# Simulation of the Impact of Statin Intolerance on the Need for Ezetimibe and/or Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor for Meeting Low-Density Lipoprotein Cholesterol Goals in a Population With Atherosclerotic Cardiovascular Disease

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**In a population with atherosclerotic cardiovascular disease, previous research indicated that approximately 86% can achieve low-density lipoprotein cholesterol (LDL-C) of <70 mg/dL with oral lipid-lowering therapies (LLT) only, whereas 14% would require a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. We aim to estimate these values accounting for varying levels of statin intolerance. A simulation model described previously was used to estimate the utilization of LLT needed to achieve LDL-C <70 mg/dL via an intensification algorithm which maximized statins before adding ezetimibe or a PCSK9 inhibitor. The current analysis took into account varying background rates of statin intolerance. We defined statin intolerance as either partial (inability to tolerate high-intensity statin) or full (inability to tolerate any statin). With treatment intensification and 10% of patients having partial statin intolerance, the use of ezetimibe (± statin ± PCSK9 inhibitor) increased from 32.7% to 34.9%, and the need for a PCSK9 inhibitor (+ ezetimibe ± statin) increased from 14.0% to 15.5%. If, instead, 10% were fully statin intolerant, the use of ezetimibe (± statin ± PCSK9 inhibitor) increased from 32.7% to 38.5%, and the use of a PCSK9 inhibitor (+ ezetimibe ± statin) increased from 14.0% to 19.7%. In conclusion, in our simulation-based study, partial statin intolerance increased the need for nonstatins only modestly (by an absolute 2.2%), whereas having 10% of patients with full statin intolerance increased the need for PCSK9 inhibitors from 14% overall to approximately 20%.**  **(Am J Cardiol 2019;123:1202−1207)**

Although statins are recommended as first-line lipid-lowering therapy (LLT) in patients with atherosclerotic cardiovascular disease (ASCVD),[1,2] recent guidelines and/or consensus statements recommend the use of ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in certain patients who are unable to achieve therapeutic goals with statins alone or who are statin intolerant.[3−5] Although no definitive rate of statin intolerance has been established,[6−8] observational studies suggest that up to 25% of patients initiating statins experience some degree of statin intolerance, which contributes to nonadherence, increased incidence of ASCVD events, and higher healthcare costs.[9−11] In a previous study, we reported estimates on the utilization of various LLTs for achieving specific low-density lipoprotein cholesterol (LDL-C) goals via an intensification algorithm which maximized statins before adding ezetimibe or a PCSK9 inhibitor.[12] We concluded that approximately 14% of the ASCVD population would require a PCSK9 inhibitor to reach an LDL-C goal of <70 mg/dL; however, a criticism of that research was a lack of accounting for statin intolerance.[13,14] The objective of this report was to re-estimate the utilization of LLTs taking into account nonzero background statin intolerance rates.

## Methods

The methodology underlying the development of a Monte Carlo simulation model for LLT intensification has been described previously.[12] Briefly, we utilized the MarketScan claims database to identify ASCVD patients ≥21 years of age during 2012 to 2013 (database cohort; n = 105,269). Patients were randomly sampled with replacement from the database cohort (simulation cohort; n = 1,000,000) and entered the simulation model on their current LLT. Each patient in the simulation cohort traced a different probabilistic path. If no statin was present,

