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Dual Antiplatelet Therapy With Ticagrelor vs Clopidogrel in Patients With Acute Coronary Syndrome

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DUAL ANTIPLATELET THERAPY WITH TICAGRELOR VS CLOPIDOGREL IN PATIENTS WITH ACUTE CORONARY SYNDROME

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Abstract

Background: Dual antiplatelet therapy (DAPT) is an effective secondary prevention and an essential component of treatment after patients suffering from acute coronary syndrome (ACS). Recently, clinicians rapidly switched to DAPT with ticagrelor as the preferred treatment option after it was introduced in 2011. Compared to clopidogrel, ticagrelor is not a prodrug and does not require metabolic activation to inhibit the platelet P2Y12 receptor. It is the first reversible oral P2Y12 receptor antagonist; and its effect on platelet inhibition is more pronounced compared to clopidogrel.

Purpose: The purpose of this comprehensive review was to evaluate the efficacy and safety data of ticagrelor when compared with clopidogrel in ACS patients.

Methods: A comprehensive literature review was conducted using Tripdatabases and Pubmed search engines was searched through June 2022 using the terms: “dual antiplatelet therapy,” “antiplatelet monotherapy,” “ticagrelor vs clopidogrel,” “reduce recurrent atherothrombotic events,” “cardiovascular adverse events,” “coronary heart disease,” “acute coronary syndrome,” “myocardial infarction.” Inclusion criteria were recently published studies (at least 15 studies within the last five years from the day this review was performed) comparing the efficacy of ticagrelor with clopidogrel or placebo. The type of trials could be retrospective studies or prospective randomized controlled studies with complete data and reportable clinical outcomes. Exclusion criteria were case reports, repeated publications, animal experiments, and studies that were poorly designed with errors, incomplete data, or without clinical outcomes.

Conclusions: Through the literature review from many blinded, randomized controlled trials and studies, ticagrelor has successfully shown its superior efficacy in reducing the rate of cardiovascular adverse events in ACS patients and shown no significant difference in the rate of major bleeding between ticagrelor and clopidogrel.

Key Words: Dual antiplatelet therapy, antiplatelet monotherapy, ticagrelor, ticagrelor vs clopidogrel, recurrent thrombotic events, cardiovascular adverse events, acute coronary syndrome, coronary heart disease, myocardial infarction, fibrinolysis.

Dual Antiplatelet Therapy with Ticagrelor vs Clopidogrel in Patients with Acute Coronary Syndrome

Introduction

Cardiovascular disease affects millions of people annually and is a leading cause of death and disability.[1] According to the global burden of Cardiovascular Diseases and Risk Factors, the incidence of coronary heart disease and deaths caused by it were increasing significantly, from 12.1 million in 1990, reaching 18.6 million in 2019.[2] After acute coronary syndrome (ACS), especially after acute myocardial infarction (AMI), patients are at high risk for further vascular events, such as ischemic stroke which is a known complication with devastating consequences. The incidence of ischemic stroke is between 1.1–4.1% during the first year after myocardial infarction (MI); and it is potentially associated with an increase in morbidity and mortality.[1] Indeed, a study showed an increase of 16% to 19% in absolute mortality rate during the first year in patients with AMI complicated by ischemic stroke.[3] Moreover, previous ischemic stroke is also a major predictor of recurrent ischemic stroke after AMI. In real life, these patients are routinely encountered in clinical practice and constitute a high-risk population with worse prognosis than the general AMI-population.[1] To help reduce the risk of vascular complications after ACS, effective secondary prevention is vital, especially to ACS patients with prior stroke.

Currently, dual antiplatelet therapy (DAPT) is an effective secondary prevention and an essential component of treatment after patients suffering from ACS.[1] A standard treatment in patients with ACS with or without ST-segment elevation and after stent procedures is DAPT involving the combination of aspirin and clopidogrel.[4] Until 2011, the standard DAPT in Sweden was still the combination of clopidogrel and aspirin.[1,3] However, this standard DAPT did not give an adequate platelet inhibition response in approximately 15% to 48% of patients.[4]

Consequently, this could contribute to a residual high risk of recurrent thrombotic events in these patients. Therefore, clinicians rapidly switched to ticagrelor, a P2Y12-inhibitor, as the preferred treatment option after it was introduced in 2011.[1] Clopidogrel is a prodrug which needs liver metabolism to be activated; and its active metabolite irreversibly binds the platelet P2Y12 receptor. Additionally, the onset of clopidogrel is slow. It needs about 2-4 hours to achieve steady-state platelet inhibition after a loading dose of 600 mg.[4] Moreover, this pathway may lead to unexpected variations in drug activity since it is susceptible to genetic polymorphism.[5] Compared to clopidogrel, ticagrelor is not a prodrug and does not require metabolic activation to inhibit the platelet P2Y12 receptor. It is the first reversible oral P2Y12 receptor antagonist; and its effect on platelet inhibition is more pronounced.[1,4,5] Since it is an active drug with more rapid onset (within 1.5-3 hours) and offset of action (within 2 hours), the inhibition and recovery of platelet function with ticagrelor is faster than clopidogrel.[5]

Because of the advantageous features of ticagrelor, many trials have been conducted to compare the clinical efficacy and safety data between the use of ticagrelor compared to clopidogrel in reducing the rate of death from vascular causes, MI or stroke in patients surviving from ACS. Therefore, the purpose of this review is to evaluate whether the use of DAPT with ticagrelor would result in a lower risk of recurrent thrombotic events in patients after experiencing ACS.

Methods

A comprehensive literature review was conducted using Tripdatabases and Pubmed search engines was searched through June 2022 using the terms: “dual antiplatelet therapy,” “antiplatelet monotherapy,” “ticagrelor vs clopidogrel,” “reduce recurrent atherothrombotic

events," "cardiovascular adverse events," "coronary heart disease," "acute coronary syndrome," "myocardial infarction."

