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Brief Communication

Simulation of lipid-lowering therapy (LLT) intensification in very high-risk patients with atherosclerotic cardiovascular disease

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We aim to estimate the number and proportion of very-high risk patients with atherosclerotic cardiovascular disease (ASCVD) who would be able to achieve low-density lipoprotein cholesterol (LDL-C) <70 mg/dL with various lipid-lowering therapies (LLTs), including statins, ezetimibe, bempedoic acid, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and evinacumab, using a Monte Carlo simulation model described previously. With current treatment options for LDL-C lowering, including statin, ezetimibe, bempedoic acid, and PCSK9 inhibitors, it was estimated that most very-high risk patients with ASCVD (99.1%) were able to achieve the LDL-C goal of <70 mg/dL. Nevertheless, approximately 88,715 patients in the USA were estimated to not be able to achieve the LDL-C goal after current available LLTs, thus remaining at elevated risk for recurrent cardiovascular events. Evinacumab may be useful to address such unmet needs effectively, as the majority of those not at goal after PCSK9 inhibitors could achieve the goal of <70 mg/dL after taking evinacumab.

In a previous study, we used a Monte Carlo simulation model to estimate the proportion of patients with atherosclerotic cardiovascular disease (ASCVD) who would require various lipid-lowering therapies (LLTs), and the proportion achieving low-density lipoprotein cholesterol (LDL-C) goals via a stepwise treatment intensification algorithm which maximized statins before adding ezetimibe and a proprotein convertase subtilisin/kexin type 9 (PCSK9 inhibitor).[1] We found that, after treatment intensification, 99.3% of patients could achieve an LDL-C level of <70 mg/dL, including 67.3% with statin monotherapy, 18.7% with statins plus ezetimibe, and 14.0% with add-on PCSK9 inhibitors.[1] In a later analysis, we updated the simulation model to account for varying background rates of statin intolerance.[2] Partial statin intolerance was defined as the inability to tolerate high-intensity statin (but able to tolerate moderate-to-low intensity statin), and full statin intolerance as the inability to tolerate statin at any dose. Allowing for 10% partial intolerance, we found that the need for non-statins increased only modestly (by an absolute 2.2%), whereas having 10% of patients with full statin intolerance increased the need for PCSK9 inhibitors from 14.0% to 19.7%.[2]

Recently, 2 novel non-statin LLTs have come to market, namely bempedoic acid and evinacumab. Bempedoic acid inhibits adenosine triphosphate-citrate lyase and has been shown to decrease LDL-C levels by approximately 15–24%

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in clinical trials.[3] Evinacumab is a monoclonal antibody against angiopoietin-like 3 and reduced LDL-C by 49% in patients with homozygous familial hypercholesterolemia (HoFH) when added to background LLTs in clinical trials, irrespective of mutation status.[4] Furthermore, in patients with refractory hypercholesterolemia, evinacumab reduced LDL-C by up to 56% when added to background LLTs.[5]

The objective of this report is to update the simulation model by adding bempedoic acid and evinacumab into the treatment intensification algorithm using more recent MarketScan data which better represents the up-to-date disease burden in the USA, in order to reevaluate the proportion and number of patients who would be able to achieve LDL-C goals with various LLTs. In this analysis, we focused on very high-risk patients with ASCVD (Supplementary Table 1), as this patient group is the most likely to have unmet needs for LDL-C lowering. Additionally, the 2018 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend the addition of non-statin lipid-lowering medications (PCSK9 inhibitors after ezetimibe) above an LDL-C threshold of 70 mg/dL for this group.[6] Furthermore, other guidelines, including the 2019 European Atherosclerosis Society/European Society of Cardiology and 2020 American Association of Clinical Endocrinology guidelines have set the strictest LDL-C goal of <55 mg/dL for those categorized as having the highest risk.[7,8]