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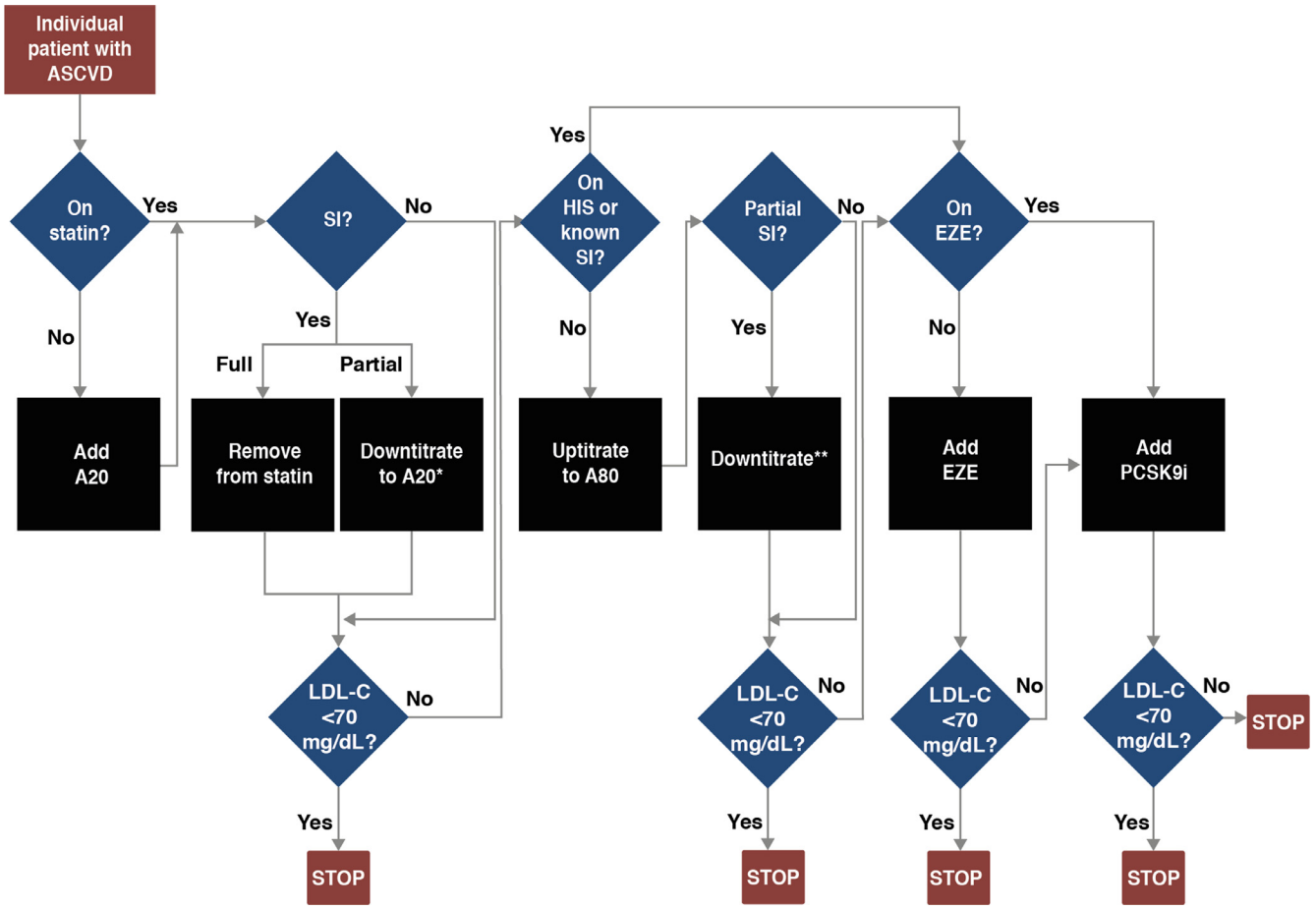


Figure 1. Logic of lipid-lowering therapy intensification in the simulation.
*Only applicable to those on HIS at baseline; **Patient downtitrated to A20 if not on statin at baseline, else downtitrated to the baseline MIS
A20 = atorvastatin 20 mg; A80 = atorvastatin 80 mg; ASCVD = atherosclerotic cardiovascular disease; EZE = ezetimibe; HIS = high-intensity statin; LDL-C = low-density lipoprotein cholesterol; MIS = moderate- to low-intensity statin; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; SI, statin intolerance.

atorvastatin 20 mg was initiated, and achieved LDL-C level was modeled probabilistically. If LDL-C was ≥70 mg/dL, treatment was further intensified in a stepwise manner using the following approach to achieve LDL-C of <70 mg/dL: uptitration to atorvastatin 80 mg, add-on ezetimibe, add-on a PCSK9 inhibitor.