Inclusion criteria were recently published studies (at least 15 studies within the last five years from the day this review was performed) comparing the efficacy of ticagrelor with clopidogrel or placebo. The type of trials could be retrospective studies or prospective randomized controlled studies with complete data and reportable clinical outcomes. Exclusion criteria were case reports, repeated publications, animal experiments, and studies that were poorly designed with errors, incomplete data, or without clinical outcomes.

In this comprehensive literature review, 20 studies were selected with 16 studies published within the last five years. Participants were ACS patients who were at least 18 years with or without ST-elevation in addition to one or more cardiovascular risk factors (for example: age ≥60 years, diabetes mellitus, chronic renal dysfunction, peripheral arterial disease, transient ischemic attack, prior myocardial infarction, or ischemic stroke).

The main outcomes were the rates of cardiovascular mortality, MI, stroke, or other atherothrombotic events and the major bleeding were evaluated in most of the selected studies.

Review of the Literature

One of the biggest trials that were designed to test the efficacy and safety of ticagrelor compared with clopidogrel in reduction of recurrent thrombotic events in patients with ACS was the PLATelet inhibition and patient Outcomes (PLATO) trial. PLATO was a multicenter, double-blinded, and randomized controlled trial in which researchers compared ticagrelor and clopidogrel for the prevention of adverse cardiovascular events and the bleeding risk.[4] The trial enrolled 18,624 ACS patients with or without ST-segment elevation admitted to the hospital

from approximately 800 sites in 43 countries.[4,6] In this trial, patients were at least 18 years old with ACS that happened within 24 hours before randomization. In addition, ACS patients without ST-elevation needed two or more of the following criteria to be enrolled, such as an electrocardiography showing ischemia, a positive test of cardiac biomarkers, or one of cardiac risk factors (for example: age ≥60 years, diabetes mellitus, chronic renal dysfunction, peripheral arterial disease, transient ischemic attack, prior myocardial infarction or ischemic stroke). For ACS patients with ST-elevation, they needed two more criteria to be enrolled, such as intention to perform primary percutaneous coronary intervention (PCI), or persistent ST-elevation (at least 0.1 mV in ≥ 2 contiguous leads) or a new left bundle-branch block. Patients who were contraindicated against the use of clopidogrel, had fibrinolytic therapy within 24 hours, or were at increased risk of bradycardia were excluded from this trial.[4,6] Within 24 hours from the onset of ACS, eligible patients were randomized in a 1:1 ratio to oral maintenance treatment with ticagrelor 90 mg twice daily (180-mg loading dose) and clopidogrel 75 mg once daily (300-to-600-mg loading dose) on a background of aspirin from 6 to 12 months with an estimated average follow-up of 11 months. The primary efficacy endpoint was the occurrence of death from vascular causes, MI, or stroke; and the primary safety variable was PLATO-defined major bleeding.[4,6] This trial showed a composite of death from vascular causes, stroke, or MI at 12 months had occurred in 9.8% of patients receiving ticagrelor and 11.7% of those receiving clopidogrel ($P<0.001$). There was no significant difference in the rates of major bleeding between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; $P=0.43$). However, a higher rate of major bleeding not related to coronary-artery bypass grafting (such as intracranial bleeding) was seen in ticagrelor group compared to clopidogrel group (4.5% vs. 3.8%, $P=0.03$).[6]

The findings from the PLATO trial were supported by the Platelet Reactivity in Acute Stroke or Transient Ischemic Attack (PRINCE) trial. The PRINCE trial compared the efficacy of ticagrelor plus aspirin with clopidogrel plus aspirin at 90 days in patients with minor stroke or with a moderate to high-risk transient ischemic attack. This trial was a prospective study conducted at 26 centers in China from 08/2015 to 03/2017. There were 675 patients enrolled in this trial. Key exclusion of this trial was diagnosis of intracranial hemorrhage, any pathology that could cause neurological symptoms, or contraindication against ticagrelor, clopidogrel, or aspirin.[7] Similar to the PLATO trial, 336 patients were randomly assigned to the ticagrelor/aspirin group (180 mg loading dose, 90 mg twice daily thereafter) and 339 patients were assigned to the clopidogrel/aspirin group (300 mg loading dose, 75 mg daily thereafter) on a background of aspirin within 24 hours of symptom onset. The outcomes of this trial were the proportion of patients with high platelet reactivity and any stroke recurrence at 90 days.[7] As a result, high platelet reactivity occurred more in the clopidogrel/aspirin group vs the ticagrelor/aspirin group at the 90th day of the treatment (29.7% vs 12.5%, respectively). This meant there would be a higher chance of recurrent thrombotic events in patients treated with clopidogrel/aspirin. Indeed, stroke occurred more in the clopidogrel/aspirin group vs the ticagrelor/aspirin group (8.8% vs 6.3%, respectively; P=0.20). However, there was no significant difference seen in the rates of major or minor hemorrhagic events between the ticagrelor/aspirin and clopidogrel/aspirin groups (4.8% v 3.5%; P=0.42).[7] These results were consistent with findings from the PLATO trial and showed that the use of ticagrelor was associated with a lower thrombotic risk in ACS patients compared to the use of clopidogrel.

