Aspirin with Low-Dose Ticagrelor or with Low-Dose Rivaroxaban for Secondary Prevention: A Cost Per Outcome Analysis

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Abstract

Introduction: Secondary prevention of cardiovascular events among patients with diagnosed cardiovascular disease and high ischemic risk poses a significant challenge in clinical practice. The combinations of aspirin with low dose (LD) Ticagrelor or LD-Rivaroxaban have shown superiority in preventing major adverse cardiovascular events (MACE) than aspirin treatment alone. The comparative value for money of these two regimens remains unexplored.

Methods: We analyzed each regimen's annual cost needed to treat (CNT) by multiplying the annualized number needed to treat (aNNT) by the annual cost of each drug. The aNNTs were based on outcome data from PEGASUS TIMI-54 and COMPASS trials. Scenario analyses were performed to overcome variances in terms of population risk. Costs were based on 2021 US prices. The primary outcome was defined as CNT to prevent one MACE across the two regimens. Secondary value analysis was performed for myocardial infarction (MI), stroke, and CV death as separate outcomes.

Results: The aNNTs to prevent MACE with LD-Ticagrelor and with LD-Rivaroxaban were 229 [95% confidence interval (CI):141-734] and 147 (95%CI:104-252), respectively. At an annual cost of 3,618$ versus 4,308$, the corresponding CNTs were 828,478$ (95%CI:510,111$-2,655,471$) with LD-Ticagrelor and 633,270$ (95%CI:448,028$-1,085,607$) with LD-Rivaroxaban. LD-Rivaroxaban.

Conclusion: Combining aspirin with LD-Rivaroxaban provides better value for money than with LD-Ticagrelor for secondary prevention of MACE.

Introduction

Secondary prevention of cardiovascular events among patients with high ischemic risk poses a significant challenge in clinical practice. Despite considerable advances in secondary cardiovascular disease prevention and implementing various effective prevention strategies, the risk for recurrent events among patients with cardiovascular disease remains significant [1]. Therefore, during the last decade, considerable research work was done to pursue measures to improve secondary prevention among patients at high ischemic risk.

Antithrombotic treatments have an immense potential to reduce long-term ischemic risk [2]. While there is a consensus on the importance of combined antithrombotic therapy in the first year after an acute coronary syndrome event [3–5], the debate remains on the long-term optimal treatment for high-risk patients with stable atherosclerosis. The Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS TIMI-54) study [6] was the first to assess the effectiveness of long term dual antiplatelet therapy with (DAPT) with aspirin and low dose Ticagrelor (A+LDT) in preventing major adverse cardiovascular event (MACE) among stable patients with prior myocardial infarction (MI), after 12 months from the sentinel event. In the PEGASUS TIMI-54, long-term A+LDT was superior to aspirin monotherapy in preventing MACE.

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial [7] assessed a novel treatment dual antithrombotic therapy (DAT) of aspirin and low dose Rivaroxaban (A+LDR) among patients with multiple-bed atherosclerosis. The COMPASS trial revealed that A+LDR is superior to aspirin monotherapy in preventing MACE among patients with multi-site atherosclerosis (>90% of whom with proven coronary atherosclerosis).

While the PEGASUS and COMPASS studies had different inclusion criteria and did not represent similar populations, there is considerable overlap between patients indicated for both regimens in real life. Therefore, the European Society of Cardiology guidelines advocate using any of the two antithrombotic regimens to prevent MACE among patients with proven coronary artery disease at high ischemic risk [8].

Previous investigations have suggested that both PEGASUS and COMPASS regimens might be cost-effective [9, 10]. A recent comparative analysis of these two treatments revealed that the COMPASS regimen is more effective in preventing stroke, regardless of cost [11]. In that report, the comparative budget impact of the two regimens regarding other outcomes (MI, CV death, and MACE) depended on the relative drug costs. However, the actual relative value for money and cost-per-outcome of these therapeutic regimens considering real-world pricing remains unknown.

Methods

Data sources for drug efficacy

Outcome data for A+LDT and A+LDR were extracted from the PEGASUS TIMI-54 and COMPASS studies, respectively.

Primary outcome measures

The primary outcome was the cost needed to treat (CNT) to prevent one MACE, defined as the composite of cardiovascular death, myocardial infarction, or stroke. We performed the analyses from the United States healthcare payer perspective. We also performed sensitivity analyses to mitigate the pricing differences between different countries.

