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

Gal Tsaban1,2 · Hilmi Alnsasra1,2 · Aref El Nasasra1,2 · Amjad Abu-Salman1,2 · Ala Abu-Dogosh1,2 · Itay Weissberg1,2 · Yael Ben-Baruch Golan1,2 · Orit Barrett1,2 · Roi Westreich1,2 · Enis Aboalhasan3 · Joseph Azuri4,5 · Ariel Hammerman6 · Ronen Arbel3,7

Accepted: 1 July 2022 / Published online: 23 July 2022 © The Author(s), under exclusive licence to Springer Nature Switzerland AG 2022

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) compared with 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 COM-PASS trials. Scenario analyses were performed to overcome variances in terms of population risk. Costs were calculated as 75% of US National Average Drug Acquisition Cost (NADAC), extracted in January 2022. 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 cardiovascular 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 US$3726 versus US$4533, the corresponding CNTs were US$853,254 (95% CI 525,366–2,734,884) with LD ticagrelor and US$666,351 (95% CI 471,432–1,142,316) with LD rivaroxaban.

Conclusion Combining aspirin with LD rivaroxaban provides better value for money than with LD ticagrelor for secondary prevention of MACE.

Key Points

Among patients with known cardiovascular disease and high ischemic risk, a combination of aspirin with low-dose (LD) rivaroxaban provides better value for money to prevent major adverse cardiovascular events, compared with aspirin and LD ticagrelor, despite higher annualized costs.

However, LD ticagrelor showed lower cost needed to treat to prevent myocardial infarction, suggesting economic preferability compared with LD rivaroxaban in patients with a specific high risk for acute coronary events.
1 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 implementation of 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 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) study [6] was the first to assess the effectiveness of long-term dual antiplatelet therapy (DAPT) with aspirin and low-dose ticagrelor (A+LDT) in preventing major adverse cardiovascular events (MACE) among stable patients with prior myocardial infarction (MI), after 12 months from the sentinel event. In 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 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 had proven coronary artery disease). 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 (ESC) 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 PEGASUS and COMPASS regimens might be cost-effective, corresponding to an incremental cost-effectiveness ratio (ICER) of US$94,917 and AUD$26,769 (Australian dollars) per quality-adjusted life-year (QALY) gained [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, cardiovascular death, and MACE) depended on the relative drug costs. However, these therapeutic regimens' actual relative value for money and cost per outcome considering real-world pricing remain unknown. In this study, we aimed to assess and compare the cost per outcome of the COMPASS and PEGASUS regimens with respect to current real-world pricings.

2 Methods

2.1 Data Sources for Drug Efficacy

Outcome data for A+LDT and A+LDR were extracted from the PEGASUS TIMI-54 and COMPASS studies, respectively [6, 7].

2.2 Primary Outcome Measures

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

2.3 Secondary Outcomes

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

2.4 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 based on the 2022 US pricing, calculated as 75% of the US National Average Drug Acquisition Cost (NADAC), extracted in January 2022. The reported risk ratios for MACE in the PEGASUS TIMI-54 [for aspirin + ticagrelor 60 mg twice daily (BID)] and COMPASS (for aspirin + rivaroxaban 2.5 mg BID) trials were 0.84 [95% confidence interval (CI) 0.74–0.95] and 0.76 (95% CI 0.66–0.86), respectively. 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 arms. The aAR of therapies was calculated by dividing the number of events in each study arm by patient-years of treatment.
2.5 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 the primary outcome 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 the NADAC price as the lower bound, as recommended for US cost-effectiveness analyses [12]. To address pricing differences between the USA and European countries, we calculated the CNT in Germany and the United Kingdom (UK) based on published tariffs [13]. Germany and the UK represent economically stable European countries that, unlike most European countries, publish official medication tariffs regularly; thus, we chose these countries as representatives of Europe, where many drug prices are significantly lower than in the USA.

3 Results

3.1 Patient Populations

The baseline characteristics of the PEGASUS TIMI-54 and COMPASS trial 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%).

3.2 Annualized Number Needed to Treat, and Cost Needed to Treat

The step-by-step calculations of the aNNT and CNT are detailed in Table 2. The annual drug costs were US$3726 for A+LDT and US$4533 for A+LDR. The CNT to prevent MACE was US$853,254 (95% CI 525,366–2,734,884) for A+LDT and US$666,351 (95% CI 471,432–1,142,316) for A+LDR.

3.3 Scenario and Secondary Outcomes Analyses

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

3.4 Sensitivity Analyses

Table 3 details the sensitivity analysis performed accounting for European Union (EU) prices. A+LDT and A+LDR were much cheaper in Germany and in the UK than in the USA (£943 and £712 vs. US$3726 and £1195 and £657 vs. US$4533, respectively). With respect to EU prices, the CNT to prevent MACE was lower for A+LDR than A+LDT both in Germany and in the UK [€175,638 (95% CI 124,261–301,094) vs. €215,858 (95% CI 132,908–691,878), respectively] and UK [£96,538 (95% CI 68,145–165,494) vs. £147,625 (95% CI 98,417–393,667), respectively].

