DM

patients undergoing PCI with DES after an initial short-course DAPT, whereas major bleeding using BARC showed a risk of 0.70 times more likely to have bleeding events (RR, 0.70; 95% CI, 0.37–1.32; $P = 0.008$, $I^2 = 79\%$). This shows considerable heterogeneity due to the time DAPT was shifted to ticagrelor monotherapy, and the high bleeding risk among patients in TWILIGHT.

As regards all-cause mortality, those who were given ticagrelor monotherapy had 0.76 times the risk of having mortality compared with those who continued DAPT (RR, 0.76; 95% CI, 0.59–0.98; $P = 0.03$, $I^2 = 0$). This also shows mild heterogeneity. Overall, there are lower events of overall death in the treatment group. There was limitation of data with regard to the thrombotic property of ticagrelor monotherapy. This meta-analysis showed that ticagrelor does not substantially reduce MI events. This showed 0.95 risk of having MI from ticagrelor compared with DAPT (RR, 0.95; 95% CI, 0.75–1.20; $P = 0.66$, $I^2 = 0\%$). Further studies are needed to evaluate their importance.

This article presented a comprehensive systematic review and meta-analysis that showed ticagrelor monotherapy after a short-term DAPT reduces the risk of bleeding but will not lead to thrombotic events. A systematic critical appraisal of included studies was done using the updated RoB 2.0 tool for the randomized controlled trial. This article has provided a systematic and detailed analysis of the assessment of the quality of evidence. There is substantial heterogeneity among each study because of the following reasons: (1) the interval from shifting DAPT to ticagrelor monotherapy: it was seen that patients in both TWILIGHT and TICO trials had 3 months of DAPT prior to shifting to ticagrelor monotherapy compared with 1 month from the GLOBAL LEADERS trial; (2) the baseline characteristics of the sample population used for the TWILIGHT trial are at high risk for both thrombosis and bleeding when compared with the other two trials, which led to a higher rate of both bleeding and thrombosis. Further studies are recommended, and more studies should be included to strengthen its recommendation.

CONCLUSION

Ticagrelor monotherapy after short-course DAPT and conventional DAPT have similar rates of major bleeding and MI among DM patients undergoing PCI with DES. However, DAPT strategy had a higher incidence of all-cause mortality, which suggests that ticagrelor monotherapy may be a preferable antiplatelet strategy in DM patients undergoing PCI.

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FUNDING, DISCLOSURE, AND CONFLICT OF INTEREST

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LIST OF FIGURES:

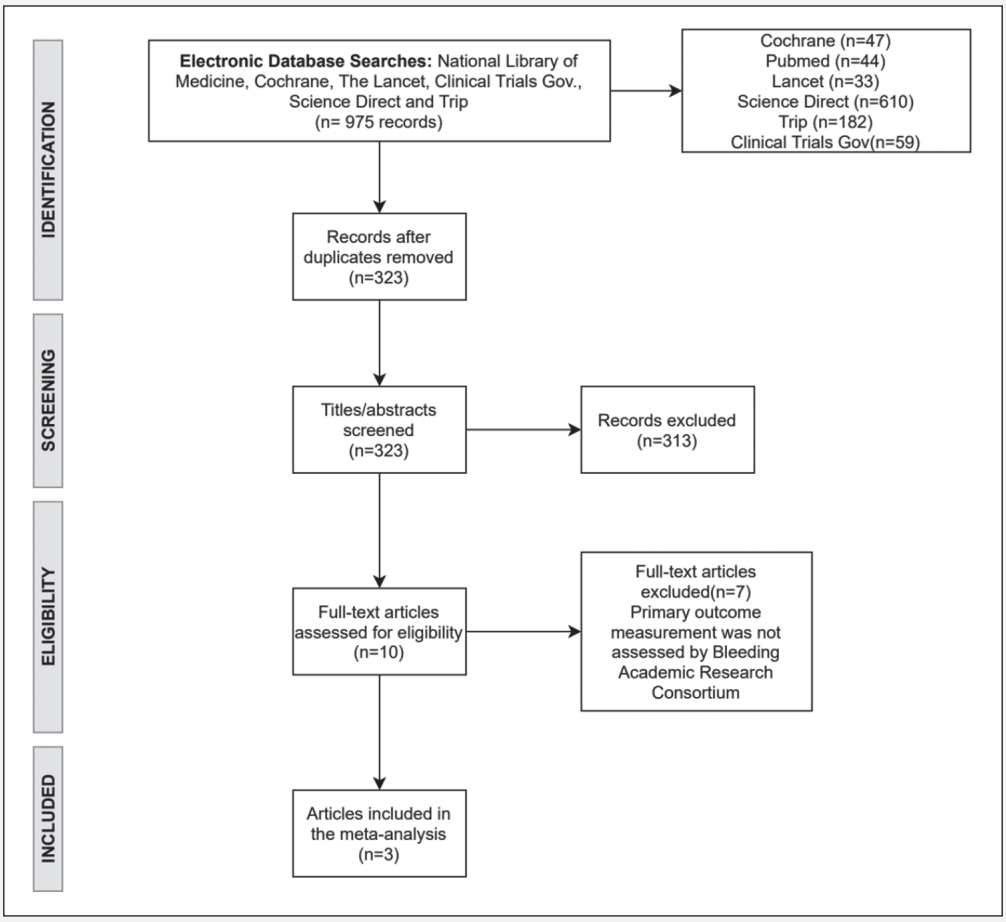

Figure 1. PRISMA flow diagram.

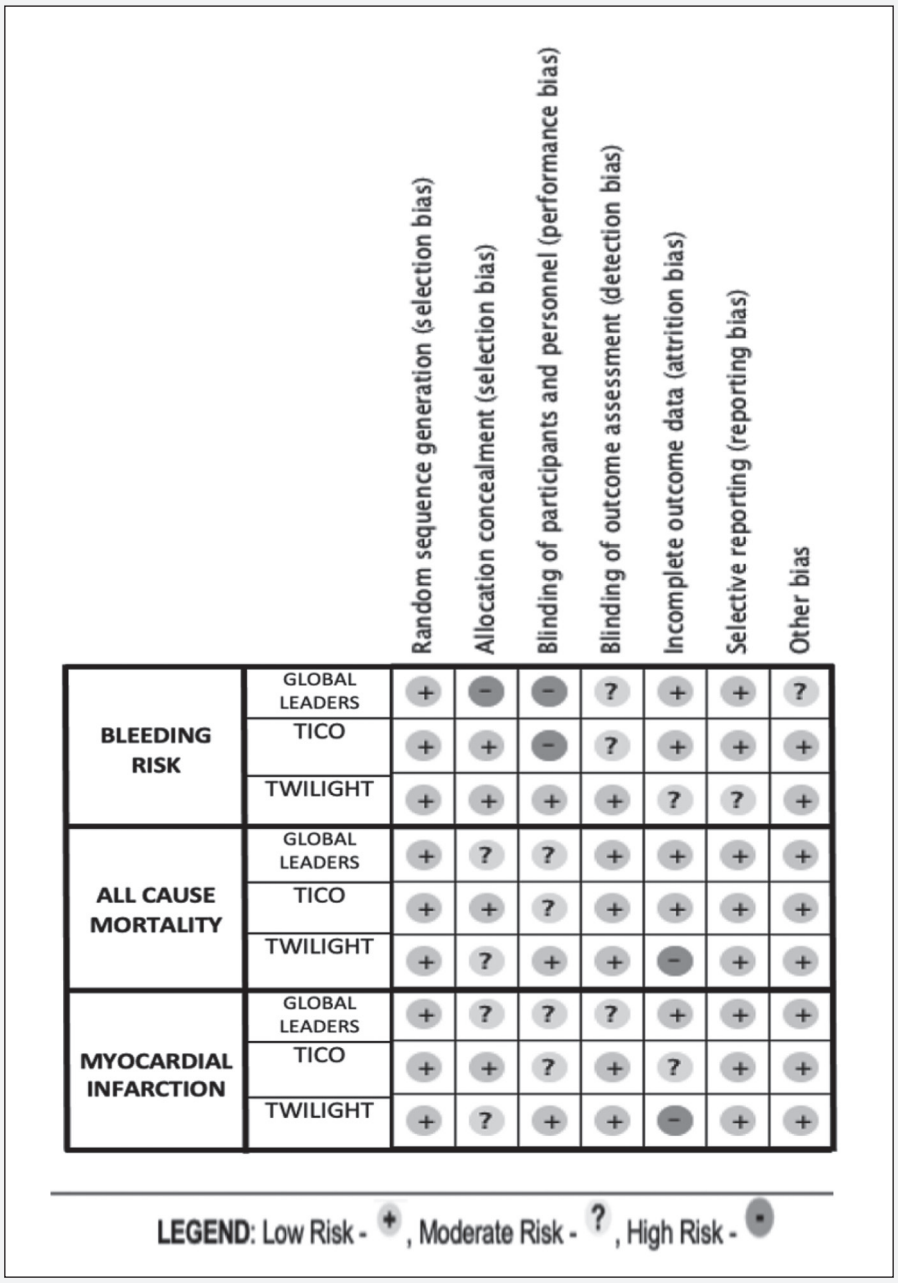

Figure 2. Cochrane Risk of Bias 2.0 assessment.
Note. The figure shows the review authors' judgments about each risk-of-bias item in the column for each included study in the rows. A green dot with a plus symbol indicates presence of a bias item in a corresponding study. A red dot with a minus symbol indicates absence of a bias item in a corresponding study.