Secondary outcomes

Secondary outcomes were the CNT to prevent one event of cardiovascular death, nonfatal myocardial infarction, or stroke as separate clinical outcomes.

Cost Needed to Treat Analysis

The CNT was calculated by multiplying the annualized number needed to treat (aNNT) by the annual therapy cost. Drug costs were calculated as 75% of US National Average Drug Acquisition Cost (NADAC), extracted in September 2020. The aNNT was calculated as one divided by the Annualized absolute risk reduction (aARR), the absolute difference between the annualized absolute risk (aAR) in the control and

treatment arm. The aAR of therapies was calculated by dividing the number of events in each study arm by patient years of treatment.

Sensitivity Analysis

To evaluate the robustness of CNT results and mitigate differences between the randomized controlled trials (RCTs) populations' baseline risk, we performed one-way sensitivity scenario analyses on parameters that may affect the aNNT and CNT figures. Specifically, for this purpose, we accounted for the risk of events in the control arm of the RCTs and the annual costs of the compared interventions. To mitigate the differences in the risk of HF events in the RCTs', we simulated each drug's effect while using each other drug's control arm's event rates. For sensitivity analysis of the cost of therapy, we used the full NADAC price as an upper bound and 50% of NADAC price as the lower bound, as recommended for use in US cost-effectiveness analyses [12]. To address pricing differences between US and European countries, we calculated the CNT in Germany, based on published tariffs, as a representative country from the EU where many drug prices are significantly lower than in the US.

Results

Patient populations

The baseline characteristics of the PEGASUS TIMI-54 and COMPASS trials participants are detailed in Table 1. As both studies were comparable in terms of patients' age, gender, ethnicity, and traditional atherosclerotic risk factors, the main differences between the studies' populations were expressed by higher rates of peripheral artery disease in the COMPASS trial (27.2% vs. 5.2%) and higher rates of previous MI in the PEGASUS TIMI-54 trial (100% vs. 61.8%)

Table 1
Key Characteristics of the PEGASUS TIMI-54 and COMPASS trials intervention groups

Intervention	Aspirin + low dose Ticagrelor	Aspirin + low dose Rivaroxaban
Trial	PEGASUS TIMI-54	COMPASS
Mean follow up (months)	33	23
Age (Mean)	65.2	68.3
White (%)	86.3%	62%
Female sex (%)	23.6%	22.5%
Coronary artery disease (%)	100%	90.8%
Peripheral artery disease (%)	5.2%	27.2%
Diabetes (%)	32.8%	37.7%
Hypertension (%)	77.5%	75.5%
Tobacco use (%)	17.1%	21.2%
Previous myocardial infarction (%)	100%	61.8%

A, aspirin; LD, low dose; PEGASUS TIMI-54, Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies

Annualized number needed to treat, and cost needed to treat

The step-by-step calculations of the annualized NNT and CNT are detailed in Table 2. The annual drug costs were 3,617.81$ for A+LDT and 4,308$ for A+LDR. The CNT to prevent MACE 633,271$ (95%CI:448,028$-1,085,608$) for A+LDR and 828,478$ (95%CI:510,111$-2,655,471$) for A+LDT.

Table 2
Step-by-step calculations of the annualized cost needed to treat

Parameter	PEGASUS TIMI-54 (A+LD Ticagrelor)	COMPASS (A+LD Rivaroxaban)
Number of patients in the Control Arm	7067	9126
Patient years of therapy in the Control Arm	21201	17491.5
Number of events - control arm	578	496
Annualized event rate - control arm	578/21201=2.73%	496/17491.5=2.84%
Number of patients - intervention arm	7045	9152
Patient years of therapy - intervention arm	21135	17541.33
Number of events - intervention arm	484	378
Annualized Event Rate - intervention Arm (95% CI)	484/21135=2.29% (2.02%-2.59%)	378/17541.33=2.16% (1.87%-2.44%)
Absolute Event Rate Reduction (annualized) (95% CI)	2.73%-2.29%=0.44% (0.14%-0.71%)	2.84%-2.16%=0.68% (0.40%-0.96%
Annualized Number Needed to Treat (95% CI)	1/0.44%=229 (141-734)	1/0.68%=147 (104-252)
Annual drug cost	$3,617.81	$4,307.97
Cost Needed To Treat to prevent one event (95% CI)	229*$3,617.81=$828,478 ($510,111-$2,655,472)	147*$4,307.97=$633,270 ($448,028-$1,085,607)
* In cases that the hazard ratio is higher than one, the NNT to benefit is defined as ∞, and the corresponding CNT is also ∞		
A, aspirin; LD, low dose		