We undertook an enhancement of the simulation model to include partial and full statin intolerance (Figure 1). We defined partial statin intolerance 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 any statin at any dose. An individual patient at baseline was probabilistically assigned as having partial, full, or no statin intolerance by sampling from a uniform distribution. An overall rate of statin intolerance across the simulation cohort was specified for a given model run. If the patient was deemed to have partial or full statin intolerance (assessed after ensuring a patient was on a statin), the individual was either downtitrated or taken off statin, respectively, with a corresponding increase in LDL-C. Only patients on a high-intensity statin at baseline could be identified as being partially statin intolerant at this initial check, and were downtitrated to atorvastatin 20 mg. In those who did not achieve LDL-C <70 mg/dL after this step, patients with established statin intolerance progressed to ezetimibe before considering a PCSK9 inhibitor. The remaining population was uptitrated to atorvastatin 80 mg and then checked for partial statin intolerance. If the patient had partial statin intolerance, the patient was downtitrated to atorvastatin 20 mg if they were not on statin at baseline or downtitrated back to their moderate- to low-intensity statin from baseline. Those who did not achieve LDL-C <70 mg/dL after this step progressed to add-on ezetimibe or a PCSK9 inhibitor, in accordance with the original simulation model. The partial and full statin intolerance rates were varied from 0% to 10% with increments of 1%, resulting in a total of 121 model runs. In order to better align with prescribing practices of PCSK9 inhibitors across the world, we also ran a scenario analysis where we increased the LDL-C threshold for intensification to a PCSK9 inhibitor from 70 mg/dL to 100 mg/dL.

## Results

Baseline characteristics of the database and simulation cohorts have been described previously.[12] Approximately