When comparing the patients in the PLATO trial (mostly younger and healthier individuals) to a real-world population, there was a knowledge gap about the effect of ticagrelor

on reducing the recurrent thrombotic events in the ACS population with AMI. Therefore, a retrospective study was conducted by obtaining data of AMI patients treated with either clopidogrel or ticagrelor from Swedish Heart Intensive Care Admission Registry to compare the treatment between clopidogrel and ticagrelor on reducing the risk of ischemic stroke in a more representative ACS population who most likely had prior MI.[3] This study included patients who were treated at discharge with either clopidogrel or ticagrelor. Participants in this study were divided into two cohorts. There were 23,447 participants in the early cohort which were treated with 100% clopidogrel. The later cohort had 24,227 participants and were treated with either clopidogrel (47.9%) or ticagrelor (52.1%).[3] After a year of treatment, the later cohort showed an increased platelet inhibition compared to the early cohort due to the higher frequency of ticagrelor treatment in the later cohort. Incidence of ischemic stroke after one year was 2.8% vs. 2.4% for the early and later cohorts, respectively ($p = 0.001$).[3] There was no significant difference between the early and later cohorts in the most serious bleeding complication, such as intracranial bleeding. Similar results were found in a pre-post case-control study using data from the Cardio-STEMI Sanremo registry in Sanremo Hospital. The study included patients >18 years old with a diagnosis of STEMI and excluded patients with type 4a or 5 AMI, who were unavailable for follow-up visits or had severe comorbidity with very short life expectancy.[5] In this study, 401 eligible patients were enrolled between February 2011 and June 2013, in which 142 patients received ticagrelor and 259 received clopidogrel. This study showed the use of ticagrelor resulted in a significant reduction of cardiovascular mortality at 1-year compared to clopidogrel (5.4% reduction with ticagrelor vs 0.7% reduction with clopidogrel).[5] This study also showed a similar rate of BARC bleeding (Bleeding Academic Research Consortium criteria) between the two groups.[5] The results from these two studies were concordant with the results

from the PLATO trial which showed the beneficial effect of ticagrelor on reducing the risk of recurrent thrombosis and mortality rate in this high-risk subgroup.[5] Therefore, these findings suggested that ticagrelor may be a valid treatment option in this ACS population with MI.[1,3]

At this point, ticagrelor has shown its effectiveness in reducing the risk of cardiovascular adverse events in ACS patients with or without AMI. Additionally, the superior efficacy of ticagrelor were also seen in high-risk ACS patients, such as in ACS patients with prior heart attack; and this was proven in the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54 (PEGASUS-TIMI 54) trial. This trial randomized 21,162 patients with prior MI (1–3 years) and additional high-risk features (≥65 years, prior MI, known multivessel CAD, diabetes mellitus, or chronic kidney disease) to the ticagrelor 60 mg or 90 mg group vs placebo twice daily in addition to aspirin. Patients with a history of coronary artery bypass graft (CABG) surgery within the last 5 years as well as patients with increased risk of bleeding were excluded. Patients were followed for a median of 33 months to evaluate the risk of adverse cardiac events and major bleeding as defined by the Thrombolysis in Myocardial Infarction (TIMI).[8,9] As a result, 213 patients in the placebo group experienced stroke vs 91 patients in the ticagrelor group experienced stroke at the 30-day follow-up. This trial showed significant reduction of the risk of stroke with ticagrelor ($P=0.034$).[9] However, the use of ticagrelor increased TIMI major bleeding ($P<0.001$) but with no statistically significant increase in intracranial hemorrhage or fatal bleeding.[9] From the PEGASUS-TIMI 54 trial, a group of researchers also performed a pre-specified study to investigate the pattern of ischemic risk over time and whether the efficacy and safety of ticagrelor were similar in early and late randomization.[10] The selection criteria and study method were described as above. In their study,

they identified 28% of participants who had ≥5 years from MI at trial conclusion. When examining patients according to the time from MI at randomization with either <2 years or ≥2 years, ticagrelor 60 mg showed greater benefit for the primary endpoint which was a composite of adverse cardiovascular events in patients <2 years from MI compared to those ≥2 years from MI.[10] Treatment with the 90-mg dose yielded similar adverse cardiovascular outcomes in these groups. This study also showed an increase in the rates of TIMI major bleeding with ticagrelor 60 mg at each year landmark, with the greatest increase in the first year (year 1 HR=3.22; year 2 HR=2.07; year 3 HR=1.65).[10] With ticagrelor 90, the rates of TIMI bleeding were generally higher than with ticagrelor 60 mg.[10] In general, patients with prior MI >1 year from their ACS event remain at long-term risk of recurrent atherothrombotic events. Ticagrelor consistently reduced the risk of recurrent atherothrombotic in patients with prior MI regardless of early or late administration of ticagrelor after an MI. The bleeding risk was also tolerable with a trend toward lesser bleeding over time. Therefore, the prolonged therapy with Ticagrelor is supported in patients who continue to tolerate the drug.[10]

Clearly, the PLATO trial as well as other blinded randomized controlled trials demonstrated that dual antiplatelet treatment (DAPT) with ticagrelor reduced the rate of death from vascular causes, stroke, or MI better than DAPT with clopidogrel. However, the PLATO-trial included overall younger and healthier individuals who were at lower risk for ischemic stroke than patients we typically would see in a real-life setting. Of the 18,624 eligible patients in the PLATO trial, 1152 (6.2%) were high-risk patients who had a history of stroke or TIA. This subgroup has a higher rate of morbidity and mortality; and we most likely encounter them in a real clinical setting. Therefore, a group of researchers aimed to determine whether the introduction of ticagrelor was associated with a lower rate of recurrent thrombotic events in ACS

patients who previously had an ischemic stroke or TIA specifically in the PLATO trial.[1,11] Their study, specifically to this subgroup, showed the reduction of a composite of death from vascular causes, stroke, or MI and total mortality at 1 year with ticagrelor versus clopidogrel, which was consistent with the overall trial results: 19.0% versus 20.8% and 7.9% versus 13.0%, respectively.[11] The major bleeding rate was not significantly different between patients assigned to clopidogrel and ticagrelor with an adjusted hazardous rate (HR) of 1.10 vs HR of 1.11, respectively. There was also no difference between clopidogrel and ticagrelor groups in intracranial bleeding seen in this study.[11]