4 Discussion

In this study, 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 than 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 greater clinical and economic efficacy in preventing MI. Of course, CNTs are sensitive to the drug’s relative costs, but in this comparison, despite the considerably higher annual cost of A+LDR compared with A+LDT (US$4533 vs. US$3726, respectively), the cost per outcome remained in favor of A+LDR, as driven by the differences in NNTs. Despite remarkable differences in drug prices between the USA and the EU, the CNTs to prevent MACE in the EU and

### Table 2 Step-by-step calculations of the annualized cost needed to treat (US$)

| 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    | 21,201                             | 17,491.5                    |
| Number of events—control arm                   | 578                                | 496                         |
| Annualized event rate—control arm              | 578/21,201 = 2.73%                 | 496/17,491.5 = 2.84%        |
| Number of patients—intervention arm            | 7045                               | 9152                        |
| Patient years of therapy—intervention arm      | 21,135                             | 17,541                      |
| Number of events—intervention arm              | 484                                | 378                         |
| Annualized event rate—intervention arm (95% CI)| 484/21,135 = 2.29% (2.02–2.59)     | 378/17,541 = 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 NNT (95% CI)                        | 1/0.44% = 229 (141–734)            | 1/0.68% = 147 (104–252)     |
| Annual drug cost                               | US$3726                            | US$4533                     |
| CNT to prevent one event (95% CI)              | 229 × US$3726 = US$853,254 (525,366–2,734,884) | 147 × US$4533 = US$666,351 (471,432–1,142,316) |

In cases where the hazard ratio is > 1, the NNT to benefit is defined as ∞, and the corresponding CNT is also ∞.

*A aspirin, BID twice daily, CI confidence interval, CNT cost needed to treat, COMPASS Cardiovascular Outcomes for People Using Anticoagulation Strategies, LD low-dose, NNT number needed to treat, 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

**LD ticagrelor: 60 mg BID; LD rivaroxaban: 2.5 mg BID**
in the UK were lower with A+LDR than A+LDT, consistency with the USA.

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 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 MI, 61.8% of the patients in the COMPASS trial had a background of MI.

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. It is also important to acknowledge that although there are differences in the design and populations included in these studies, the A+LDR and A+LDT regimens were generally developed to treat patients with a similar profile who have proven clinical atherosclerotic disease along with high ischemic risk. The great overlap in these regimens’ indications is also reinforced by the ESC guidelines, where these two regimens were recommended under the same indication of prolonged antithrombotic treatment options for patients with high ischemic risk [8].

Another critical issue to consider is the counterbalance of the decrease in thrombotic events by increased risk for bleeding under intensified long-term antithrombotic regimens [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 RCT populations [9, 10]. While the A+LDT regimen showed intermediate cost-effectiveness with a QALY of 0.078 and an ICER of US$94,917 per QALY-gained, specific high-risk subgroups of patients had more favorable ICERs, leaving some uncertainty concerning the cost-effectiveness of this regimen. Our findings are well in line with these reports regarding the cost estimation of the two regimens, yet add the comparative value for money considering the real-world prices and the reported clinical efficacy of these two regimens. The results of our study are consistent with a recent study that analyzed the relative budget impact of these two regimens and 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 preventing cardiovascular death with an extensive margin of...
cost differences [11]. Comparatively, the A+LDT regimen showed an economic advantage in preventing MACE and MI, whereas A+LDR had a comparable economic impact only when the pricing of that regimen was 30–40% cheaper than A+LDT. 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 to that of 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, while a comparative budget impact analysis has been published [11]. Also, actual costs widely differ according to patients’ insurance coverage, yet the relative drug costs, even in the case of subsidization, are affected by the NADAC. Thus, and since the full NADAC is infrequently charged, we used 75% of that price, which serves as an expected estimation of the average pricing in real life. In that perspective, it is also essential to recognize that the insurance cost counterbalances the lower drug costs with private insurance. Therefore, CNT analyses provide a good proxy for comparing different medications’ actual costs. Another limitation is that the CNT figure relies mainly on annual NNT estimates, which have many limitations by themselves. 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] and has also been shown to be of greater fit than absolute NNT to reflect actual differences between drugs [18] credibly. It should also be noted that the current study addressed the CNT to prevent ischemic events, but not the possible occurrence of significant bleeding events, which might potentially impact the cost of management. Although, it should also be highlighted that this analysis relies on the COMPASS and PEGASUS TIMI-54 trials, where the net clinical benefit was clearly driven by a reduction in ischemic events [6, 7].

In conclusion, among patients with high ischemic risk, in the US healthcare setting, the COMPASS regimen with A+LDR provides better value for money than the PEGASUS regimen with A+LDT 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 patients who are especially prone to this specific condition.

Declarations

Funding This work has not been funded by external grants.