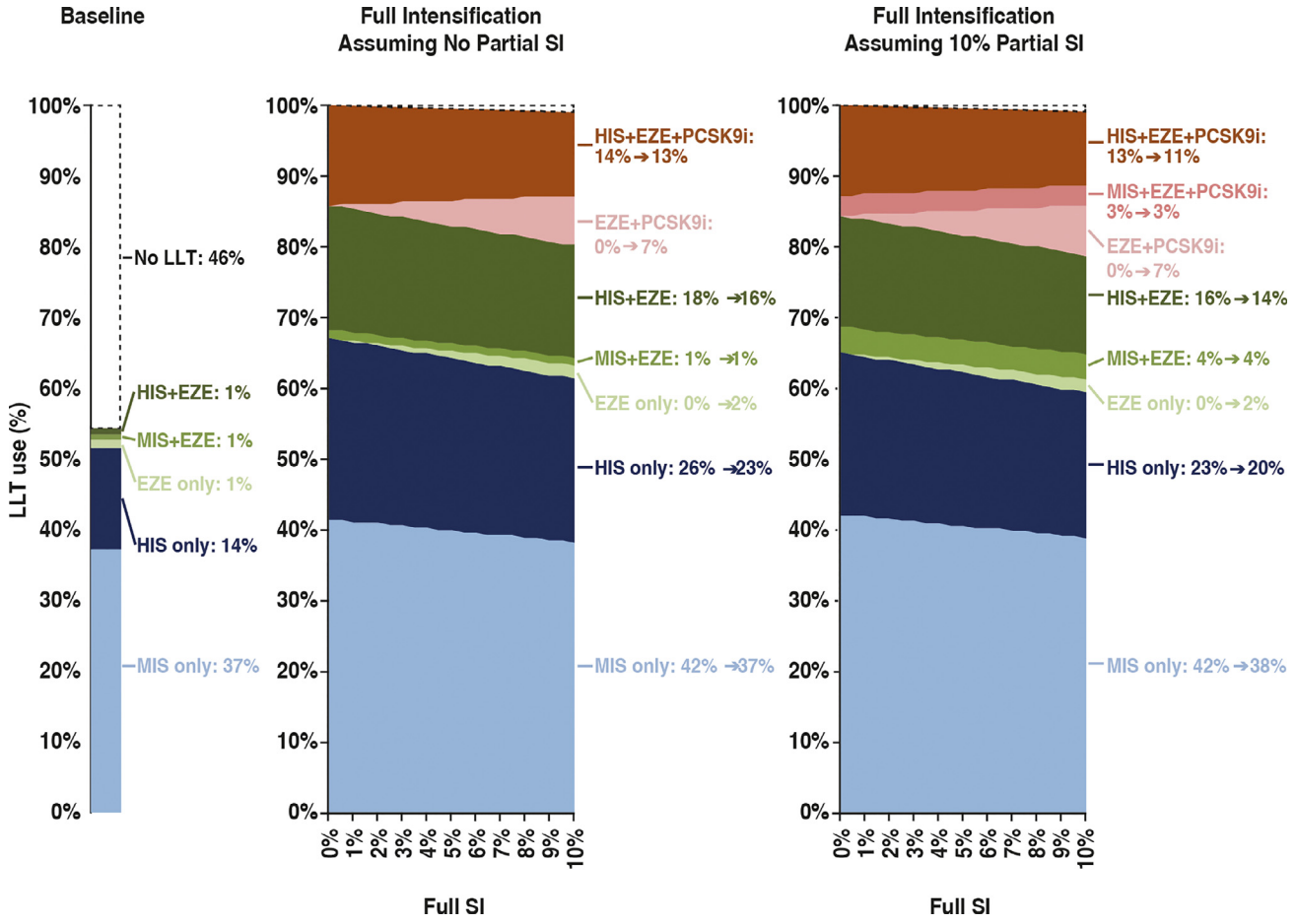


Figure 2. Use of lipid-lowering therapies with full intensification by varying rates of full SI.
Percentages in legends under full treatment intensification scenarios (XX% → XX%) represent use of LLTs with 0% and 10% full SI.
EZE = ezetimibe; HIS = high-intensity statin; LLT = lipid-lowering therapy; MIS = moderate- to low-intensity statin; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; SI = statin intolerance.

5.4% of the simulated population had recent acute coronary syndrome, 66.3% had coronary heart disease, 26.6% had ischemic cerebrovascular disease, and 31.4% had peripheral arterial disease. The median baseline LDL-C of the simulated cohort was 88 mg/dL (interquartile range 69 to 113).

Figure 2 provides a summary of the utilization of various LLTs at baseline, and with full intensification accounting for varying rates of full and partial statin intolerance rates of 0% and 10%. Assuming zero statin intolerance, approximately 68% were able to achieve LDL-C goal on statin alone; however, when 10% had full statin intolerance, the percentage on statins alone decreased to 60%. If an additional 10% had partial statin intolerance only 58% were able to achieve LDL-C goal on statins alone, whereas the remaining 41% required a nonstatin LLT.

Figure 3 provides a summary of the impact on the use of ezetimibe and PCSK9 inhibitors when both partial and full statin intolerance were simultaneously varied from 0% to 10%. When we begin modeling some percentages of patients as having statin intolerance, the use of ezetimibe and PCSK9 inhibitors increased to differing degrees. For example, in a model where 10% of patients had partial statin intolerance, the use of ezetimibe (± statin ± PCSK9 inhibitor) increased modestly from 32.7% to 34.9% and use of PCSK9 inhibitor (+ ezetimibe ± statin) increased from 14.0% to just 15.5%. If, instead, we examined a scenario where 10% of patients have full statin intolerance, the use of ezetimibe (± statin ± PCSK9 inhibitor) increased from 32.7% to 38.5% and use of PCSK9 inhibitor (+ ezetimibe ± statin) increased from 14.0% to 19.7%. In a scenario with a 10% rate for both partial and full statin intolerance versus a scenario with 0% rate for both full and partial statin intolerance, the use of ezetimibe (± statin ± PCSK9 inhibitor) increased from 32.7% to 40.7%, and the use of PCSK9 inhibitor (+ ezetimibe ± statin) increased from 14.0% to 21.1%.

When we increased the threshold for intensification to PCSK9 inhibitor from 70 mg/dL to 100 mg/dL, the use of PCSK9 inhibitor decreases from 14% to 2.3% in a scenario where there is no statin intolerance. However, with a 10% rate for both partial and full statin intolerance, the need for PCSK9 inhibitors increases from 2.3% to 6.5% in a population with ASCVD (Figure 4).

## Discussion

With clinical trial evidence supporting the addition of nonstatin agents to lower LDL-C to achieve additional cardiovascular benefit,[15–17] the cost of adding the newest class