Since the PLATO trial excluded patients who received fibrinolytic therapy within 24 hours of ACS, consequently, there was a lack of evidence on the longer-term effects of ticagrelor in ACS patients with STEMI treated with fibrinolytic therapy. Therefore, TicagRElor in pAtients with ST-elevation myocardial infarction treated with pharmacological Thrombolysis (TREAT) trial was conducted to evaluate the efficacy and safety data of ticagrelor when compared with clopidogrel in this subgroup that was excluded from the PLATO trial.[12] The TREAT trial was a multicenter, international, blinded, and randomized controlled study involving 10 countries. This trial enrolled 3,799 patients (age less than 75 years) with STEMI receiving fibrinolytic therapy from November 2015 to November 2017. The trial excluded individuals who were contraindicated against the study drugs, on other oral anticoagulation therapy, and who were at an increased risk of bradycardia. Eligible patients were randomly assigned, in a 1:1 ratio, to ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) or clopidogrel (300- to 600-mg loading dose, 75 mg daily thereafter). The rates of cardiovascular mortality, MI, stroke, or other arterial thrombotic events were evaluated at two periods: 30 days and 12 months.[12,13] As a result, the trial showed better reduction in the rates of cardiovascular mortality in the ticagrelor group at

both timelines. Mortality outcomes occurred in 4.0% (in 30 days) and 6.7% (in 12 months) of patients receiving ticagrelor vs 4.3% (in 30 days) and 7.3% (in 12 months) of patients receiving clopidogrel.[13] Again, there were no significant differences between ticagrelor and clopidogrel groups in major, fatal, and intracranial bleeding.[13] Overall, these findings would provide useful data to assist physicians in clinical decision and suggested that ticagrelor may represent a potential alternative antiplatelet agent that can be used after fibrinolytic therapy.[12,13]

Elderly patients represent a significant proportion of those with ACS. Unfortunately, this ACS subgroup is at higher risk of recurrent thrombotic events and major bleeding. Indeed, an 80-year-old ACS patient has three-fold higher risk of recurrent ischemic stroke compared to a 60-year-old ACS patient.[2] Since the PLATO trial were mostly younger and healthier individuals, a group of researchers conducted a meta-analysis to evaluate the efficacy of ticagrelor in this compromised subgroup. This included six qualified randomized controlled trials (RCT) with complete data published between 2009-2020 comparing the efficacy between the two groups, ticagrelor vs clopidogrel, on a background of aspirin at the 12-month follow-up.[2] Overall, this study included 21,827 patients who were greater than or equal to 60 years old with coronary heart disease, such as stable angina, unstable angina, STEMI or non-STEMI. This review found a significant decrease in the incidence of adverse cardiovascular events in the ticagrelor group vs clopidogrel group (9.23% vs 10.57%, respectively). However, the use of ticagrelor also increased the incidence of minor or major bleeding compared with the use of clopidogrel in the elderly population (11.51% vs 10.34 %, respectively).[2]

The use of ticagrelor has shown the beneficial effect on reducing the risk of subsequent thrombotic events in general ACS patients and even in high-risk individuals who either had prior MI or stroke. However, its effect on ACS patients with comorbidities such as diabetes mellitus

(DM) was unclear. Therefore, a double-blinded, randomized controlled trial was performed to examine whether adding ticagrelor to aspirin improves the outcomes in patients with stable coronary artery disease (CAD) and DM.[14] A total of 19,220 patients were enrolled in this trial. Eligible patients are at least 50 years with stable CAD and type 2 DM. Patients with previous MI or stroke or patients who were receiving dual antiplatelet therapy were excluded. Enrolled patients were assigned to receive either ticagrelor (90 mg twice daily) plus aspirin (75 to 150 mg) or placebo plus aspirin (75 to 150 mg) in a 1:1 ratio. After the results from the PEGASUS–TIMI 54 trial were published, the protocol of this trial was amended; and the dose of ticagrelor was reduced to 60 mg twice daily instead of 90 mg twice daily in May 2015.[14] The primary efficacy outcome was a composite of cardiovascular death, MI, or stroke. The primary safety outcome was major bleeding as defined by the Thrombolysis in Myocardial Infarction (TIMI).[14] At the median follow-up of 39.9 months, this trial showed a lower incidence of ischemic cardiovascular events in the ticagrelor group than in the placebo group, which was 7.7% vs. 8.5%, respectively.[14] The incidence of major bleeding was higher in the ticagrelor group compared to the clopidogrel group (0.2% vs. 0.1%, respectively).[14] Since the risk of a composite outcome was not significantly lower in the ticagrelor group than in the placebo group while the risk of major bleeding tended to be higher in the Ticagrelor group, the findings suggested that ticagrelor therapy did not have a favorable risk–benefit ratio in this trial population.[14] Addition to these findings, a trial from Korea was conducted between November 2011 and December 2015 to compare 1-year clinical outcomes between ticagrelor and clopidogrel in this ACS with DM subgroup.[15] This trial obtained data from Acute Myocardial Infarction Registry which enrolled 3985 patients with MI and diabetes who underwent PCI to ticagrelor (90 mg twice daily) and clopidogrel (75 mg once daily). This trial excluded patients with age ≥75, body weight <60 kg,

history of transient ischemic attack (TIA) or stroke, or contraindication to ticagrelor.[15] Same as the previous described trial, this study showed no significant difference in the composite of cardiac death, recurrent MI, or stroke (p=.084), but an increase in the major bleeding risk in the ticagrelor group (p=.042) at 1-year follow-up.[15]

Despite the superior efficacy of DAPT with ticagrelor over clopidogrel, the increased risk of bleeding was a concern when using ticagrelor in patients after ACS. Therefore, a group of researchers performed a study using data from the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions to examine any association between ticagrelor and intracranial hemorrhage (ICH) in AMI patients.[16] The population in their study were 47,674 ACS patients with AMI which were divided into two cohorts. The first cohort had 23,447 patients and treated with 100% clopidogrel, while the later cohort had 24,227 patients and treated with either clopidogrel (47.8%) or ticagrelor (52.1%).[16] This study showed no significant difference in the incidence of ICH between the two cohorts with 0.59% of patients with ICH found in the first cohort and 0.52% found in the second cohort.[16] Even though this study showed no increased risk of the fatal bleed-ICH associated with the use of ticagrelor, many previous studies showed that DAPT of ticagrelor and aspirin could cause an increase in minor and major bleeding events. Therefore, several groups of researchers had conducted studies to develop strategies to reduce this known adverse effect of ticagrelor.