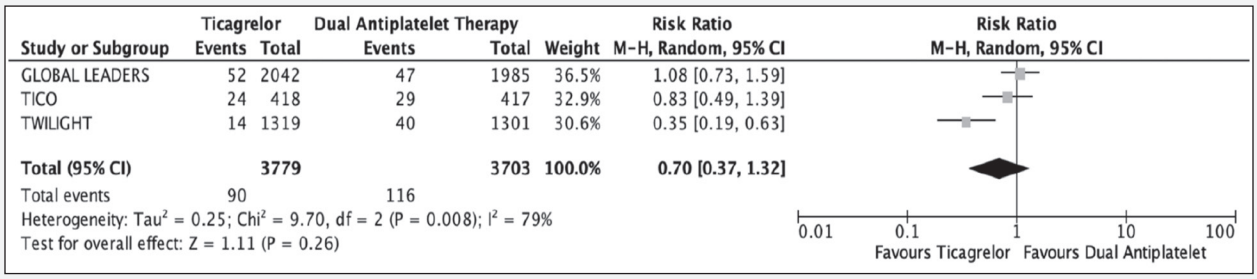

Figure 3. Forest plot comparison: ticagrelor monotherapy versus DAPT on Bleeding Risk using the BARC 3 to 5.
BARC=Bleeding Academic Research Consortium; CI=confidence interval; DAPT=dual-antiplatelet therapy; M-H=Mantel-Haenszel.

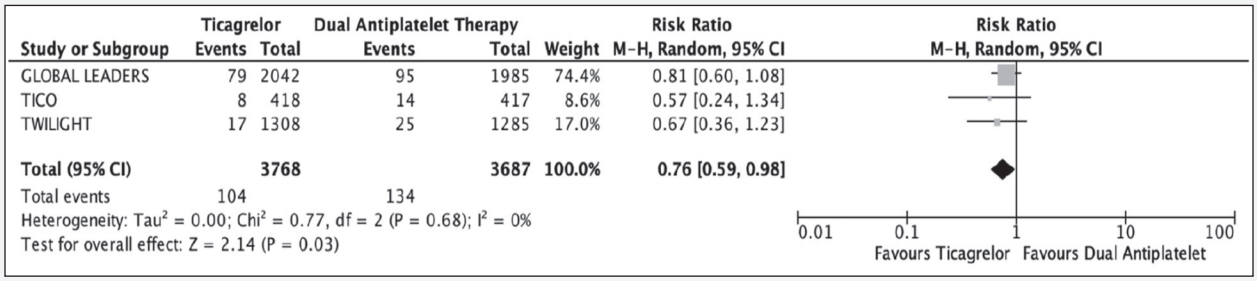

Figure 4. Forest plot comparison: ticagrelor monotherapy versus DAPT on all-cause mortality.
DAPT=dual-antiplatelet therapy; M-H=Mantel-Haenszel.

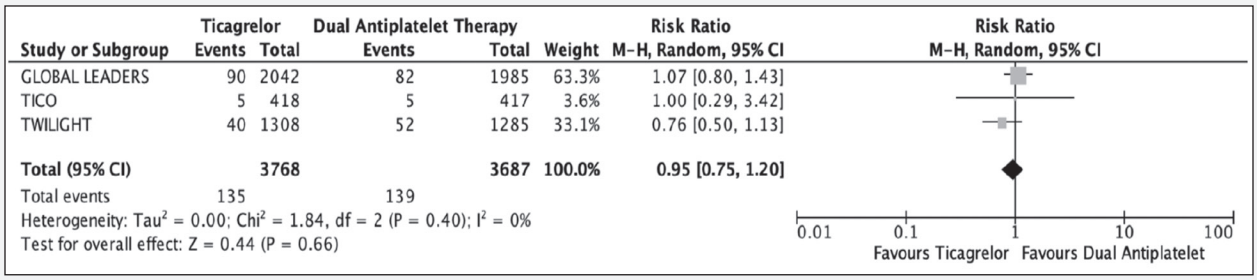

Figure 5. Forest plot comparison: ticagrelor monotherapy versus DAPT on myocardial infarction.
CI=confidence interval; DAPT=dual-antiplatelet therapy; M-H=Mantel-Haenszel.