Estimated Aggregate Treatment Benefit
With Addition of Multiple Novel Medications
for Secondary Prevention of Atherosclerotic
Cardiovascular Disease

Robert W. Ariss, BS\textsuperscript{1}, and Rajesh Gupta, MD\textsuperscript{1}\textsuperscript{e}

Abstract

Purpose: Interest in improving residual cardiovascular (CV) risk by targeting multiple causative pathways has been growing. Several medications including icosapent ethyl, rivaroxaban, and ezetimibe have been shown to individually improve outcomes in the secondary prevention of atherosclerotic cardiovascular disease (ASCVD) beyond conventional therapy consisting of aspirin and statins. While each drug has been shown to individually improve outcomes, the expected treatment benefit of the combined use of these drugs for enhanced secondary prevention of ASCVD is not known. Methods: In this cross-trial analysis, we estimated the aggregate treatment effect of comprehensive medical therapy consisting of icosapent ethyl, rivaroxaban, and ezetimibe added to background aspirin and statin therapy through established methods of indirect comparisons of the results of three key clinical trials (REDUCE-IT [n = 8,179], COMPASS [n = 27,395], and IMPROVE-IT [n = 18,144]). The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal stroke. Secondary endpoints included each individual component of the primary endpoint. Results: The hazard ratio (HR) of the imputed aggregate treatment effects for enhanced secondary prevention of ASCVD with comprehensive disease modifying therapy compared to aspirin and statin alone for the primary endpoint was 0.51 (95% confidence interval [CI] 0.42-0.61). The HR for CV death was 0.62 (95% CI 0.46-0.85), non-fatal MI was 0.52 (95% CI 0.40-0.69), and non-fatal stroke was 0.35 (95% CI 0.23-0.54). The results were similar in sensitivity analyses. Conclusion: The estimated aggregate treatment effect of enhanced secondary prevention of ASCVD through comprehensive medical therapy is substantial. This exploratory analysis supports further study of comprehensive therapy to reduce residual CV risk for the secondary prevention of ASCVD.

Keywords

secondary prevention, atherosclerotic cardiovascular disease, coronary artery disease, peripheral artery disease, residual cardiovascular risk

Introduction

Aspirin and high-intensity statin therapy are recommended for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD).\textsuperscript{1} Despite background aspirin and statin medical therapy, patients with ASCVD have residual cardiovascular (CV) risk and are at substantial risk for recurrent adverse CV events. Similar to the multidrug treatment regimen utilized for heart failure with reduced ejection fraction (HFrEF), interest in multimodal reduction of residual CV risk for ASCVD through targeting of additional disease pathways, such as lipid, thrombotic, or inflammatory pathways has been growing.\textsuperscript{2-4} Recent randomized controlled trials (RCTs) have assessed added medications such as icosapent ethyl, rivaroxaban, or ezetimibe for the secondary prevention of ASCVD and have individually demonstrated significant reductions in adverse events. Moreover, in a recent study assessing eligibility of patients with prior MI for multiple secondary prevention therapies, 30%-40% of patients were eligible for three additional drug classes beyond statins, and these patients had increased rates of recurrent major cardiovascular events compared with those who were not eligible for novel therapies.\textsuperscript{5} However, to our

\textsuperscript{1} Division of Cardiovascular Medicine, University of Toledo College of Medicine, Toledo, OH, USA

Manuscript submitted: December 15, 2021; accepted: February 15, 2022.

Corresponding Author:

Rajesh Gupta, Division of Cardiovascular Medicine, University of Toledo, 3000 Arlington Ave, MS# 1118, Toledo, OH 43614, USA.

Email: rajesh.gupta@utoledo.edu

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
knowledge, the treatment effect of a combination therapy of these novel agents has yet to be described. We sought to determine the aggregate treatment effect of multiple medications added to aspirin and statin therapy for enhanced secondary prevention of ASCVD.

