Usefulness of Ezetimibe Versus Evolocumab as Add-On Therapy for Secondary Prevention of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

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Evolocumab and ezetimibe, were both proven to significantly reduce the incidence of major adverse cardiovascular events (MACE), in type 2 diabetes patients with atherosclerotic cardiovascular disease and low-density lipoprotein (LDL) cholesterol >70 mg/dl despite statin therapy. Providing evolocumab for all such patients may be a significant burden on healthcare systems. Therefore, we analyzed the treatment cost of ezetimibe versus evolocumab to prevent 1 MACE. We extracted the number needed to treat (NNT) with evolocumab or with ezetimibe for avoiding MACE from the published FOURIER and IMPROVE-IT trials respectively. Drug costs were based on 2018 US prices. Sensitivity and scenario analyses were performed to overcome variances in terms of population risk, efficacy of therapies, and costs. In FOURIER, the 1-year NNT for avoiding MACE with evolocumab was 104 (95% confidence intervals [CI] 66 to 235). In IMPROVE-IT, the 1-year NNT with ezetimibe was 124 (95% CI 73 to 288). The annual cost of evolocumab and ezetimibe is $6,540 and $88, respectively. Therefore, the cost to prevent 1 MACE in the FOURIER and IMPROVE-IT trials would have been $678,981 (95% CI $429,810 to $1,537,910,149) and $10,870 (95% CI $6,384 to $25,322), respectively. Ezetimibe was consistently a cost-saving strategy compared with evolocumab, in all analyses performed, except for the case where evolocumab price is significantly reduced and the branded ezetimibe is used. In conclusion, treatment with ezetimibe seems to be a major cost-saving strategy for preventing MACE in this patient population.   © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;123:1273−1276)

The presence of type 2 diabetes, hypercholesterolemia and atherosclerotic cardiovascular disease (ASCVD) significantly increases the risk of major adverse cardiovascular events (MACE).[1] Various lipid-modifying agents, such as evolocumab and ezetimibe provided to such patients as add-on to statin therapy, have both demonstrated a significant improvement in avoiding MACE in the FOURIER and IMPROVE-IT trials, respectively.[2,3] The PCSK9 inhibitor evolocumab has demonstrated a significantly higher improvement in lowering LDL levels in patients with type 2 diabetes, when compared with ezetimibe,[4] but evidence that this translates to better avoidance of MACE is lacking. Moreover, the addition of evolocumab to patients' current diabetes treatment regimen imposes a significant burden on healthcare systems, and therefore, the adoption of PCSk9 inhibitors is still very limited.[5] To assist in choosing the cost-efficient strategy for reducing MACE in patients with type 2 diabetes, hypercholesterolemia, and ASCVD, we compared the cost of preventing 1 MACE in this population using either ezetimibe or evolocumab, by utilizing currently available outcome and cost data.

Methods

MACE risk reduction ratios with evolocumab and ezetimibe therapies were extracted from the published data, regarding ASCVD patients with type 2 diabetes, in FOURIER[2] and IMPROVE-IT[3] trials, respectively. The primary efficacy end-point in both trials was MACE, defined as: CV death, stroke, myocardial infarction (MI), and hospitalization for unstable angina or coronary revascularization.

The key characteristics, demographics, and results of the 2 trials are compared in Table 1. Of notice, patients in FOURIER trial were slightly younger, with a higher median LDL at randomization, and had a shorter follow-up period, compared with IMPROVE-IT.

We analyzed the absolute risk reduction (ARR) of MACE per intervention, to calculate the 1-year number needed to treat (NNT). Accordingly, the primary economic end point in this study was the cost of drug needed to prevent 1 MACE. Drug costs were based on the 2018 US National Average Drug Acquisition Cost (NADAC) prices.[6]

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Table 1
Comparison of IMPROVE_IT and FOURIER patients with type 2 diabetes

Variable Intervention	FOURIER (n = 11,031) Evolocumab	IMPROVE-IT (n = 4,933) Ezetimibe
Follow-up (years)	2.2	7
Mean age - (SD) (years)	62.6 (8.7)	65.3 (9.2)
Women	2,940 (27%)	1,407 (28.5%)
Mean body mass index (kg/m^2)	30.7	29.2
Median LDL at randomization	89	75
Hazard ratio for major adverse cardiovascular events (95% CI)	0.83 (0.72-0.93)	0.85 (0.78, 0.94)
Hazard ratio for cardiovascular death (95% CI)	1.05 (0.83-1.34)	0.96 (0.80, 1.16)
Hazard Ratio for Myocardial Infarction (95% CI)	0.77 (0.65-0.92)	0.76 (0.66, 0.88)
Hazard ratio for stroke (95% CI)	0.79 (0.62-1.01)	0.73 (0.56, 0.95)

Because evolocumab and ezetimibe were not compared in a randomized-controlled trial (RCT) and because IMPROVE-IT and FOURIER were not identical in several parameters (Table 1), we carried out a scenario analysis, in which we simulated the potential effect of each drug in the comparing trial.