The Ticagrelor With Aspirin or Alone in High Risk Patients After Coronary Intervention (TWILIGHT) trial was conducted to determine whether ticagrelor monotherapy would cause less clinically relevant bleeding while still maintaining the benefit in reducing thrombotic events in ACS patients undergoing PCI with drug-eluting stents (DES).[17] TWILIGHT was a randomized controlled trial conducted in 187 sites across 11 countries at Mount Sinai. This study had 9006

participants with high-risk features undergoing PCI with DES. These patients were on dual antiplatelet therapy (DAPT) with ticagrelor plus aspirin for 3 months. Then, 7119 patients who were adherent and had no cardiovascular events were randomized to ticagrelor plus aspirin and ticagrelor plus placebo for 12 months.[17] Inclusion criteria were ACS patients aged ≥65 years with additional comorbidities (prior MI, diabetes mellitus or chronic kidney disease). Patients who had contraindication to aspirin or ticagrelor, had need for oral anticoagulation, or had prior cardiogenic shock were excluded. The main outcome in this study were the Bleeding Academic Research Consortium (BARC) bleeding rate and the composite of stroke, MI, or all-cause death.[17] Among this patient population, 7.6% of patients with ticagrelor plus aspirin and 3.6% of patients with ticagrelor plus placebo experienced BARC bleeding ($P < 0.001$). In the meantime, 4.4% of patients with ticagrelor plus aspirin and 4.3% patients with ticagrelor plus placebo were reported of having stroke, MI or death ($P = 0.84$).[17] This study showed that ticagrelor monotherapy reduced clinically bleeding events without increasing ischemic risk compared to ticagrelor plus aspirin in ACS patients undergoing PCI with DES who have completed an initial 3-month course of DAPT.[17] A study with a similar design was conducted in Korea found the same results. It was a multicenter, randomized trial conducted in 3056 patients with ACS treated with drug-eluting stents between August 2015 and October 2018.[18] In this study, after the prior 3 months of DAPT, eligible patients were randomly assigned in a 1:1 ratio to receive ticagrelor monotherapy ($n = 1527$) vs ticagrelor-based 12-month DAPT ($n = 1529$). Similarly, researchers found a decrease in the rate of major bleeding in the ticagrelor monotherapy group vs the ticagrelor-based DAPT group (1.7% vs 3.0%, respectively).[18] In the meantime, there was also a reduction of adverse clinical events in patients with ticagrelor monotherapy at 1-year follow-up, in which cardiovascular events occurred in 3.9% of patients with ticagrelor alone vs in 5.9% of

patients with ticagrelor plus aspirin.[18] Therefore, the findings from these two trials suggested that ticagrelor monotherapy could be a promising strategy to reduce the bleeding risk while still maintaining a maximal platelet inhibition activity after a short-term DAPT in ACS patients with PCI.[18]

Another strategy to reduce the risk of major or fatal bleeding that several groups of researchers had conducted studies on was to use a reduced dose of ticagrelor (60 mg) instead of the standard dose (90 mg). Therefore, a single-center, randomized controlled trial in Bydgoszcz was performed to compare the efficacy (antiplatelet effect) of the two ticagrelor maintenance dose regimens (60 mg bid vs. 90 mg bid) in stable patients 1 month after AMI treated with PCI, following an initial DAPT with ticagrelor 90 mg bid during the first 30 days after the ACS onset.[19] This study included ACS patients with STEMI or non-STEMI and excluded patients who had chronic inflammatory disease, indications for chronic anticoagulation, or contraindication to ticagrelor. There were 52 enrolled patients equally randomized to receive either reduced (60 mg bid) or standard (90 mg bid) dose of ticagrelor after they received 90 mg ticagrelor bid and aspirin 75 mg once daily for the first 30 days after AMI happened.[19] After 15 days of randomization (45 days after AMI), the primary endpoint which was platelet reactivity index (PRI) was assessed with the VASP (a platelet function testing assay). As a result, the reduced dose (60 mg) vs. standard dose (90 mg) of ticagrelor showed no significant difference in platelet inhibition activity [VASP: 10.4 vs. 14.1].[19] Additionally, the same result was found in an experimental study conducted in 1000 participants, in which ticagrelor 60 and 90 mg twice daily both achieved near maximal platelet inhibition in patients with stable CAD with or without history of MI.[20] Therefore, these findings suggested the favorable effect of the reduced dose (60 mg) over the standard dose (90 mg) with less bleeding risk in treating ACS patients.[19]

Discussion/Analysis

Overall, dual antiplatelet therapy (DAPT) with ticagrelor compared with clopidogrel was associated with the lower rate of death from vascular causes, MI, or stroke without an increase in the rate of major bleeding in ACS patients in many trials and studies. The PLATO trial was one of the biggest trials that successfully showed the superior efficacy of DAPT with ticagrelor over DAPT with clopidogrel. One of the strengths of the PLATO trial was that it was a multicenter, double-blinded, randomized controlled trial conducted from approximately 800 sites in 43 countries. The trial also had a big study size with 18,624 participants.[4,6] Therefore, the results from this study were reliable and had high generalizability to the intended population. Moreover, these findings from the PLATO trial were also supported by the Platelet Reactivity in Acute Stroke or Transient Ischemic Attack (PRINCE) trial, which was a prospective study conducted at 26 centers in China from 2015-2017. In the PRINCE trial, treatment with ticagrelor again showed significant reduction in recurrent thrombotic events at the 90th day of treatment, which were consistent with the PLATO results.[7] The PRINCE trial had some limitations such as 15% of patients were lost to follow-up for evaluation. However, researchers observed similar results after assuming all the missing data in both ways, high platelet activity vs not.[7] With the advantage of a randomized controlled trial that had an adequate study size of 675 participants, the findings from the PRINCE trial were still considered reliable and useful data to support bigger trials.