The methodology of developing the simulation model has been described elsewhere.[1,2] We utilized the MarketScan claims database and identified 53,450 ASCVD patients ≥21 years of age at very high risk during 2013 and 2019. Information on their current LDL-C levels and LLTs was obtained from the database. The number of patients from the database was then extrapolated to approximate national figures based on known national demographic and ASCVD prevalence numbers. The extrapolation method has been described previously.[9] We then developed the simulation cohort by randomly sampling 1 million patients with bootstrapping from the database cohort. Each patient entered the simulation model on their current LLT. If no statin was present, atorvastatin 20 mg was initiated. As shown in Fig. 1, a stepwise approach was taken to achieve the goal of LDL-C <70 mg/dL by first up-titrating atorvastatin to 80 mg, then adding on ezetimibe, bempedoic acid, alirocumab 75 mg up-titrated to 150 mg, and then finally evinacumab if needed to achieve LDL-C goal. At each step in the treatment intensification pathway for an individual, the achieved LDL-C level was modeled probabilistically from the distribution of LDL-C reduction with a given LLT. The treatment effect for statins, ezetimibe, and PSCK9 inhibitors has been defined elsewhere.[1] For bempedoic acid and evinacumab, the LDL-C-lowering effect was sampled from a β probability density function, with parameters estimated from the means and standard deviations (SDs) as reported in the literature. The mean (SD) of LDL-C reduction for bempedoic acid was 22.9% (16.5%) and for evinacumab was 49.0% (8.0%).[4,10] We assumed that 10% of patients have partial statin intolerance and 10% have full statin intolerance. Individuals who were deemed to have full intolerance are taken off the statin and those who were deemed to have partial intolerance would be down-titrated to atorvastatin 20 mg. In an alternative scenario, we dropped bempedoic acid in the treatment algorithm and investigated how results would change comparing to the base case. We also explored how results would change if the LDL-C goal was changed from 70 mg/dL to 55 mg/dL in scenarios with or without bempedoic acid.

We estimated there were approximately 9,464,916 ASCVD patients with very high risk in the USA. A summary of baseline characteristics for the database cohort (53,450 patients; 55.5% male, average age of 69.3 years) and simulation cohorts (1 million patients; 52.2% male, average age of 70.6 years) is provided in Supplementary Table 2. All subsequent results were based on the simulation cohort. At baseline, only 60.4% of these patients were currently on LLT, with 19.6% on high-intensity statins only, 38.0% on moderate-intensity statins only, 2.6% on ezetimibe with or without statins, and 0.3% on PCSK9 inhibitors (with or without statins or ezetimibe).

We calculated the proportions of patients on different LLTs after treatment intensification, for scenarios with or without bempedoic acid and LDL-C goal at 55 or 70 mg/dL (Table 1). In the base case where bempedoic acid was included and LDL-C goal was set to 70 mg/dL, after treatment intensification 55.5% of patients were on statin monotherapy, 20.4% were on statin plus ezetimibe or ezetimibe alone, 12.5% were on add-on bempedoic acid, 9.7% were on add-on PCSK9 inhibitors, and 0.9% were on add-on evinacumab. When the LDL-C goal was lowered to 55 mg/dL, fewer patients were on statin monotherapies (35.2%) and more patients were on ezetimibe (23.8%) and bempedoic acid (18.7%), and the proportions on PCSK9 inhibitors and evinacumab nearly doubled (to 19.8% and 2.1%, respectively). In the scenario without bempedoic acid and LDL-C goal set at 70 mg/dL, more patients would require PCSK9 inhibitors (20.8%) and evinacumab (2.2%) compared to the base case. When we lowered the LDL-C goal to 55 mg/dL, we again found fewer patients on statin monotherapies (35.2%) and more patients on ezetimibe (23.8%), PCSK9 inhibitors (35.9%), and evinacumab (4.7%), compared to when the LDL-C goal was 70 mg/dL.

We further described the LDL-C levels of patients who did not achieve the LDL-C goal after taking PCSK9 inhibitors, and the number of patients who were able to reach the goal after taking evinacumab, as shown in Table 2. Results were reported separately for scenarios with or without bempedoic acid, and for LDL-C goals of 55 or 70 mg/dL. We found that with statin, ezetimibe, bempedoic acid, and PCSK9 inhibitors, only 0.9% of patients were unable to achieve the LDL-C goal of <70 mg/dL (estimated to be 88,715 patients in the USA). Out of these patients, the majority (n = 63,075) had LDL-C of 70–100 mg/dL. All patients with LDL-C within this range were able to achieve the goal of 70 mg/dL after evinacumab. There were 16,648 patients whose

