Simulation of impact on cardiovascular events due to lipid-lowering therapy intensification in a population with atherosclerotic cardiovascular disease

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Background In patients with atherosclerotic cardiovascular disease (ASCVD), guidelines recommend statins as first-line lipid-lowering therapy (LLT) with addition of nonstatin agents in those with persistently elevated low-density lipoprotein cholesterol levels.

Methods To estimate the cardiovascular (CV) risk reduction implications of treatment intensification, we used a previously reported simulation model with enhancements. An ASCVD cohort was developed from a US claims database. A Cox model was used to estimate baseline risk of CV events: myocardial infarction, ischemic stroke, unstable angina hospitalization, elective coronary revascularization, or cardiovascular death. Patients were sampled with replacement (bootstrapping) and entered the simulation model, which applied stepwise LLT intensification logic, with a goal of achieving low-density lipoprotein cholesterol less than 70 mg/dL at each step. CV risk reduction assumptions were based on published data. Two treatment intensification scenarios were investigated: ideal and real-world (which accounted for statin intolerance, nonadherence, and payer restrictions).

Results In a cohort of 1,000 patients with ASCVD, approximately 813 (809-818) would require treatment intensification with LLT under an ideal treatment intensification scenario. Before treatment intensification, 183 (179-187) events would be expected to occur over 5 years. With treatment intensification, 40 (34-45) of these events could be avoided. In a real-world scenario, about 818 (813-823) patients require treatment intensification with LLT, resulting in 29 (24-34) events avoided over 5 years.

Conclusions Intensification of LLT in an ASCVD population translates into a substantial number of CV events avoided. This simulation-based model could assist in assessing the potential benefits of various types of population-level LLT interventions. (Am Heart J 2019;216:30-41.)

Low-density lipoprotein cholesterol (LDL-C) reduction with statins, and more recently with nonstatins, has been shown to reduce the risk of cardiovascular (CV) events, especially in individuals with established atherosclerotic CV disease (ASCVD).[1-4] The 2018 American College of Cardiology/American Heart Association guidelines, 2017 American College of Cardiology consensus pathway, 2016 European Society of Cardiology/European Atherosclerosis Society guidelines, and the 2017 European Society of Cardiology/European Atherosclerosis Society consensus statement recommend similar strategies in patients with ASCVD. Generally, a strategy using high-intensity or maximally tolerated statins as first-line therapy, with consideration of add-on nonstatin therapy in those with LDL-C $\geq$70 mg/dL while on statin therapy, is recommended.[5-8] In a prior study, we reported findings from a simulation model to evaluate lipid-lowering therapies (LLTs) that would need to be added or uptitrated if a

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patient's LDL-C was greater than 70 mg/dL.[9] In the current study, we expanded the scope of the simulation model to incorporate statin intolerance, nonadherence, and payer restrictions, and sought to evaluate implications on how many CV events could be prevented with LLT intensification.

Methods

The methodology for the development of the ASCVD cohort that was simulated has been described in detail in a previous report,[9] although several additional analyses were conducted in the current study. Briefly, we identified a population at least 21 years of age with ASCVD in the MarketScan research database during 2012-2013. Patients' ASCVD conditions, clinical characteristics, treatment status with LLT and other medications, and lipid levels were assessed as of a point in time (index date), defined as the most recent LDL-C measurement during 2012-2013. A lookback period of 2 years was used to ascertain prevalent ASCVD and other clinical conditions, whereas treatment status, lipid levels, and demographic characteristics (eg, age) were ascertained as of the index date.

Patients were classified into ASCVD subpopulations representing the following conditions: recent acute coronary syndrome (ACS; defined as myocardial infarction [MI] or unstable angina [UA] hospitalization during past 1 year), ischemic cerebrovascular disease (ICBVD; representing ischemic cerebrovascular conditions with and without a history of ischemic stroke), stable coronary heart disease (stable CHD; excluding recent ACS), and peripheral arterial disease (PAD). As it was possible for a patient to have several of these ASCVD conditions, to facilitate mutually exclusive categorization, we classified patients into the highest mutually exclusive ASCVD condition (using the aforementioned order) for which they qualified. As an example, an individual with a history of elective coronary revascularization and PAD was classified as having stable CHD. Thus, while the recent ACS category could represent other concomitant ASCVD conditions, the PAD category represented patients with only PAD. This method of categorization into mutually exclusive groups helped facilitate a comparison of findings between ASCVD subpopulations in a manner that is not influenced by an overlap between them.