To confirm the robustness of our results, we also performed several 1-way sensitivity analyses, considering the following parameters:

1. An alternative definition of MACE, to include only CV death, MI, and stroke.
2. The annual risk of MACE in the standard of care (SOC) population of each trial; we used each of the trials SOC results as baseline. Half that risk as a low estimate and double that risk as the high estimate.
3. The annual costs of therapy; for evolocumab, the US list price was used as the high estimate; the current US NADAC cost was used as baseline, and the suggested price by the Institute for Clinical and Economic Review (to justify cost-effectiveness at $100,00 per quality adjusted life year)[8] as the low estimate. For ezetimibe, the generic and branded US NADAC costs were used as low and high estimates, accordingly.

Results

IMPROVE-IT and FOURIER RCTs have demonstrated statistically significant benefit in reduction of total MACE. The rate of MACE in SOC arm of both trials was comparable: 6.5%/year in IMPROVE-IT versus 6.1%/year in FOURIER. In FOURIER, 739 MACE were reported in the SOC arm compared with 622 for evolocumab. Therefore, 12,133 patient-years of evolocumab treatment in the study period resulted in the prevention of 117 MACE (95% CI 52 to 185). The ARR was 0.0096, which translates to a 1-year NNT of 104 (95% CI 66-235). In IMPROVE-IT, there were 949 MACE in the SOC arm compared with 824 for ezetimibe. Therefore 14,574 patient-years treatment with ezetimibe resulted in the prevention of 125 MACE (95% CI 57-209). The ARR was 0.008, which translates to a 1-year NNT of 124 (95% CI 73 to 288).

The NADAC US annual cost of evolocumab is $6,540, and $88 for ezetimibe, as of December 2018.[7] Therefore, the cost to prevent 1 MACE in the FOURIER and IMPROVE-IT trials would have been $678,981 (95% CI $429,810 to $1,537,910,149) and $10,870 (95% CI $6,384 to $25,322), respectively. Consequently, the potential monetary saving by treating with ezetimibe could reach $668,112 (95% CI $423,426 to $1,512,583) per each avoided MACE.

The simulation of using evolocumab in IMPROVE-IT lowers evolocumab 1-year NNT to 95 (95% CI 64 to 243), which results in a 12% lower cost to avoid 1 MACE. However, this cost is still 50-fold higher than the costs to prevent 1 MACE by ezetimibe (Table 2). The simulation of using ezetimibe in FOURIER resulted in an NNT of 124 (95% CI 73 to 288), which lowers the cost to prevent MACE to $9,627 (95% CI $6,562 to $24,112). These estimates, again, reflect a 50-fold higher cost for evolocumab versus ezetimibe to prevent 1 MACE.

Ezetimibe performs better than evolocumab when the secondary end point of hard MACE (CV death, stroke, and MI) is used: 1-year NNT of 129 versus 133. In most of the sensitivity analyses performed, ezetimibe was consistently a significant cost-saving strategy compared with evolocumab (Table 3). The only case where ezetimibe will cost more to prevent MACE than evolocumab is if the price of evolocumab will be lowered to the price recommended by the Institute for Clinical and Economic Review[8] and branded (Zetia) instead of generic ezetimibe is used.

Discussion

This cost-consequence analysis suggests that use of ezetimibe for secondary prevention of MACE in patients with ASCVD and type 2 diabetes has a clear economic advantage over the use of the PCSK9 inhibitor evolocumab for the same purpose.

The strength and weakness of this study is that it relies on the straightforward costs and outcomes of the published RCTs of the medications and does not include any extrapolations, assumptions, and modeling. Its major advantage is that it can be easily adjusted to various healthcare settings, risk of patients, and price schemes, to provide prompt and relevant information for decision-making.