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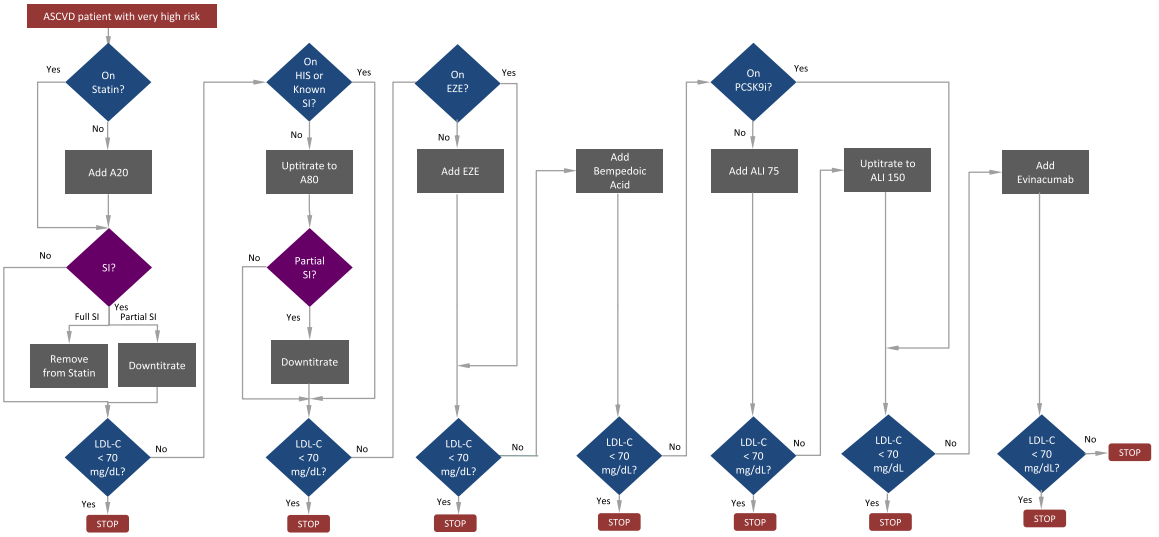

Fig. 1 Logic of lipid-lowering treatment intensification and proportion of patients flowing through the intensification logic in the simulation. A20, atorvastatin 20 mg; A80, atorvastatin 80 mg; ALI 75, alirocumab 75 mg; ALI 150, alirocumab 150 mg; ASCVD, atherosclerotic cardiovascular disease; EZE, ezetimibe; HIS, high-intensity statin; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; SI, statin intolerance.

Table 1 Use of lipid-lowering therapies after treatment intensification.

LDL-C goal (%)	With bempedoic acid		Without bempedoic acid	
	<70 mg/dL	<55 mg/dL	<70 mg/dL	<55 mg/dL
High-intensity statin				
Monotherapy only	19.1	13.9	19.1	13.9
Plus ezetimibe	14.7	19.2	14.7	19.2
Plus bempedoic acid	8.8	15.0	N/A	N/A
Plus PCSK9 inhibitors	4.1	11.5	12.2	25.0
Plus evinacumab	0.2	0.7	0.8	2.2
Moderate-intensity statin				
Monotherapy only	36.5	21.3	36.5	21.3
Plus ezetimibe	3.8	3.5	3.8	3.5
Plus bempedoic acid	1.7	2.2	N/A	N/A
Plus PCSK9 inhibitors	1.1	2.5	2.7	4.4
Plus evinacumab	0.1	0.2	0.2	0.5
Ezetimibe				
Monotherapy only	1.9	1.2	1.9	1.2
Plus bempedoic acid	2.0	1.5	N/A	N/A
Plus PCSK9 inhibitors	4.5	5.8	5.9	6.5
Plus evinacumab	0.6	1.2	1.2	2.0
No lipid-lowering therapies	1.0	0.4	1.0	0.4

LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

LDL-C was 100–130 mg/dL, and 89.7% of them achieved the goal of 70 mg/dL after evinacumab. The remaining 8,992 patients had LDL-C ≥130 mg/dL after PCSK9 inhibitors, and 26.0% of them could achieve the goal of 70 mg/dL after evinacumab. In total, after simulation of all LLTs, only 8,396 patients (0.1% of 9,464,916 very-high risk ASCVD patients) were unable to achieve this LDL-C goal. If the LDL-C goal was lowered to 55 mg/dL, 197,391 patients (2.1% of all very-high risk ASCVD patients) were unable to achieve the goal after PCSK9 inhibitors. Among them, 106,320 (1.1%) had LDL-C 55–70 mg/dL, 66,169 (0.7%) had LDL-C 70–100 mg/dL, 15,891 (0.2%) had LDL-C 70–130 mg/dL, and 9,011 (0.1%) had LDL-C ≥130 mg/dL. Most patients whose LDL-C was 55–100 mg/dL after PCSK9 inhibitors were able to reach the goal of 55 mg/dL after evinacumab. However, <50% of patients with LDL-C 100–130 mg/dL and only 5.5% of patients with LDL-C ≥130 mg/dL after PCSK9 inhibitors were able to achieve the goal of 55 mg/dL with evinacumab. In the scenario without bempedoic acid, the number of patients who did not achieve the goal after PCSK9 inhibitors increased significantly from 88,715 (0.9%) to 212,355 (2.2%), and 22,366 (0.2%) were

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Table 2 Number and proportion of patients whose LDL-C levels were above certain thresholds after treatment intensification.