Estimation of baseline CV event risk

Patients in the database were followed for CV events from the index date up to December 31, 2014, which facilitated analyses of 1-year risk for CV events; these were defined as CV death, MI, ischemic stroke, UA hospitalization, and elective coronary revascularization. Except for CV death, all events were defined as nonfatal. Diagnosis and procedure codes used for identifying these events are summarized in Supplementary Table SI and have been investigated in previous reports. For example, the codes used for identifying MI and ischemic stroke were reported to have positive predictive values of 96.9% and 91.1%, respectively.[10,11] MI, ischemic stroke, and UA hospitalization required inpatient hospitalization, whereas criteria for elective coronary revascularization were applied to either the inpatient or outpatient settings. CV death in the inpatient setting was based on discharge of death along with other CV-related discharge diagnoses (Supplementary Table SI).

Mortality in the outpatient setting was ascertained via the Social Security Administration Death Master File (SSA-DMF).[12] Only a subset of the ASCVD cohort qualified for a link to the SSA-DMF; as such, the analysis of baseline CV risk was limited to this subpopulation (baseline risk analysis subset). We compared the characteristics of the baseline risk analysis subset with the remaining ASCVD population. The assignment of death as being CV related in the outpatient setting was probabilistic and based on an imputation methodology that relied on a logistic model derived from the inpatient setting. As we used the public version of the SSA-DMF, the mortality recording was expected to be incomplete, resulting in an underestimation of CV deaths in the outpatient setting.[12] We estimated the degree of incompleteness in the SSA-DMF by comparison of death rates with the US Life Table Data[13] and adjusted CV death rates in our analysis by this factor. The details of the estimation of this adjustment factor are available in the "Methods" section of the supplement. As a sensitivity analysis, we summarized our main findings with and without this adjustment (Supplementary Table SII).

A multivariate Cox model based on patients' baseline demographic and clinical characteristics, as ascertained during the 2-year baseline period prior to the index date, was developed to estimate patient-specific baseline CV risk for the composite of CV death, MI, ischemic stroke, UA hospitalization, or elective coronary revascularization (Supplementary Figure S1). Validation of the Cox model was conducted by comparing 1-year risk estimates from the Cox model to those from a Kaplan-Meier (KM) analysis. A multinomial logistic regression based on the same baseline patient characteristics (Supplementary Figure S2) was used together with the Cox model to probabilistically model the occurrence of individual CV event types in the simulation. Validation of the multinomial model was also based on a comparison of 1-year risk estimates by CV event types from the multinomial model to those from KM analysis. The 1-year Cox multinomial risk model was then implemented in the simulation at the patient level and iteratively used over a 5-year horizon to probabilistically generate first CV events. As only first events were captured in this model, any subsequent references to events refer to first events.

One of the variables in the 1-year Cox multinomial risk model was an indicator variable for an ACS event during

the prior 1 year (recent ACS flag). For a patient with recent ACS, the simulation proceeded by switching the recent ACS flag on and applying the recent ACS risk over 1-year follow-up post index date. After the 1-year period, the recent ACS flag is switched off and baseline risk is reestimated. As such, the simulation methodology effectively captured an elevated risk in those with an ACS event during the prior 1 year, for up to 1 year of follow-up, after which the risk returned to a level as predicated by other factors.