Methods

Randomized placebo-controlled trials evaluating outcomes of novel secondary prevention therapies were included within this study. It is unlikely that patients will be on multiple novel drugs that target similar therapeutic pathways (ie, ticagrelor and rivaroxaban); therefore, studies targeting different biological pathways in pivotal RCTs were chosen. This method for selection has been previously used in a study describing the eligibility of real-world patients with prior MI or ischemic heart disease for multiple novel secondary prevention medications from recent RCTs.6

Results from the IMPROVE-IT (n = 18,144), COMPASS (n = 18,144), and REDUCE-IT (n = 8,179) RCTs were analyzed to assess the imputed aggregate treatment effect for enhanced secondary prevention therapy added to background aspirin and statin treatment.6–8 In brief, the IMPROVE-IT trial studied the addition of ezetimibe to statin for the secondary prevention of cardiovascular events. The COMPASS trial studied the addition of rivaroxaban with or without aspirin for the secondary prevention of cardiovascular events. In this trial, data from the low-dose rivaroxaban plus aspirin arm were utilized. Finally, the REDUCE-IT trial studied the addition of icosapent ethyl to statin therapy for the primary or secondary prevention of cardiovascular events. All of the trials except REDUCE-IT were solely secondary prevention trials. REDUCE-IT included approximately 70% secondary prevention subjects and 30% primary prevention subjects. In addition, a post hoc analysis which included the same study population from the REDUCE-IT trial analyzed for total ischemic events was used to extract the relevant remaining baseline characteristics.9

Statistical Analysis

All trials were assessed for the composite endpoint of CV death, non-fatal myocardial infarction, or non-fatal stroke and each individual component of this composite to ascertain the treatment effect for a similar study endpoint. Baseline characteristics, HRs and associated 95% confidence intervals (CI) for the endpoints were extracted from the RCTs. Established methods for indirect comparisons were used to estimate the imputed aggregate treatment effect as reported previously.10,11 In a study by Mills et al, imputed additive treatment effects by indirect comparisons of combination therapies were shown to demonstrate similar estimates to combination therapies studied directly within trials.11 To calculate the additive treatment effect, selected drugs should target different biological pathways to minimize interaction effects and provide a reasonable additivity assumption.11 In addition, well-designed RCTs of the single agents with minimal biases (high loss to follow-up, small sample size, etc.) are preferred.11 Extracted HRs were log transformed and summed to estimate the effect of combination therapy. Next, 95% CIs for the combination therapy were calculated from the square root of the sum of the squared standard errors of log transformed HRs.10,11 In a sensitivity analysis, the results from the IMPROVE-IT trial results were replaced with those from the ODYSSEY OUTCOMES which studied the addition of alirocumab to statin for the secondary prevention of cardiovascular events.12 The IMPROVE-IT trial was replaced as the effect sizes of ezetimibe on the endpoints were modest.

Statistical analyses and hazard ratios with confidence intervals (CI) were displayed on forest plots using GraphPad Prism V9.00 (GraphPad Software, San Diego, California, United States). This study was exempt from local Institutional Review Board approval as the data were extracted from previously published RCTs.

Results

Baseline Characteristics and Trial Hazard Ratios

Baseline characteristics of the IMPROVE-IT, COMPASS, and REDUCE-IT trial are listed in Table 1. All three trials enrolled a lower proportion of female patients. In addition, the REDUCE-IT trial had an increased prevalence of hypertension and diabetes mellitus consistent with the high-risk population studied within this trial. The trials had a similar amount of lipid-lowering/statin and antiplatelet/aspirin agents as part of background medical therapy.

The HR for the reduction of the composite endpoint from the individual trials for CV death, non-fatal myocardial infarction, or non-fatal stroke of icosapent ethyl was 0.74 (95% CI 0.65-0.83), ezetimibe was 0.90 (95% CI 0.84-0.96), and rivaroxaban was 0.76 (95% CI 0.66-0.86; Figure 1A). The HRs for the individual endpoints of CV death, non-fatal MI, or non-fatal stroke for each therapy are seen in Figure 1B to D.

Imputed Aggregate Treatment Benefit

For the composite endpoint of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke, there was a HR 0.51 (95% CI 0.42-0.61) with comprehensive therapy (Figure 1A). The HRs for each individual endpoint were estimated at 0.62 (95% CI 0.46-0.85) for CV death, 0.52 (95% CI 0.40-0.69) for non-fatal MI, and 0.35 (95% CI 0.23-0.54) for non-fatal stroke (Figure 1B-D).

