Applicability and Cost Implications for Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors Based on the ODYSSEY Outcomes Trial

Insights From the Department of Veterans Affairs

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In the recently presented ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab trial,[1] alirocumab use in patients with acute coronary syndrome (ACS) and low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dL (or non–high-density lipoprotein cholesterol ≥100 mg/dL or apolipoprotein B ≥80 mg/dL) resulted in a 15% relative (1.6% absolute) reduction in the risk of major adverse cardiovascular events. We evaluated what proportion of patients in the VA Health Care System would qualify for alirocumab on the basis of ODYSSEY Outcomes criteria, how they are currently treated with LDL-C–lowering medications, and the cost implications if other evidence-based medications were used first before a proprotein convertase subtilisin/kexin type 9 inhibitor was considered.

Using a national cohort,[2] we identified veterans with ischemic heart disease (with ACS or with a history of percutaneous coronary angiography or coronary artery bypass graft) receiving care in the VA system between October 1, 2014, and September 30, 2015 (n=1 015 971). We excluded 25 314 patients with metastatic cancer or those receiving hospice care. Among those remaining, 164 446 had a history of ACS. We excluded 154 104 patients using various ODYSSEY Outcomes trial exclusions (age <40 years, ACS <4 weeks before or >52 weeks after the index primary care visit, systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg, history of hemorrhagic stroke, triglycerides >400 mg/dL, percutaneous coronary angiography or coronary artery bypass graft within 2 weeks, liver function test elevation >3 times the upper limit of normal, estimated glomerular filtration rate <30 $mL \cdot min^{-1} \cdot m^{-2}$ or end-stage renal disease, use of gemfibrozil, or LDL-C<70 mg/dL and non–high-density lipoprotein cholesterol <100 mg/dL). The largest number of patients were excluded because of the diagnosis of ACS <4 weeks (n=18 605) or >52 weeks (n=130 770) from the index visit or because of LDL-C <70 mg/dL and non–high-density lipoprotein cholesterol <100 mg/dL (n=7285). The protocol was approved by the Institutional Review boards at Baylor College of Medicine and the Michael E. DeBakey VA Medical Center.

Of 10 342 patients who met inclusion criteria, 50.8% were on high-intensity, 28.5% were on moderate-intensity, and 5.3% were on low-intensity statins; 15.3% were not on a statin, whereas 1.3% were on ezetimibe. From pharmacy refill data, 43.5% had poor statin adherence (proportion of days covered <0.8).

Assuming a 6% LDL-C reduction with each doubling of statin dose[3] and 20% LDL-C reduction with ezetimibe,[4] we calculated what proportion of these 10 342 patients will remain alirocumab eligible (LDL-C ≥70 mg/dL) after transition to high-intensity statin, added ezetimibe therapy, or a combination of high-intensity statin plus ezetimibe. Transition to high-intensity statin, ezetimibe, or a combination of high-intensity statin plus ezetimibe would lead to 33%, 42.5%, and 65.3% of patients dropping their LDL-C levels to <70 mg/dL, with mean LDL-C levels of 57, 59, and 53 mg/dL, respectively, among those with LDL-C <70 mg/dL in each of the 3 scenarios.