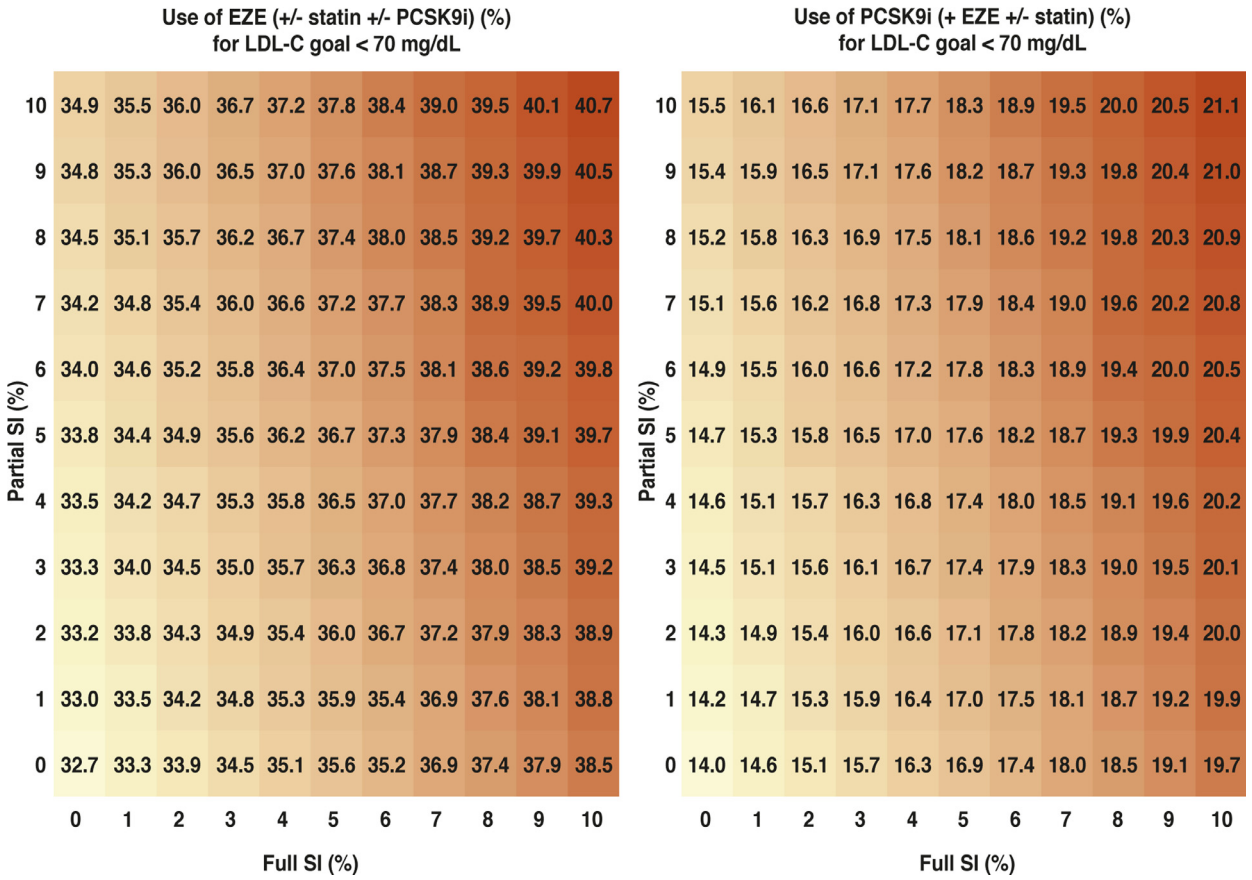


Figure 3. Use of ezetimibe and PCSK9 inhibitor with full intensification by varying rates of full and partial SI.
The contours of shading are intended to represent the varying levels of ezetimibe and PCSK9 inhibitor use.
EZE = ezetimibe; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; SI = statin intolerance.

of drugs, PCSK9 inhibitors, has come into focus.[2] In our previous study, we reported on the implications on the use of statins, ezetimibe, and PCSK9 inhibitors, for achievement of an LDL-C goal of <70 mg/dL in an ASCVD population. Although we assumed no tolerability issues in that study, in the current analysis, we assessed the impact of the incidence of statin intolerance on the findings. We found that the use of PCSK9 inhibitor (+ ezetimibe ± statin) was influenced by both partial and full statin intolerance, with full statin intolerance having a relatively larger impact (10% rate of full statin intolerance increased use from 14.0% to 19.7%). When both partial and full statin intolerance were assumed simultaneously at a rate of 10%, the overall impact on the use of ezetimibe (± statin ± PCSK9 inhibitor) increased by 8 percentage points, from 32.7% to 40.7%, whereas the overall impact on the use of PCSK9 inhibitor (+ ezetimibe ± statin) increased by 7 percentage points, from 14.0% to 21.1%. This analysis suggests that utilization of these newer PCSK9 inhibitor agents could increase by 50% in the scenario where up to 20% of patients have some degree of statin intolerance. As such, careful management and trials of oral agents will be helpful in managing the cost of the newer class of drugs.