In the sensitivity analyses, we replaced ezetimibe with alirocumab using the data from the ODYSSEY OUTCOMES trial and found similar results.12 We also add colchicine based on data from LoCoDo2 and found even stronger treatment benefits. Also, we utilized the overall trial results for REDUCE-IT because detailed results for individual endpoints have not been reported for the secondary prevention cohort of REDUCE-IT. Although REDUCE-IT secondary prevention cohort results for each individual component of the composite endpoint are not reported, the results for the composite endpoint of CV death, non-fatal MI, and non-fatal stroke in the secondary prevention
Table 1. Baseline Characteristics of the IMPROVE-IT, COMPASS, and REDUCE-IT Trials.

| Comparison | IMPROVE-IT (n = 18,144) | COMPASS (n = 27,395) | REDUCE-ITa (n = 8,179) |
|------------|-------------------------|----------------------|------------------------|
| Comparison | Ezetimibe plus Simvastatin vs Simvastatin alone | Low-dose rivaroxaban plus aspirin vs rivaroxaban alone vs aspirin alone | Icosapent ethyl vs placebo |
| Enrollment period | 2005-2010 | 2013-2016 | 2011-2016 |
| Follow-up, months | 72 months | 23 months | 58.8 months |

Demographics and comorbidities

| Age, years | 64 | 68.2 | 64 |
| Female | 4,416 (24.3%) | 6,020 (22.0%) | 2,357 (28.8%) |
| Hypertension | 11,137 (61.4%) | 20,632 (75.3%) | 7,084 (86.6%) |
| Diabetes | 4,933 (27.2%) | 10,341 (37.7%) | 4,787 (58.5%) |
| Smoking or tobacco use | 5,978 (32.9%) | 5,867 (21.4%) | Not Reported |
| Heart failure | 790 (4.35%) | 5,902 (21.5%) | 1,446 (17.7%) |

Medications

| Lipid-lowering agent or statin use | Statin: 18,144 (100%) | Lipid-Lowering Agent: 24,601 (89.8%) | Statin: 8,145 (99.6%) |
| Antiplatelet agent or aspirin use | Aspirin: 17,592 (97.0%) | Aspirin: 100%b | Antiplalette Agent: 6,493 (79.4%) |
| Enrollment period | 2005-2010 | 2013-2016 | 2011-2016 |
| Average follow-up, months | 72 months | 23 months | 58.8 months |

aBaseline characteristics compiled from the REDUCE-IT trial and Total Ischemic Events post hoc analysis.9
bData extracted for aspirin use for COMPASS trial are based on the low-dose rivaroxaban plus aspirin versus aspirin alone cohorts. All patients in these cohorts received aspirin.

Figure 1. Estimated treatment effects of enhanced secondary prevention of ASCVD on key cardiovascular events. A, Hazard ratio of the imputed aggregated treatment effect (red) on the primary outcome of CV death, non-fatal MI, or non-fatal stroke. B, Hazard ratio of the imputed aggregated treatment effect (red) on the secondary outcome of CV death. C, Hazard ratio of the imputed aggregated treatment effect (red) on the secondary outcome of non-fatal MI. D, Hazard ratio of the imputed aggregated treatment effect (red) on the secondary outcome of non-fatal stroke. CV indicates cardiovascular; MI, myocardial infarction; HR, hazard ratio; CI, confidence interval.
cohort have been reported with HR 0.72 (0.63-0.82). Icosapent ethyl had greater efficacy in the secondary prevention cohort than the primary prevention cohort in the REDUCE-IT trial, so our results are a conservative estimate.

Discussion

Despite the widespread use of aspirin and statin therapy for secondary prevention of ASCVD, patients with ASCVD have residual CV risk as demonstrated by the high recurrent adverse event rates in control groups of contemporary RCTs. Efforts to reduce residual CV risk have largely focused on further reductions in LDL cholesterol levels; however, other pathways beyond lowering of LDL cholesterol should be simultaneously considered in light of recent data. For example, rivaroxaban is an anticoagulant while icosapent ethyl may target triglyceride-rich lipoproteins and additional mechanisms for secondary prevention of ASCVD.

Combination therapy has been described in the treatment of HFrEF with recent exploratory modeling analyses describing the benefit of simultaneous initiation of multidrug therapy. However, there is an absence of exploratory modeling analyses for enhanced secondary prevention for ASCVD with combination therapy despite the considerable morbidity and mortality also associated with these diseases. In a real-world registry analysis of patients with prior MI, approximately 30%-40% of patients were eligible for 3 simultaneous novel therapies based on RCT criteria. In addition, patients who were eligible for additional therapies had increased rates of major cardiovascular events compared to those who were not eligible. Considering the large group of real-world patients eligible for simultaneous multiple drug therapies, our novel results have shown that a combination of these medications may provide a substantial benefit in reducing adverse events within this high-risk population.