Scenario and secondary outcomes analyses

The CNT results of the scenario and secondary outcomes are presented in Figure 1. A+LDR regimen had lower CNT compared with A+LDT regimen to prevent cardiovascular death or stroke. Conversely, the CNT to prevent nonfatal myocardial infarction was lower with the A+LDT regimen than with the A+LDR regimen.

Sensitivity Analyses

Table 3 details the results of the sensitivity analysis performed accounting for EU prices. LDT and LDR were much cheaper in the EU than in the US (942.61€ vs. 3,617.81$ and 1,194.82€ vs. 4,307.97$, respectively). With respect to EU prices, the CNT to prevent MACE was lower for A+LDR than A+LDT [175,638€ (95%CI: 124,261€-301,094€) vs. 215,858€ (95%CI: 132,908€-691,878€), respectively].

Table 3
Sensitivity analysis accounting for European Union average prices

Price Estimate	Annual cost-A+LD Ticagrelor	Annual cost-A+LD Rivaroxaban	CNT – A+LD Ticagrelor	CNT -A+LD Rivaroxaban
Baseline (75% of US NADAC)	$3,617.81	$4,307.97	$828,478 ($510,111-$2,655,472)	$633,270 ($448,028-$1,085,607)
US – Low Estimate	$2,412	$2,872	$552,319 ($340,074-$1,770,314)	$422,181 ($298,686-$723,738)
US- High Estimate	$4,824	$5,744	$1,104,638 ($680,148-$3,540,629)	$844,361 ($597,371-$1,447,476)
EU (Germany)	€942.61	€1,194.82	€215,858 (€132,908-€691,878)	€175,638 (€124,261-€301,094)

A, aspirin; LD, low dose; CNT, cost needed to treat; US, United States; EU, European Union

Discussion

In this report, we examined the comparative cost-per-outcome of A+LDT (i.e., PEGASUS) and A+LDR (i.e. COMPASS) regimens to prevent MACE among patients at high ischemic risk in secondary prevention settings. The results suggest that the COMPASS regimen provides lower NNTs and CNTs for preventing MACE compared to the PEGASUS regimen. Specifically, the COMPASS regimen was more valuable in preventing cardiovascular death and stroke than the PEGASUS regimen. However, the PEGASUS regimen had more considerable clinical and economic efficacy in preventing myocardial infarction events. Of course, CNTs are sensitive to the drug's relative costs, but in this comparison, despite the considerably higher annual cost of LDR compared with LDT (4308$ vs. 3,618$, respectively), corresponding with the NNTs differences. Despite considerable differences in drugs prices between US and EU, the CNT to prevent MACE in the EU was lower with A+LDR than A+LDT, similar to the US.

Despite considerable advances in secondary prevention measures, cardiovascular morbidity and mortality rates among patients at high ischemic risk are still high and present a challenge in clinical practice [1, 2, 8]. Currently, the ESC guidelines advocate using either the COMPASS or PEGASUS regimens for long-term secondary prevention in patients at high ischemic risk in whom MACE is the primary concern [8]. The PEGASUS TIMI-54 trial [6] examined the efficacy of long-term A+LDT in preventing MACE

among stable patients with myocardial infarction diagnosed more than 12 months before the study. Conversely, the COMPASS trial [7] explored the effect of A+LDR regimen in preventing MACE among patients with stable coronary artery disease, peripheral artery disease, or both. As a derivative of their inclusion criteria, the PEGASUS TIMI-54 and COMPASS trials included slightly different patient populations. Notably, the COMPASS trial included more patients with diagnosed peripheral arterial disease than PEGASUS TIMI-54 (27.2% vs. 5.2%, respectively). Unlike the PEGASUS TIMI-54 trial, where all patients had a previous myocardial infarction, 61.8% of the patients in the COMPASS trial had a background of myocardial infarction.