ACS patients with prior heart attack comprise a large number of the ACS population. This subgroup is considered high-risk patients since they have a higher chance of recurrent atherothrombotic events after experiencing ACS. The superior efficacy of ticagrelor was again

proven for this high-risk population in many studies. In a retrospective study with data of AMI patients treated with either clopidogrel or ticagrelor obtained from the Swedish Heart Intensive Care Admissions Registry, the use of DAPT with ticagrelor showed reduction of ischemic stroke in this ACS population who had prior MI. To avoid selection bias, this study compared the efficacy between ticagrelor vs clopidogrel in two different cohorts. This was a big-scale study with 23,447 participants in the first cohort and 24,227 participants in the second cohort.[1,3] However, since it was a retrospective study, the results from this study demonstrated the need for a randomized trial to further support the efficacy of ticagrelor in ACS patients with prior MI. The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54 (PEGASUS-TIMI 54) trial was one of the biggest randomized controlled trials that supported these findings. In this trial, ticagrelor consistently reduced the risk of recurrent atherothrombotic in patients with prior MI regardless of early or late administration after MI. The bleeding risk was also tolerable with a trend toward lesser bleeding over time.[8,9] Because of this, the prolonged therapy with ticagrelor was supported in patients who continue to tolerate the drug.[8,9] Since this was a randomized controlled trial with a very big study size (21,162 patients), the results from this study had high generalizability to the intended population and were useful to physicians in selecting dual antiplatelet therapy in ACS patients with prior MI.

The PLATO was a big trial, however, it excluded patients who received fibrinolytic therapy within 24 hours of ACS onset. Therefore, TREAT (TicagRElor in pAtients with ST-elevation myocardial infarction treated with pharmacological Thrombolysis) trial was conducted to evaluate the efficacy and safety data of ticagrelor when compared with clopidogrel in STEMI patients treated with fibrinolytic therapy. In this study, the use of ticagrelor was again

superior compared to the use of clopidogrel in reducing the rate of cardiovascular mortality, MI, stroke, or other arterial thrombotic events at 3-months and 12-month follow-ups. Moreover, there was no significant difference between ticagrelor and clopidogrel groups in major, fatal, and intracranial bleeding.[12,13] Since TREAT was a multicenter, international, blinded, and randomized controlled study involving 10 countries with 3,799 participants, the results from this study had high generalizability and would provide useful data to assist physicians in choosing an effective alternative antiplatelet agent that can be used after fibrinolytic therapy.

The use of ticagrelor has shown the beneficial effect on reducing the risk of subsequent thrombotic events in many ACS high-risk subgroups, such as ACS with prior MI (STEMI or non-STEMI), prior stroke, or with fibrinolytic therapy. However, in an ACS subgroup with diagnosis of diabetes mellitus, two randomized controlled studies that were reviewed in this paper showed no significant difference in the composite of cardiac death, recurrent MI or stroke ($p=.084$), but an increase in the major bleeding risk in the ticagrelor group.[14,15] Since the risk of a composite outcome was not significantly lower in the ticagrelor group than in the placebo group while the risk of major bleeding tended to be higher in ticagrelor group, the findings suggested that ticagrelor therapy did not have a favorable risk–benefit ratio in this ACS subgroup..

Nonetheless, ticagrelor has shown its superior efficacy in reducing the risk of recurrent atherothrombotic events over clopidogrel in the overall ACS population and even in high-risk subgroups, such as elderly patients, or patients with prior MI or stroke. Since my literature review was conducted from mostly prospective, blinded, and randomized controlled trials with adequate study sizes, the findings from these studies were reliable and could be used to answer my PICO question which was whether the use of DAPT with ticagrelor would prevent recurrent thrombotic events better than DAPT with clopidogrel. Through these studies, my PICO question

was answered. Treatment with ticagrelor as compared to clopidogrel significantly reduced the rate of recurrent cardiovascular adverse events such MI or stroke. The safety data of ticagrelor was also evaluated in these studies/trials. Even though most of the studies showed no significant increase in the rate of overall major bleeding in patients with ACS, bleeding was still a known adverse outcome of ticagrelor administration. Many studies have been conducted to figure out strategies to reduce the risk of bleeding while still maintaining the maximal platelet inhibition activity of ticagrelor. Indeed, researchers have tried to compare ticagrelor monotherapy with DAPT. They also tried to compare the efficacy and safety of the reduced dose (60 mg) with the standard dose (90 mg) of ticagrelor. Interestingly, the reduction of bleeding events was observed in these studies while a maximal platelet inhibition activity was still maintained. Therefore, the findings from these studies suggested ticagrelor monotherapy or reduced dose of Ticagrelor (60 mg) could be a promising strategy for clinicians in adjusting the bleeding risk when it was a concern.[17,18]

Conclusion

Cardiovascular disease is a great concern and a leading cause of death worldwide. After experiencing acute coronary syndrome, patients are at risk for further cardiovascular adverse events such as MI or stroke. Patients with prior stroke or MI comprises high-risk ACS subgroups since they are even at higher risk of having subsequent atherothrombotic events. Patients with prior ischemic stroke are often treated conservatively with either medications or interventions such as percutaneous coronary intervention (PCI). Indeed, dual antiplatelet therapy (DAPT) is an effective secondary prevention and an essential component of treatment after the patient suffering from ACS. Until 2011, the standard DAPT in Sweden was still the combination of

clopidogrel and aspirin.[1,2] However, clinicians rapidly switched to ticagrelor, a P2Y12-inhibitor, as the preferred treatment option after it was introduced in 2011.[1] It is because clopidogrel is a prodrug which needs liver metabolism to be activated. Therefore, the onset of clopidogrel is slow, and many unexpected variations in drug activity are observed.[4] Compared to clopidogrel, ticagrelor is not a prodrug and does not require metabolic activation. Moreover, its effect on platelet inhibition is more pronounced; and recovery of platelet function with ticagrelor is faster than clopidogrel.[5] With these advantageous features, ticagrelor was a promising alternative dual antiplatelet therapy that was worth studying. Indeed, through the literature review from many big blinded, randomized controlled trials and studies, ticagrelor has successfully shown its superior efficacy in reducing the rate of cardiovascular adverse events in ACS patients compared to clopidogrel. Even though the risk of bleeding was a main concern of ticagrelor, many studies showed no significant differences in the rate of major bleeding between ticagrelor and clopidogrel. In conclusion, compared to DAPT with clopidogrel, DAPT with ticagrelor is an effective alternative secondary prevention which better reduces recurrent thrombotic events in patients currently experiencing ACS. Hopefully, the findings from this comprehensive review would help clinicians in selecting DAPT for ACS patients and therefore further prevent deaths and disabilities in these patients.