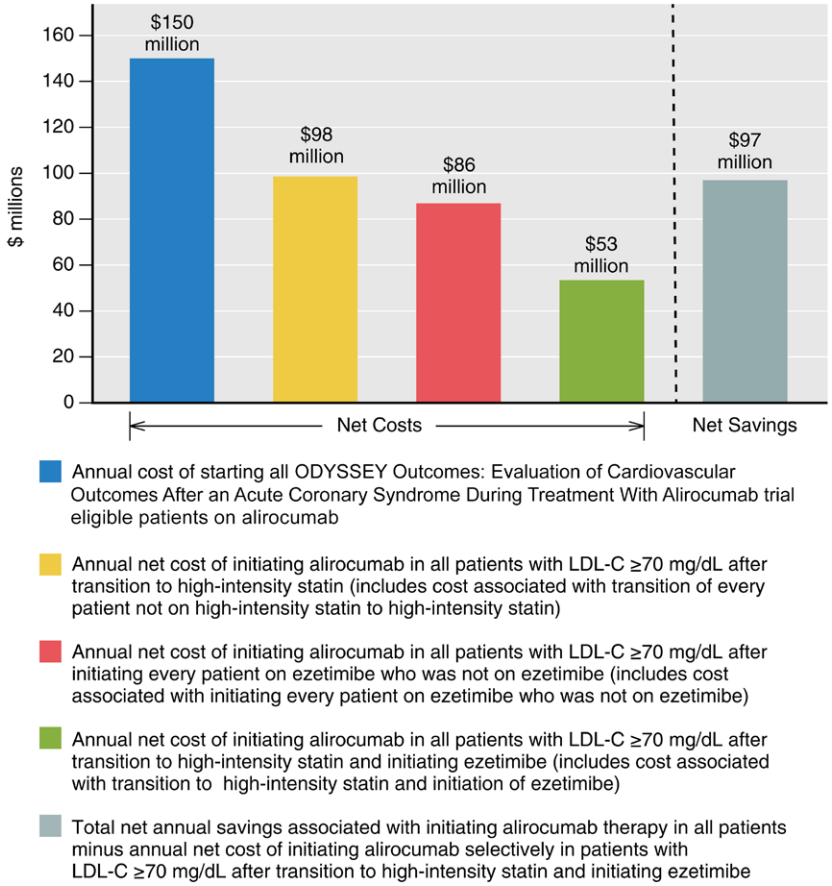

Figure. Cost implications of transitioning ODYSSEY Outcomes–eligible patients to high-intensity statin and ezetimibe.
LDL-C indicates low-density lipoprotein.

With the use of an annual retail price of alirocumab of $14 560,[5] the annual cost of treating 10 342 patients would be $150 579 520 (Figure). Alternatively, selective use of alirocumab in patients with LDL-C ≥70 mg/dL after transition to high-intensity statin and ezetimibe would cost $53 419 010.40 This would lead to an average savings of $97 160 509.6 (64.5%) to treat all eligible patients accounting for costs associated with transition to high-intensity statin, ezetimibe use, and selective use of alirocumab in patients with LDL-C ≥70 mg/dL after transition to high-intensity statins and ezetimibe added. Restricting alirocumab use to 4401 patients (42.7%) with LDL-C ≥100 mg/dL (shown to derive the most benefit in the ODYSSEY Outcomes trial) will lead to an annual cost of $64 078 560, which will be further reduced to $15 253 081.60 after accounting for the cost of transition to high-intensity statin therapy plus ezetimibe. Lastly, using the recently suggested value-based price range of $2306 to $3441 by the Institute for Clinical and Economic Review[4] based on ODYSSEY Outcomes trial results, the cost would be $23 848 652 to $35 586 822 for the entire cohort of 10 342 patients.

In these analyses from the VA System, we note that only half of the patients who would qualify for alirocumab on the basis of ODYSSEY Outcomes trial criteria were on evidence-based high-intensity statin therapy as opposed to 89% of the patients in ODYSSEY Outcomes trial. The number of patients who would qualify using ODYSSEY Outcomes trial criteria (n=10 342) is lower than the number of those who would qualify using much broader FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk) criteria (154 823) shown in a prior analysis.[3] Second, transition to evidence-based high-intensity statin therapy as recommended by the treatment guideline and ezetimibe (shown to improve outcomes in patients with ACS)[4] will lead to LDL-C levels dropping to <70 mg/dL in two-thirds of the patients with LDL-C levels, comparable with the active arm of ODYSSEY Outcomes trial (LDL-C, 66.4 mg/dL in the intent-to-treat analyses). This assumes that all patients will tolerate high-intensity statin therapy, which may not be the case. Lastly, despite recent ACS, statin adherence remains low in a substantial proportion of these patients.

Although statin undertreatment could be a result of provider clinical inertia, patient intolerance, or refusal to take statin or high-intensity statin therapy, our analyses suggest a modest role for proprotein convertase subtilisin/kexin type 9 inhibitors if current guideline-based lipid-lowering therapy is optimized.

ARTICLE INFORMATION

Data sharing: The data, methods, and study materials will not be made available to other researchers for purposes of reproducing the results.

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Disclosures

Dr Virani reports honoraria from the American College of Cardiology (associate editor, Innovations, ACC.org) and National Lipid Association. Dr Nambi reports a provisional patent from Roche and serves as an event adjudicator for Siemens and site principal investigator for Merck. Dr Michos has served as an event adjudicator at Siemens. Dr Morris reports being on the advisory board or a consultant to Amgen, Sanofi, and Regeneron and on the Steering Committee for Esperion and Amgen. Dr Nasir served on the Advisory Board for Regeneron. Dr Ballantyne reports receiving grant/research support (paid to institution) from Abbott Diagnostic, Amarin, Amgen, Esperion, Ionis, Novartis, Pfizer, Regeneron, Roche Diagnostic, Sanofi-Synthelabo, National Institutes of Health, American Heart Association, and American Diabetes Association, as well as serving as a consultant to Abbott Diagnostics, Amarin, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Esperion, Ionis, Matinas BioPharma Inc, Merck, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo. The other authors report no conflicts.

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