Monte Carlo simulation model

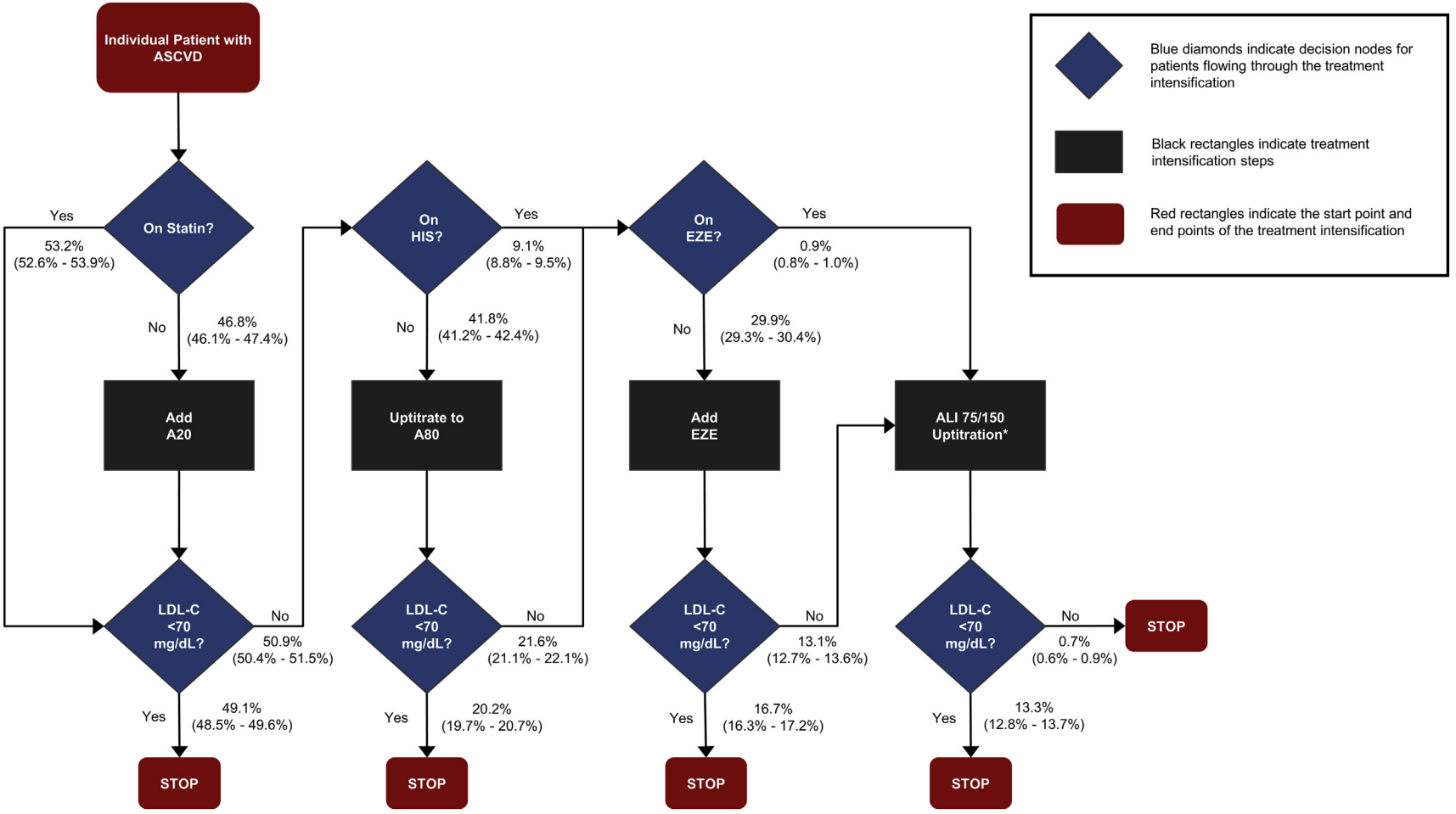
The development of the Monte Carlo simulation model for treatment intensification has been described in detail previously.[9] The Monte Carlo simulation model was reprogrammed in Python[14] to support the additional complexity and objectives of the current study. The study population used for the simulation model was developed by randomly sampling patients with replacement (bootstrapping methodology) from the database cohort. The random sampling continued until at least 25,000 patients per treatment intensification step were simulated. This process was repeated 1,000 times to estimate confidence intervals (CIs) and ensure stable results for key measures, such as the CV risk reduction. The proportion of patients (95% CI) at each intensification step was estimated from the median (2.5th-97.5th percentile) of 1,000 simulations of 25,000 patients. This was multiplied by 1,000 to obtain the number of patients (95% CI) at each intensification step such that the results can be interpreted in terms of a base population of 1,000 patients simulated. The number of events avoided (95% CI) at each intensification step was estimated by multiplying the number of patients by the median, lower 95% CI, and upper 95% CI absolute risk reductions (ARRs) as estimated from 1,000 simulations of 25,000 patients per intensification step. Sampling weights were used in the bootstrap sampling methodology to account for quantifiable differences in the characteristics of the database cohort relative to generalizable sources and to allow for findings that are more representative of the overall US population with ASCVD.[9] These weights were calculated by first segmenting patients from the database cohort into distinct groups (or strata) based on their combination of comorbidities, gender, and age ranges. Discrete scaling factors were then determined for each of these strata based on the national prevalence of various comorbidities. Further details regarding this estimation methodology are available in a previous report.[9]