References

1. Henriksson R, Björklund F, Mooe T. The introduction of ticagrelor is associated with lower rates of recurrent ischemic stroke after myocardial infarction. *PLoS One*. 2019;14(5): e0216404. Published 2019 May 6. doi: 10.1371/journal.pone.0216404
2. Akkaif M, Sha'aban A, Daud N, Ng M, Kader M, Ibrahim B. Efficacy and safety of ticagrelor versus clopidogrel in elderly patients with coronary heart disease, a systematic review and meta-analysis. *PROSPERO 2021* CRD42021257283 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021257283
3. Henriksson R, Ulvenstam A, Söderström L, Mooe T. Increase in ticagrelor use over time is associated with lower rates of ischemic stroke following myocardial infarction. *BMC Cardiovasc Disord*. 2019;19(1):51. Published 2019 Mar 4. doi:10.1186/s12872-019-1030-6
4. James S, Akerblom A, Cannon CP, et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. *Am Heart J*. 2009;157(4):599-605. doi: 10.1016/j.ahj.2009.01.003
5. Vercellino M, Sànchez FA, Boasi V, et al. Ticagrelor versus clopidogrel in real-world patients with ST elevation myocardial infarction: 1-year results by propensity score analysis. *BMC Cardiovasc Disord*. 2017;17(1):97. Published 2017 Apr 5. doi:10.1186/s12872-017-0524-3
6. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057. doi:10.1056/NEJMoa0904327
7. Wang Y, Chen W, Lin Y, et al. Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischemic attack: open label, blinded endpoint, randomized controlled phase II trial. *BMJ*. 2019;365: l2211. Published 2019 Jun 6. doi:10.1136/bmj.l2211
8. Furtado RH, Nicolau JC, Magnani G, Im K, Bhatt D, Storey R, Steg P G, Spinar J, Budaj A, Kontny F, Corbalan R, Kiss R, Abola M, Johanson P, Jensen E, Braunwald E, Sabatine M, Bonaca M, Long-term ticagrelor for secondary prevention in patients with prior myocardial infarction and no history of coronary stenting: insights from PEGASUS-TIMI 54, *European Heart Journal*, Volume 41, Issue 17, 1 May 2020, Pages 1625–1632, https://doi.org/10.1093/eurheartj/ehz821
9. Bonaca MP, Goto S, Bhatt DL, et al. Prevention of Stroke with Ticagrelor in Patients with Prior Myocardial Infarction: Insights from PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54). *Circulation*. 2016;134(12):861-871. doi:10.1161/CIRCULATIONAHA.116.024637
10. Bonaca MP, Storey RF, Theroux P, et al. Efficacy and Safety of Ticagrelor Over Time in Patients With Prior MI in PEGASUS-TIMI 54. *J Am Coll Cardiol*. 2017;70(11):1368-1375. doi:10.1016/j.jacc.2017.07.768
11. James SK, Storey RF, Khurmi NS, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes and a history of stroke or transient ischemic attack. *Circulation.* 2012;125(23):2914-2921. doi:10.1161/CIRCULATIONAHA.111.082727

12. Berwanger O, Lopes RD, Moia DDF, et al. Ticagrelor Versus Clopidogrel in Patients with STEMI Treated With Fibrinolysis: TREAT Trial. *J Am Coll Cardiol*. 2019;73(22):2819-2828. doi: 10.1016/j.jacc.2019.03.011
13. Berwanger O, Nicolau JC, Carvalho AC, et al. Ticagrelor vs Clopidogrel After Fibrinolytic Therapy in Patients With ST-Elevation Myocardial Infarction: A Randomized Clinical Trial [published correction appears in JAMA Cardiol. 2018 May 1;3(5):445]. *JAMA Cardiol*. 2018;3(5):391-399. doi:10.1001/jamacardio.2018.0612
14. Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in Patients with Stable Coronary Disease and Diabetes. *N Engl J Med*. 2019;381(14):1309-1320. doi:10.1056/NEJMoa1908077
15. Ahn KT, Seong SW, Choi UL, et al. Comparison of 1-year clinical outcomes between prasugrel and ticagrelor versus clopidogrel in type 2 diabetes patients with acute myocardial infarction underwent successful percutaneous coronary intervention. *Medicine (Baltimore)*. 2019;98(11):e14833. doi:10.1097/MD.0000000000014833
16. Graipe A, Söderström L, Mooe T. Increased Use of Ticagrelor After Myocardial Infarction Is Not Associated with Intracranial Hemorrhage. *Stroke*. 2018;49(12):2877-2882. doi:10.1161/STROKEAHA.118.022970
17. Baber U, Dangas G, Angiolillo DJ, Cohen DJ, Sharma SK, Nicolas J, Briguori C, Cha JY, Collier T, Dudek D, Džavik V, Escaned J, Gil R, Gurbel P, W Hamm C, Henry T, Huber K, Kastrati A, Kaul, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta S, Moliterno M, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz S, Steg PG, Weisz G, Witzenbichler B, Han Y, Pocock S, Gibson CM, Mehran R, Ticagrelor alone vs. ticagrelor plus aspirin following percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes: TWILIGHT-ACS, *European Heart Journal*, Volume 41, Issue 37, 1 October 2020, Pages 3533–3545, https://doi.org/10.1093/eurheartj/ehaa670
18. Kim BK, Hong SJ, Cho YH, et al. Effect of Ticagrelor Monotherapy vs Ticagrelor with Aspirin on Major Bleeding and Cardiovascular Events in Patients with Acute Coronary Syndrome: The TICO Randomized Clinical Trial. *JAMA*. 2020;323(23):2407-2416. doi:10.1001/jama.2020.7580
19. Kubica J, Adamski P, Buszko K, Barańska M, Sikora J, Marszałł MP, Sobczak P, Sikora A, Kuliczkowski W, Fabiszak T, Kubica A, Jilma B, Alexopoulos D, Navarese E P, Platelet inhibition with standard vs. lower maintenance dose of ticagrelor early after myocardial infarction (ELECTRA): a randomized, open-label, active-controlled pharmacodynamic and pharmacokinetic study, *European Heart Journal - Cardiovascular Pharmacotherapy*, Volume 5, Issue 3, July 2019, Pages 139–148, https://doi.org/10.1093/ehjcvp/pvz004
20. Åstrand M, Amilon C, Röshammar D, et al. Pharmacokinetic-pharmacodynamic modeling of platelet response to ticagrelor in stable coronary artery disease and prior myocardial infarction patients. *Br J Clin Pharmacol*. 2019;85(2):413-421. doi:10.1111/bcp.13812