The conclusions from this analysis should be considered in the context of several limitations. First and most important, our comparison is based on available outcome data

Table 2
Scenario analysis of MACE prevented and corresponding costs

Variable	Evolocumab in FOURIER	Simulation of ezetimibe in FOURIER	Simulation of evolocumab in IMROVE-IT	Ezetimibe in IMROVE-IT
Patient-years of therapy	12,133	12,133	14,754	14,754
Major adverse cardiovascular events prevented (95% CI)	117 (52-185)	111 (44-163)	161 (66-237)	125 (57-209)
Absolute risk reduction (95% CI)	0.0096 (0.0043-0.0152)	0.0091 (0.0036-0.0134)	0.0105 (0.0041-0.0157)	0.0081 (0.0035-0.0138)
Number Needed to Treat- One Year (95% CI)	104 (66-235)	110 (75-274)	95 (64-243)	124 (73-288)
cost of annual therapy per patient	$6,540	$88	$6,540	$88
Cost to prevent one major adverse cardiovascular event (95% CI)	$678,981 ($429,810-$1,537,906)	$9,627 ($6,562-$24,112)	$620,218 ($416,815-$1,590,265)	$10,870 ($6,384-$25,322)

from 2 different trials. We compared data of 2 diverse drugs that have different mechanisms of action, with nonidentical patient populations enrolled into and different follow-ups. Nevertheless, because both these therapies are already recommended in clinical guidelines for the same use and because they are being regularly utilized, it is still reasonable to compare indirectly the clinical and economic implications of both these therapies, using the available data on both drugs. Because data on patients with type 2 diabetes were available for evolocumab and not for alirocumab, this study did not analyze this second approved PCSK9 inhibitor. However, preliminary data from the ODYSSEY outcomes trial suggest that the hazard ratio for MACE in patients with type 2 diabetes is comparable to evolocumab.[8] Our results are also restricted by difficulties to extrapolate findings from short-term RCTs performed only in selected populations. However, the sensitivity and scenario analyses performed attempted to overcome some of these uncertainties, in terms of overall risk, the relative efficacy of therapies, and various cost scenarios. Another limitation of this analysis is that we did not consider the financial savings evolving from reduction of MACE, and rather considered solely the cost of therapy. We assumed this was appropriate, as the difference in avoided MACE between the 2 therapies is negligible compared with the significant differences in the drug costs.

PCSK9 inhibitors have been scrutinized for their costs to prevent MACE. Cost-effectiveness studies of PCK9 inhibitors consistently suggested that it is not a cost-effective therapy at current prices.[9] It was also demonstrated that the cost of preventing 1 MACE with these therapies may exceed $2,000,000.[10] The cost to prevent 1 MACE with evolocumab was much lower in this study, for a few reasons. First, we used a reduced price which is much lower than the US list price but may be more representative of the current costs of evolocumab, which are expected to be even lower in 2019.[11] The second reason is that the definition of MACE was much broader and included also coronary revascularization and unstable angina pectoris hospitalizations. The third reason is that the population in this study includes only patients with type 2 diabetes, which have a higher risk of MACE.

The study results should be considered in the context of other drug-specific and individual patient factors, as recommended by the American Diabetes Association guidelines.[12] Future studies regarding the long-term effects of evolocumab on MACE may affect these findings. An RCT comparing evolocumab and ezetimibe would be the optimal method to evaluate the comparative effectiveness of these interventions.

Table 3
Sensitivity analysis

Parameter analyzed	Value base case (low−high)		One-year NNT base case (low−high)		Cost to prevent 1 MACE base case (low−high)	
	FOURIER	IMPROVE-IT	Evolocumab	Ezetimibe	Evolocumab	Ezetimibe
Baseline (95% CI)			104 (66-235)	124 (73-288)	$678,981 ($429,810-$1,537,906)	$10,870 ($6,384-$25,322)
"Hard" adverse cardiovascular events *Hazard Ratios	0.82 (0.72-0.93)	0.80 (0.71-0.90)	133 (85-342)	129 (81-244)	$872,859 ($558,220-$2.237,229)	$11,360 ($7,099-$21,459)
Annual MACE rate in standard of care arm	5.7% (2.85%-11.4%)	6.5% (3.25%-13%)	104 (52-208)	124 (62-247)	$678,981 ($339,491-$1,357,470)	$10,870 ($5,435-$21,739)
Annual cost of therapy (USD)	$6,540 ($1,725-$14,153)	$88 ($88-$4,035)	104	124	$678,981 ($179,089-$1,506,736)	$10,870 ($10,870-$499,268)

CI = confidence interval.
* "Hard" MACE—CV death, stroke, and MI.

In conclusion, although evolocumab seems to be more effective than ezetimibe for preventing MACE in patients with ASCVD and type 2 diabetes by decreasing LDL cholesterol levels, the cost for preventing each MACE is significantly lower with ezetimibe. From an economic point of view, ezetimibe may be considered a preferred add-on therapy for this patient population, especially due to the higher costs of evolocumab therapy that might not be affordable for the whole needed population.

Disclosures

The authors report no relation that could be construed as a conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.01.021.

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