The Monte Carlo simulation model was adapted to run an ideal and real-world treatment intensification scenario. The ideal treatment intensification scenario (referred to as the *base-case scenario* in a previous report)[9] used a treatment intensification logic (Figure 1), which maximized the use of statins before augmenting with ezetimibe or alirocumab (a proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitor), if needed, to achieve an LDL-C of less than 70 mg/dL. At each step in the treatment intensification pathway for an individual patient, the achieved LDL-C was modeled probabilistically from the distribution of LDL-C reduction with a given LLT.[9] An alternate real-world treatment intensification scenario used the same treatment intensification logic as the ideal scenario, with the addition of real-world treatment-limiting factors (Figure 2). The factors implemented in this scenario were nonadherence to LLTs, statin intolerance, and payer restrictions for PCSK9 inhibitors. In this scenario, 10% of patients who entered the simulation already on an LLT at baseline and 20% who were not on an LLT at baseline were deemed nonadherent and removed from their LLTs half-way (at 2.5 years) through the simulation horizon of 5 years. Furthermore, 5% of all patients entering the treatment logic were considered to be fully statin intolerant and 5% partially statin intolerant. The methodology underlying modeling full and partial statin intolerance is similar to the one adopted in a previous report.[15] Finally, 50% of all patients not reaching goal with add-on ezetimibe were assumed to be unable to access a PCSK9 inhibitor due to payer restrictions.[16]

If a patient received treatment intensification with atorvastatin 20 or 80 mg, the CV risk was modified in accordance with the Cholesterol Treatment Trialists' (CTT) 2010 meta-analysis.[1] This same relationship was applied to model the CV risk reduction with add-on ezetimibe, as findings from the IMPROVE-IT trials are supportive of this assumption.[2] A log-linear model of the form $\ln(RR) = \ln(1-\alpha)\,\Delta$LDL-C was assumed, where RR denotes the ratio of risk after and before LDL-C reduction. The summary interpretation of parameter α is the relative risk reduction per unit LDL-C reduction, with $\alpha \approx 22\%$ as per CTT data. Regarding PCSK9 inhibitors, we estimated α as $1-\exp(\ln(HR)/\Delta\text{LDL-C})$, where HR denotes the hazard ratio, by directly using data at the median follow-up from ODYSSEY OUTCOMES and FOURIER trials.[3,4]