Dual Antiplatelet Therapy with Ticagrelor vs Clopidogrel in Patients with Acute Coronary Syndrome

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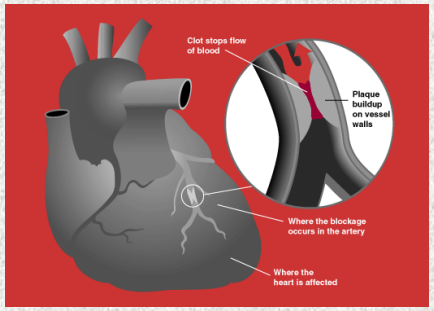

BACKGROUND

Dual antiplatelet therapy (DAPT) is an essential component of treatment after patients suffering from acute coronary syndrome (ACS). Compared to clopidogrel, ticagrelor is not a prodrug and does not require metabolic activation to inhibit the platelet P2Y12 receptor. Therefore, its effect on platelet inhibition is more pronounced compared to clopidogrel.

PURPOSE

- To evaluate the efficacy and safety data of ticagrelor when compared with clopidogrel in patients with ACS.
- To help clinicians in selecting DAPT for ACS patients and therefore further prevent deaths and disabilities in these patients.

METHODOLOGY

The review was conducted using Tripdatabases and Pubmed search engines with terms: “dual antiplatelet therapy,” “antiplatelet monotherapy,” “ticagrelor vs clopidogrel,” “cardiovascular adverse events,” “coronary heart disease,” “acute coronary syndrome,” “myocardial infarction.” Inclusion criteria were retrospective or prospective randomized controlled studies with complete data that recently published. Exclusion criteria were case reports, repeated publications, animal experiments, and studies with incomplete data. 20 studies were selected in this review with 16 studies published within the last five years. Participants were ACS patients who were at least 18 years old with or without ST-elevation in addition to one or more cardiovascular risk factors. In most of the selected studies, the main outcomes were the rate of cardiovascular mortality, MI, stroke, or other atherothrombotic events and the major bleeding risk.
“IRB application has been submitted to Augsburg University Institutional Review Board.”

ANALYSIS & LIMITATIONS

- As a multicenter, double-blinded, and randomized controlled trial with big sample size of 18,624 ACS participants, PLATO trial successfully showed the superior efficacy of DAPT with ticagrelor over DAPT with clopidogrel in reduction of recurrent thrombotic event after ACS, in which a composite of death from vascular causes, stroke, or MI at 12 months had occurred in 9.8% of patients receiving ticagrelor vs 11.7% of those receiving clopidogrel ($P<0.001$).[1]
- ACS patients with prior ischemic stroke or TIA have higher risk of recurrent thrombotic events. Introduction of ticagrelor was also associated with a lower rate of total mortality at 1 year with ticagrelor versus clopidogrel, 7.9% versus 13.0% respectively.[2]
- PEGASUS-TIMI 54 was a randomized trial with 21,162 ACS participants with prior MI again showing the superior efficacy of ticagrelor over placebo, in which 213 patients in the placebo group vs 91 patients in the ticagrelor group experienced stroke at the 30-day follow-up.[3]
- DAPT with ticagrelor was associated with the major bleeding risk in some trials. However, using a reduced dose of ticagrelor (60 mg) or ticagrelor monotherapy had showed a lower risk of this complication.[4]

DISCUSSION

Compared to DAPT with clopidogrel, DAPT with ticagrelor is an effective alternative secondary prevention which better reduces recurrent thrombotic events in patients currently experiencing ACS. The findings from this review would be useful sources for clinicians in selecting DAPT for ACS patients and therefore further prevent deaths and disabilities in these patients.

REFERENCES

1. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057. doi:10.1056/NEJMoa0904327
2. James SK, Storey RF, Khurmi NS, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes and a history of stroke or transient ischemic attack. *Circulation.* 2012;125(23):2914-2921. doi:10.1161/CIRCULATIONAHA.111.082727
3. Bonaca MP, Goto S, Bhatt DL, et al. Prevention of Stroke with Ticagrelor in Patients with Prior Myocardial Infarction: Insights from PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54). *Circulation*. 2016;134(12):861-871. doi:10.1161/CIRCULATIONAHA.116.024637
4. Kim BK, Hong SJ, Cho YH, et al. Effect of Ticagrelor Monotherapy vs Ticagrelor with Aspirin on Major Bleeding and Cardiovascular Events in Patients with Acute Coronary Syndrome: The TICO Randomized Clinical Trial. *JAMA*. 2020;323(23):2407-2416. doi:10.1001/jama.2020.7580

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