Despite these baseline differences in the profile of the atherosclerotic disease, patients in both trials were in the same age range and had similar risk factor profiles. To account for the possible differences between the patient populations of these two studies, we also performed scenario analyses where each intervention group effect was compared with the placebo group results of the comparative study. The results of these sensitivity analyses revealed that, regardless of the compared control group, A+LDR was more cost-saving than A+LDT for preventing MACE, while A+LDT was more cost-saving in preventing re-coronary events specifically. Another substantial difference between the COMPASS and PEGASUS TIMI-54 trials was the mean follow-up time, 23 months and 33 months, respectively. Thus, to avoid comparing clinical impact in such odd follow-up lengths, we compared these two regimens' yearly standardized (annualized) NNTs and CNTs.

Another critical issue to consider is the counterbalance of the decrease in thrombotic events by increased risk for bleeding under intensified long-term antithrombotic regimen [13]. In that perspective, both COMPASS and PEGASUS TIMI-54 trials showed a clear net clinical benefit for those treatments, favoring the antithrombotic outcomes over the significant bleeding events. However, choosing suitable patients by assessing the ischemic versus bleeding risk is essential and probably irreplaceable when tailoring personalized antithrombotic treatment regimens [14, 15].

Importantly, these two antithrombotic regimens were separately shown as cost-effective in analyses based on the original RCTs populations [9, 10]. A recent study that analyzed the relative budget impact of these two regimens showed the superiority of A+LDR over A+LDT in preventing stroke, regardless of cost differences between drugs and a similar relative economic advantage in the prevention of CV death with an extensive margin of cost differences [11]. Comparatively, A+LDT regimen showed an economic advantage in preventing MACE and MI, where A+LDR had a comparable economic impact only when the pricing of that regimen was 30-40% cheaper than A+LDR. While this study provided a sense of the cost per outcome effectiveness of these two treatments, it did not provide practical and current evidence on the cost per outcome in real-life settings. The current report provides information on the cost-per-outcome of the A+LDR vs. A+LDT regimens, combining real-world pricing with findings from the landmark RCTs. Thus, it may be of value for healthcare providers and national health economists when deciding on a specific long-term treatment plan or examining the subsidization of these two treatments for different indications.

Our analysis has several limitations. The significant inherent limitation is that the PEGASUS TIMI-54 trial had a different patient population than the COMPASS trial (Table 1). Our sensitivity analysis attempted to overcome these differences to ensure our primary analysis by simulating each drug's effect in each RCT. A second limitation is that our analysis cannot replace a comprehensive cost-effectiveness evaluation regarding achieved QALYs, and cost savings from preventing MACE. Nevertheless, although warranted, direct complete economic comparisons of these interventions are unavailable at this time, although a comparative budget impact analysis has been published [11]. Another limitation is that the CNT figure relies mainly on annual NNT estimates, which has many limitations by itself. However, NNT has been found helpful for assisting decision-making in many clinical settings and is required by the Consolidated Standards of Reporting Trials (CONSORT) statement to be reported in RCT publications [16]. Annualizing the NNT to compare RCTs and therapies has been suggested and utilized in previous comparable studies [17].

In conclusion, among patients with high ischemic risk, In the USA healthcare setting, the COMPASS regimen with A+LDR provides better value for money than the PEGASUS regimen with A+LDR for secondary prevention of MACE. However, the PEGASUS regimen is more efficient and has a higher value for money than the COMPASS regimen in preventing MI and should be considered in cases where this is the primary concern.

Declarations

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COMPETING INTERESTS

None of the authors has any competing interest related to this work

AUTHOR CONTRIBUTIONS

Gal Tsaban, Hilmi Alnasasra, and Ronen Arbel conceived the study and analysis. Material preparation and data collection were performed by Gal Tsaban, Hilmi Alnasasra, Aref El-Nasasra, Amjad Abu-Salman, and Enis Aboalhasan. Statistical analysis was performed by Enis Aboalhasan and was reviewed by Ariel Hammerman and Joseph Azuri. The first draft of the manuscript was written by Gal Tsaban, Hilmi Alnsasra, and Ronen Arbel. All authors critically reviewed the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL

This work is based on previously published RCT’s and does not include new research in humans or animals. Thus, no ethical aspects are relevant to this work.