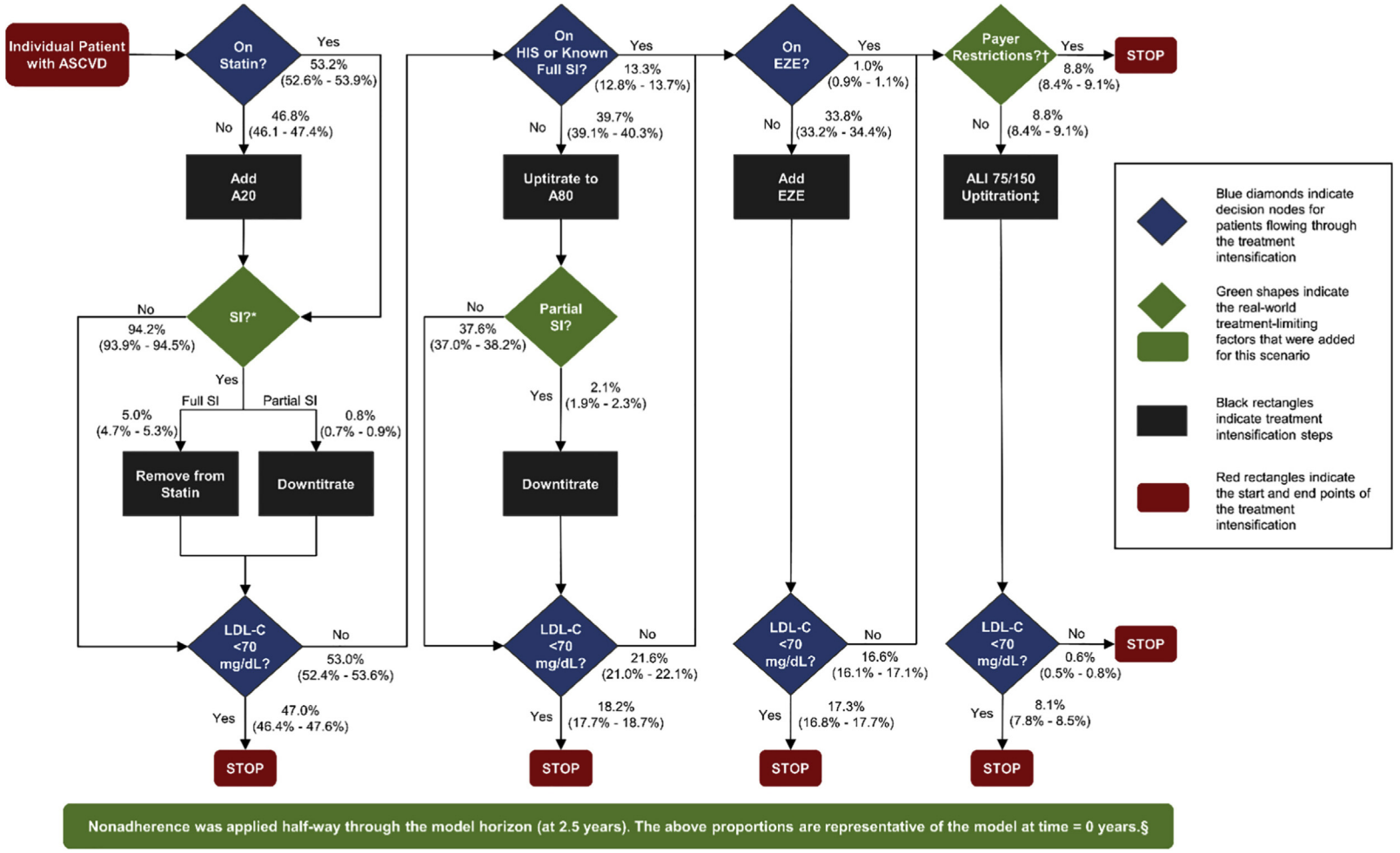
The simulation used alirocumab as the PCSK9 inhibitor therapy, with assumptions informed from the ODYSSEY OUTCOMES trial. A scenario analysis used evolocumab as the PCSK9 inhibitor, with assumptions informed from the FOURIER trial. In the simulation, α varied by CV event types (eg, by nonfatal MI, ischemic stroke, and CV death end points) and was probabilistically determined per patient iteration with assumptions informed by reported CIs in the CTT 2010 meta-analysis, as well as the ODYSSEY OUTCOMES and FOURIER trials. CV events were probabilistically generated for each patient over 5 years by iteratively using the 1-year risk model for baseline risk along with modeled risk reduction (RR in the previous formula) due to LLT intensification. A 5-year horizon in the simulation was chosen to better align relevance of findings to clinicians and healthcare

Figure 1



Logic of LLT intensification and proportion of patients at intensification steps for the ideal treatment intensification scenario. An individual patient initiates the simulation at the top box in red background and flows though the simulation logic via decision nodes (diamond symbols) and LLT intensification steps (boxes with a black background). The percentages represent the proportion of patients taking a specified path out of the total ASCVD cohort. Estimates are based on the median (95% CI) of 1,000 iterations of a simulation of 25,000 patients. All patients in the simulation end up at one of the STOP nodes. *The proportion of patients achieving goal after these steps is combined for figure simplicity. A20, atorvastatin 20mg; A80, atorvastatin 80mg; ALI 75, alirocumab 75 mg; ALI 150, alirocumab 150 mg; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; EZE, ezetimibe; HIS, high-intensity statin; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy.

Figure 2



Logic of LLT intensification and proportion of patients at various intensification steps for the real-world treatment intensification scenario. Please see next page for figure footnote.

providers. For the real-world treatment intensification scenario, nonadherence to LLTs was implemented halfway through this time horizon at 2.5 years. At this point, patients not having an event in the first 2.5 years had a chance of becoming nonadherent (10% chance for those who entered the simulation already on an LLT at baseline and 20% for those who were not on an LLT at baseline). Each patient traced a unique path in the simulation depending on their baseline characteristics, probabilistic sampling of LDL-C reduction with a given LLT, and probabilistically determined time to CV events.