The combination of ezetimibe, rivaroxaban, and icosapent ethyl may be able to reduce CV death, MI, or stroke rates by approximately 50% beyond the treatment effect of background aspirin and statin medical therapy. High-risk ASCVD subgroups, such as those with polyvascular disease, or congestive HF, chronic kidney disease, or diabetes mellitus, may have greater absolute treatment benefits from comprehensive medical therapy for enhanced secondary prevention. In addition, young patients with ASCVD may also derive an increased benefit of comprehensive medical therapy over their expected longer treatment duration. However, careful attention to individual patient profiles should also be considered. In the COMPASS trial, the risk of nonfatal bleeding events was significantly increased in the aspirin with rivaroxaban group. Therefore, patients at high risk of bleeding events, such as those with anemia, prior major bleeding, or advanced CKD, may not be good candidates for long-term low-dose anticoagulation as part of secondary prevention of ASCVD. Considering the potential treatment benefit, it is imperative to achieve higher utilization of these evidence-based therapies and, importantly, begin to consider comprehensive therapy for ASCVD to further reduce residual CV risk.

In addition to safety profiles, patient and physician adherence to multidrug regimens and patient cost are important considerations. Patient adherence to complex treatment regimens provides a barrier to adoption of multidrug therapies. Polypharmacy has been reported to be associated with poorer medication adherence likely due to the added cost, complexity, and other barriers, especially within older adults. In the Heart Failure Adherence Retention Trial, 37% of patients were determined to be nonadherent to their heart failure regimen. Therefore, adherence to a multidrug regimen for ASCVD may also prove to be difficult. However, despite challenges of adherence to multidrug regimens, secondary prevention therapies may still be beneficial even in patients with polypharmacy.

In an analysis from the COMPASS trial, the addition of low-dose rivaroxaban in patients with polypharmacy (>4 cardiovascular drugs) resulted in a greater absolute risk reduction in CV death, myocardial infarction, or stroke compared to patients without polypharmacy suggesting benefit of the addition of low-dose rivaroxaban despite multiple comorbid conditions or taking multiple medications. Physician adherence to prescribing novel medications and clinical inertia may also impact adoption for these therapies. In patients with HFrEF, many patients do not achieve target doses of guideline-recommended therapies and there is suboptimal use of well-studied medications such as spironolactone. Therefore, similar issues of clinical inertia may also apply for a multidrug regimen for the secondary prevention of ASCVD.

There are several limitations to our study. Although the methods used to impute the aggregate treatment effect are previously established, it is unknown if the total treatment effect of multiple medications would be additive. However, additive treatment effect analyses have been shown to estimate the effectiveness of treatment combinations and have previously utilized in other studies of multidrug treatment combinations for HFrEF. In addition, given that the medications studied within this analysis target different biological pathways, the additivity assumption is reasonable and is further supported by the large sample sizes of each RCT included within this study. Second, this analysis does not address the potential safety issues related to comprehensive medical therapy. Third, the RCT cohorts that were analyzed within this study may have variations in baseline characteristics and clinical risk profiles. However, similar results were obtained in the sensitivity analyses with alirocumab data from the ODYSSEY OUTCOMES trial and with the secondary prevention cohort results from the REDUCE-IT trial. Finally, we did not account for cost which may be a barrier for adoption of these contemporary therapies. Icosapent ethyl and rivaroxaban appear cost-effective in a report from the Institute for Clinical and Economic Review (ICER), and ezetimibe is available as a low-cost generic medication. However, although rivaroxaban and icosapent ethyl both fall within cost-effectiveness thresholds, annual spending
may exceed ICER budget impact thresholds due to high prevalence of ASCVD within the United States, and these therapies may be especially difficult to afford for older adults on fixed incomes and multiple existing prescription medications.\textsuperscript{22,23} Future research should investigate the cost-effectiveness of combination therapy for secondary prevention of ASCVD in general, and for high-risk ASCVD subgroups.

Overall, these exploratory results demonstrate significant opportunities for enhanced secondary prevention of ASCVD and may encourage greater utilization of a combination of contemporary medical therapies. Further clinical studies are required to assess the benefit of multimodal comprehensive therapy on ASCVD outcomes.

**Authors’ Note**

Availability of data and material: Publicly available data from published RCTs. This study was exempt from approval of the institutional review board because of the use of anonymized and previously published data. This manuscript utilizes publicly available data from published RCTs.