Competing interests Gal Tsaban, Hilmi Alnsasra, Aref El Nasasra, Amjad Abu-Salman, Ala Abu-Dogosh, Itay Weissberg, Yael Ben-Baruch Golan, Orit Barrett, Roi Westreich, Enis Aboualhasan, Joseph Azuri, Ariel Hammerman, and Ronen Arbel declare no competing interest related to this work or any relevant conflicts of interest.

Author contributions GT, HA, and RA conceived the study and analysis. Material preparation and data collection were performed by GT HA, AEN, AAS, and EA. Statistical analysis was performed by EA and was reviewed by AH and JA. The first draft of the manuscript was written by GT, HA, and RA. All authors critically reviewed the manuscript. All authors read and approved the final manuscript.

Ethics approval Not applicable.

Code availability Not applicable.

Consent to participate and/or publish Not applicable.

Data availability statement The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA J Am Med Assoc [Internet]. American Medical Association 2010;304:1350–7. https://jamanetwork.com/journals/jama/fullarticle/186626. Accessed 12 Oct 2021.

2. Capodanno D, Alberts M, Angiolillo DJ. Antithrombotic therapy for secondary prevention of atherothrombotic events in cerebrovascular disease. Nat Rev Cardiol [Internet]. Nat Rev Cardiol 2016;13:609–22. https://pubmed.ncbi.nlm.nih.gov/27489191/. Accessed 12 Oct 2021.

3. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes: commentary. Rev Port Cardiol [Internet]. Massachusetts Medical Society 2007;26:1297–8. https://doi.org/10.1056/nejmoa0706482. Accessed 12 Oct 2021.

4. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsen H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med [Internet]. Massachusetts Medical Society 2009;361:1045–57. https://doi.org/10.1056/nejmoa0904327. Accessed 12 Oct 2021.

5. Investigators TC in UA to PRET. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without

△ Adis
Ticagrelor or Rivaroxaban for Secondary Prevention

1. st-segment elevation. N Engl J Med [Internet]. Massachusetts Medical Society 2001;345:494–502. https://doi.org/10.1056/nejmoa010746. Accessed 12 Oct 2021.

2. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med [Internet]. Massachusetts Medical Society 2015;372:1791–800. https://doi.org/10.1056/nejmaa1500877. Accessed 12 Oct 2021.

3. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med [Internet]. Massachusetts Medical Society 2017;377:1319–30. https://doi.org/10.1056/nejmaa000740. Accessed 12 Oct 2021.

4. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur Heart J [Internet]. Oxford Academic 2018;39:213–54. https://academic.oup.com/eurheartj/article/39/3/213/4095043. Accessed 12 Oct 2021.

5. Zomer E, Si S, Hird TR, Liew D, Owen AJ, Tonkin A, et al. Cost-effectiveness of low-dose rivaroxaban and aspirin versus aspirin alone in people with peripheral or carotid artery disease: An Australian healthcare perspective. Eur J Prev Cardiol [Internet]. 2019;26:858–68. https://pubmed.ncbi.nlm.nih.gov/30526023/. Accessed 12 Oct 2021.

6. Magnuson EA, Li H, Wang K, Vilain K, Shafiq A, Bonaca MP, et al. Cost-Effectiveness of Long-Term Ticagrelor in Patients With Prior Myocardial Infarction: Results From the PEGASUS-TIMI 54 Trial. J Am Coll Cardiol [Internet]. J Am Coll Cardiol 2017;70:527–38. https://pubmed.ncbi.nlm.nih.gov/28750695/. Accessed 12 Oct 2021.

7. Brunetti ND, De Gennaro L, Correale M, Ieva R, Santoro F. COMPASS vs PEGASUS approach in a comparative budget impact analysis. Eur J Intern Med [Internet]. Elsevier 2021;83:102–4. http://www.ejin.me/article/S0953620520303794/fulltext. Accessed 12 Oct 2021.

8. Levy J, Rosenberg M, Vanness D. A transparent and consistent approach to assess US outpatient drug costs for use in cost-effectiveness analyses. Value Heal [Internet]. Value Health 2018;21:677–84. https://pubmed.ncbi.nlm.nih.gov/29909872/. Accessed 8 Nov 2021.

9. Drug Tariff NHSBSA [Internet]. 2022. https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff. Accessed 28 Jun 2022.

10. Magnus G, Ardissino D, Im KA, Budaj A, Storey RF, Steg PG, et al. Predictors, type, and impact of bleeding on the net clinical benefit of long-term ticagrelor in stable patients with prior myocardial infarction. J Am Heart Assoc [Internet]. American Heart Association Inc. 2021;10:1–9. https://doi.org/10.1161/JAHA.120.017008. Accessed 12 Oct 2021.

11. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ [Internet]. British Medical Journal Publishing Group 2010;340:698–702. https://www.bmj.com/content/340/bmj.c332. Accessed 8 Nov 2021.

12. Chew DP, Huynh LT, Liew D, Astley C, Soman A, Brieger D. Potential survival gains in the treatment of myocardial infarction. Heart [Internet]. Heart 2009;95:1844–50. https://pubmed.ncbi.nlm.nih.gov/19666459/. Accessed 12 Oct 2021.