Based on cost and/or clinical considerations, recommendations on the use of PCSK9 inhibitors have been issued. For example, among patients with ASCVD, the European Atherosclerosis Society/European Society of Cardiology recommends using PCSK9 inhibitors when LDL-C is ≥140 mg/dL. However, for those at very high risk, a PCSK9 inhibitor may be considered if LDL-C is ≥70 or 100 mg/dL, depending on the geographic region.[2,5] In our analysis, restricting PCSK9 inhibitors to only those with LDL-C ≥100 mg/dL resulted in a significant decrease in their use. When a 10% rate of partial statin intolerance was considered, the use of PCSK9 inhibitors decreased from 15.5% to 2.7%. When both a 10% rate of partial and full statin intolerance were considered, the use of PCSK9 inhibitors decreased from 21.1% to 6.5%, a 70% decrease in their predicted use.

Unfortunately, tolerability issues with statins, most notably "statin associated muscle symptoms" have resulted in underutilization and/or suboptimal dosing,[18] which leads to untoward effects. Although nonstatin LLT can be effective treatment options for high-risk patients, the use of these agents should be considered only after adequate trials of statins. Although identification of "real" statin intolerance can be challenging, one study examining patients who discontinued statin with documented statin-related events found that 92.2% were able to tolerate the statin after rechallenge.[19] Recently, Rosenson et al reported on the development of Statin Associated Muscle Symptom − Clinical Index (SAMS-CI) instrument to better understand whether adverse muscle symptoms experienced by a patient can be attributed to statins.[20] The negative predictive value of the SAMS-CI was found to be 91%, suggesting that

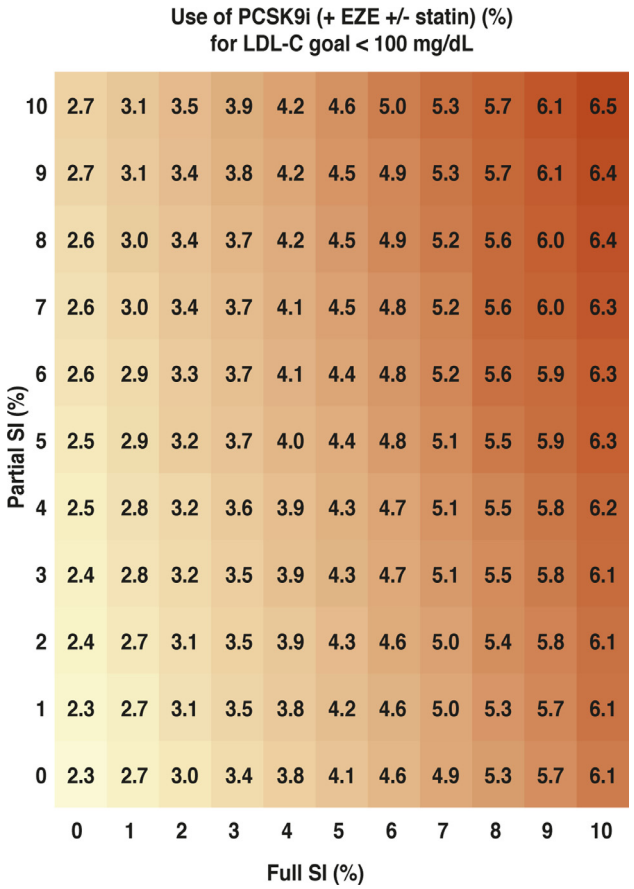


Figure 4. Use of PCSK9 inhibitor with full intensification by varying rates of full and partial SI when LDL-C threshold increases from 70 mg/dL to 100 mg/dL.
EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; SI = statin intolerance.

clinicians may use the tool to encourage statin continuation in patients who believe they have statin intolerance because of muscle-related symptoms.[21]

The present study has several limitations. The rates of statin intolerance modeled were somewhat arbitrary. We also assigned patients to either partial and full statin intolerance at random, which assumed independence of statin intolerance status and patient characteristics. Nonetheless, our estimates found that the need for ezetimibe and PCSK9 inhibitors was only modestly increased with partial statin intolerance, and PCSK9 use increased from 14% to 21% if 10% full and 10% partial statin intolerance existed in 10% of the patients, highlighting the need to pay careful attention to this issue since it will have an impact on the need for this new class of drugs.

## Disclosures

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## Additional Contributions

Natasha Kulkarni, BS, and Divya Gaur, MS, Axtria, supported the development and execution of simulation model and development of manuscript drafts. Xue Song, PhD, Truven Health Analytics, an IBM company, supported the development of the baseline ASCVD cohort. All additional contributors were funded by Sanofi and Regeneron Pharmaceuticals, Inc.

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