n (%)	With bempedoic acid		Without bempedoic acid	
	LDL-C goal <70 mg/dL	LDL-C goal <55 mg/dL	LDL-C goal <70 mg/dL	LDL-C goal <55 mg/dL
Total very-high risk ASCVD patients	9,464,916 (100)			
Not at goal after PCSK9 inhibitors	88,715 (0.9)	197,391 (2.1)	212,355 (2.2)	442,996 (4.7)
55≤LDL-C<70 mg/dL after PCSK9 inhibitors	N/A	106,320 (1.1)	N/A	226,174 (2.4)
Achieved goal after evinacumab[a]	*N/A*	*106,319 (100.0)*	*N/A*	*226,164 (100.0)*
70≤LDL-C<100 mg/dL after PCSK9 inhibitors	63,075 (0.7)	66,169 (0.7)	146,640 (1.5)	152,574 (1.6)
Achieved goal after evinacumab[a]	*63,046 (100.0)*	*63,037 (95.3)*	*146,573 (100.0)*	*144,851 (94.9)*
100≤LDL-C<130 mg/dL after PCSK9 inhibitors	16,648 (0.2)	15,891 (0.2)	40,595 (0.4)	39,601 (0.4)
Achieved goal after evinacumab[a]	*14,935 (89.7)*	*6,720 (42.3)*	*36,705 (90.4)*	*17,766 (44.9)*
LDL-C≥130 mg/dL after PCSK9 inhibitors	8,992 (0.1)	9,011 (0.1)	25,120 (0.3)	24,647 (0.3)
Achieved goal after evinacumab[a]	*2,338 (26.0)*	*492 (5.5)*	*6,711 (26.7)*	*937 (3.8)*

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.
[a]Percentages in these rows denote the relative percentages of each subgroup within a certain LDL-C range.

not at goal after evinacumab. When LDL-C goal was set to 55 mg/dL, the number of patients not at goal after PCSK9 inhibitors further increased to 442,996 patients (4.7%), and 279,442 (3.0%) were not at goal after evinacumab.

In conclusion, based on the simulation model, most ASCVD patients with very high risk may be able to achieve the goal of LDL-C <70 mg/dL with the current treatment options for LDL-C lowering. On top of statins and ezetimibe, 12.5% of patients would require bempedoic acid, and its use decreased the proportion of patients who would require PCSK9 inhibitors from 20.8% to 9.7%. Nevertheless, many patients were not able to achieve the LDL-C goal after taking statins, ezetimibe, and PCSK9 inhibitors as recommended by the 2018 AHA/ACC guidelines, thus remaining at elevated risk for recurrent cardiovascular events. Evinacumab may be useful to address such unmet needs effectively, as the majority of those not at goal after PCSK9 inhibitors simulated in the model could achieve the goal of <70 mg/dL after taking evinacumab. It is important to note that evinacumab is currently indicated for HoFH only. This model did not consider the current limited indication and the potential high cost of an orphan drug.

It is worth noting that there are several assumptions related to the model design. First, we designed our algorithm to have bempedoic acid added prior to PCSK9 inhibitors in the treatment paradigm, mainly because bempedoic acid has a lower cost and is taken orally and not via injection, as is required for PCSK9 inhibitors. We acknowledge that bempedoic acid lacks efficacy data with respect to cardiovascular outcomes and achieves only a modest LDL-C reduction vs PCSK9 inhibitors; patients and providers may therefore elect to pursue PCSK9 inhibitors prior to bempedoic acid. However, since bempedoic acid only achieves a modest LDL-C reduction, whether it is added prior or after PCSK9 inhibitors does not meaningfully affect the results. Second, in this model we accounted for full and partial statin intolerance caused by muscle-related adverse effects. Because other LLTs to date have not shown any evidence that such muscle-related adverse effects are a common cause of intolerance, we assumed perfect compliance and tolerance to other LLTs. Third, we used distribution of LDL-C reduction of different LLTs from clinical trials reflective of the broad population. However, about 1% of the evaluated population is expected to carry the diagnosis of familial hypercholesterolemia (FH), which makes them more likely to not achieve LDL-C goals because of reduced responses to LLTs. Due to the small size of the FH population, we do not expect the differences in LLT efficacy among FH patients to have significant impact on the overall results.

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Authors' contributions

J.G., R.J.S., S.F. and **R.S.R.** contributed to the study conceptualization. **A.C.** executed the formal analysis. All authors contributed to the formal analysis, writing - original draft, and writing - review and editing.

Conflicts of interest

J.G., R.J.S., and **S.F.** are employees of and stockholders in Regeneron Pharmaceuticals, Inc. **A.C.** is an employee of Axtria. **R.S.R.** reports grants and/or personal fees for scientific advisory board participation from Regeneron Phar-

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2022.10.001.

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