CONSENT TO PARTICIPATE AND/OR PUBLISH

This manuscript is based on information from previously published RCTs and from published tariffs and does not directly involve human subjects. Thus, consent declaration is irrelevant to this paper.

DATA AVAILABILITY

Study's data will be available upon request.

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Figures

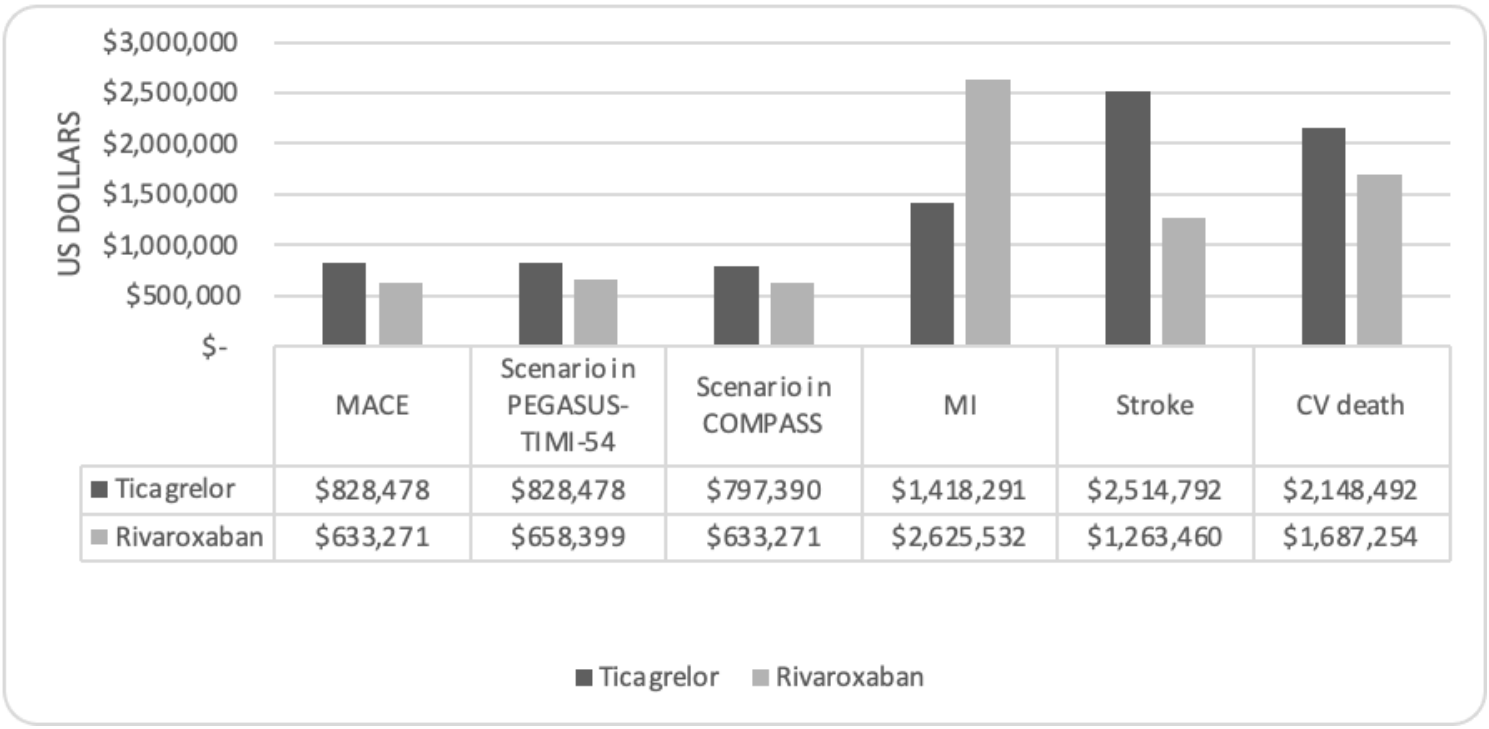

Figure 1

Annualized Cost Needed to Treat Analyses across outcomes and scenario analyses

MACE, major adverse cardiovascular event; 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; COMPASS, Cardiovascular Outcomes for People Using Anti-Coagulation Strategies; MI, myocardial infarction; CV, cardiovascular; CVM: cardiovascular mortality.