**Author Contributions**

RWA—Writing: original draft, formal analysis. RG—Supervision, Writing: original draft, conceptualization.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**ORCID iD**

Rajesh Gupta \(\text{https://orcid.org/0000-0001-7428-7671}\)

**References**

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. \textit{J Am Coll Cardiol.} 2019;73(24):e285-e350.
2. Aday AW, Ridker PM. Targeting residual inflammatory risk: a shifting paradigm for atherosclerotic disease. \textit{Front Cardiovasc Med.} 2019;6:16.
3. Welsh RC, Peterson ED, De Caterina R, Bode C, Gersh B, Eikelboom JW. Applying contemporary antithrombotic therapy in the secondary prevention of chronic atherosclerotic cardiovascular disease. \textit{Am Heart J.} 2019;218(31):100-109.
4. Dhindsa DS, Sandesara PB, Shapiro MD, Wong ND. The evolving understanding and approach to residual cardiovascular risk management. \textit{Front Cardiovasc Med.} 2020;7:88.
5. Mortensen MB, Blaha MJ, Nordestgaard BG. Eligibility and preventive potential for new evidence-based cardiovascular drugs in secondary prevention. \textit{JAMA Cardiol.} 2020;5(2):209-215.
6. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. \textit{N Engl J Med.} 2019;380(1):11-22.
7. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. \textit{N Engl J Med.} 2015;372(25):2387-2397.
8. Eikelboom JW, Connolly SJ, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. \textit{N Engl J Med.} 2017;377(10117):1319-1330.
9. Bhatt DL, Steg PG, Miller M, et al. Effects of icosapent ethyl on total ischemic events: from REDUCE-IT. \textit{J Am Coll Cardiol.} 2019;73(22):2791-2802.
10. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. \textit{The Lancet.} 2020;396(10244):121-128.
11. Mills EJ, Thorlund K, Ioannidis JP. Calculating additive treatment effects from multiple randomized trials provides useful estimates of combination therapies. \textit{J Clin Epidemiol.} 2012;65(12):1282-1288.
12. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. \textit{N Engl J Med.} 2018;379(22):2097-2107.
13. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. \textit{J Am Coll Cardiol.} 2011;58(20):2047-2067.
14. Bassi NS, Ziaean B, Yancy CW, Fonarow GC. Association of optimal implementation of sodium-glucose cotransporter 2 inhibitor therapy with outcome for patients with heart failure. \textit{JAMA Cardiol.} 2020;5(8):948-951.
15. Greene SJ, Butler J, Fonarow GC. Simultaneous or rapid sequence initiation of quadruple medical therapy for heart failure—optimizing therapy with the need for speed. \textit{JAMA Cardiol.} 2021;6(7):743-744.
16. Marcum ZA, Gellad WF. Medication adherence to multidrug regimens. \textit{Clin Geriatr Med.} 2012;28(2):287-300.
17. Calvin JE, Shanbhag S, Avery E, Kane J, Richardson D, Powell L. Adherence to evidence-based guidelines for heart failure in physicians and their patients: lessons from the Heart Failure Adherence Retention Trial (HART). \textit{Congest Heart Fail.} 2012;18(2):73-78.
18. Vanassche T, Verhamme P, Anand SS, et al. Low-dose rivaroxaban plus aspirin in patients with polypharmacy and multimorbidity: an analysis from the COMPASS trial. \textit{Eur Heart J Cardiovasc Pharmacother.} 2021.
19. Albert NM, Yancy CW, Liang L, et al. Use of aldosterone antagonists in heart failure. \textit{JAMA.} 2009;302:1658-1665.
20. Packer M, Metra M. Guideline-directed medical therapy for heart failure does not exist: a non-judgmental framework for describing the level of adherence to evidence-based drug treatments for patients with a reduced ejection fraction. \textit{Eur J Heart Fail.} 2020;22(10):1759-1767.
21. Verhestraeten C, Heggermont WA, Maris M. Clinical inertia in the treatment of heart failure: a major issue to tackle. \textit{Heart Fail Rev.} 2021;26(6):1359-1370.
22. Symmott PG, McQueen RB, Ollendorf DA, Campbell JD, Pearson SD. The effectiveness and value of rivaroxaban and icosapent
ethyl as additive therapies for cardiovascular disease: a summary from the Institute for Clinical and Economic Review’s Midwest Comparative Effectiveness Public Advisory Council. *J Manag Care Spec Pharm*. 2020;26(6):782-785.

23. Magness JW, Arnwine C, Lockwood K, Reinert A. Add-on therapies in cardiovascular disease: reviewing ICER’S report and the potential effect on payers. *J Manag Care Spec Pharm*. 2020;26(6):786-788.