Statistical analyses

Demographics, clinical characteristics, and medication utilization at baseline for the database and simulation cohorts were summarized descriptively via means, medians, and proportions as appropriate. Key summary measures from the simulation cohort such as the 5-year CV event risk, ARR, relative risk reduction (RRR), number needed to treat (NNT), and number of events avoided were estimated from patient-level simulated results. Reported summary measures represent the median of 1,000 iterations of the simulation with n = 25,000 patients at each iteration, unless otherwise stated. Using these iterations, 95% CIs were estimated by using the 2.5th and 97.5th percentiles. A choice of n per iteration had to be made a priori, as the estimated CIs depend on this choice. We chose n = 25,000 to align with typical population size in recent clinical trials for LLTs (eg, IMPROVE-IT, ODYSSEY OUTCOMES, and FOURIER) and also as an ASCVD population size that is potentially relevant for stakeholders (eg, payers and healthcare systems) for which the findings are likely to be useful.

Results

We identified 105,269 patients with ASCVD in the database cohort (Supplementary Figure S3). The mean (SD) age was 65.1 (12.1) years, 57.2% were male, and the mean (SD) LDL-C was 93.9 (34.9) mg/dL. Table I provides a summary of the baseline characteristics for the database and simulation cohorts. Also summarized in Table I are characteristics of the database cohort with and without availability of mortality information, where the subset with mortality information was used for the estimation of baseline CV risk. All subsequent results are estimated from a cohort of 25,000 patients with ASCVD randomly sampled from the database cohort 1,000 times (for generating the CIs), as described in the "Methods" section.

Key results for the ideal treatment intensification scenario regarding treatment with LLTs, and LDL-C levels at baseline and with treatment intensification were either similar or identical to those in the previous report describing the simulation model.[9] Out of the overall cohort at baseline, approximately 53.2% (52.6%-53.9%) were already on a statin, and 25.3% (24.7%-25.8%) achieved LDL-C of less than 70 mg/dL. Approximately 81.3% (80.9%-81.8%) of the cohort required treatment intensification because of either a lack of statin treatment at baseline or not achieving LDL-C of less than 70 mg/dL. After full treatment intensification, 99.3% (99.1%-99.4%) achieved LDL-C of less than 70 mg/dL. Of those, 67.3% (66.7%-67.8%) required statin monotherapy, 18.7% (18.3%-19.2%) required statins and ezetimibe only, and 14.0% (13.6%-14.4%) required an add-on PCSK9 inhibitor. Supplementary Table SIII provides a comprehensive summary of the proportion of patients requiring treatment intensification and who achieved LDL-C levels by treatment intensification steps and ASCVD subpopulations.

In the real-world treatment intensification scenario, approximately 81.8% (81.3%-82.3%) of patients required treatment intensification. After full treatment intensification, only 90.6% (90.2%-91.0%) achieved LDL-C of less than 70 mg/dL (as compared to 99.3% in the ideal scenario). The main driver behind the decrease in the proportion of patients reaching goal was the addition of payer restrictions (50% of the patients that were eligible for a PCSK9 inhibitor were not given the treatment). In total, 62.8% (62.2%-63.5%) required statin monotherapy, 25.2% (24.6%-25.7%) required statins and ezetimibe only, and 17.6% (17.0%-18.0%) required an add-on PCSK9 inhibitor (with only 8.8% [8.4%-9.1%] getting treatment due to payer restrictions). Figure 2 provides a detailed picture of the real-world treatment intensification

Logic of LLT intensification and proportion of patients at various intensification steps for the real-world treatment intensification scenario. An individual patient initiates the simulation at the top box in red background and flows though the simulation logic via decision nodes and LLT intensification steps. The percentages represent the proportion of patients taking a specified path out of the total ASCVD cohort. Estimates are based on the median (95% CI) of 1,000 iterations of a simulation of 25,000 patients. All patients in the simulation end up at one of the STOP nodes. *Patients entering this step had a 5% chance of becoming fully statin intolerant, and a 5% chance of becoming partially intolerant. Of those that are partially intolerant, only 0.8% are downtitrated in the initial check since it is limited to patients already on an HIS at baseline, 2.1% are downtitrated at the next check, and about 2.0% are on an MIS at baseline and are not downtitrated. †50% of patients eligible for add-on PCSK9i were randomly assigned not to initiate treatment to simulate payer restrictions. ‡The proportion of patients achieving goal after these steps is combined for figure simplicity. §10% of patients who entered the simulation already on an LLT at baseline and 20% who were not on an LLT at baseline were deemed non-adherent and removed from their LLTs. A20, atorvastatin 20 mg; A80, atorvastatin 80 mg; ALI 75, alirocumab 75 mg; ALI 150, alirocumab 150 mg; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; EZE, ezetimibe; HIS, high-intensity statin; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; SI, statin intolerance.

Table I. Baseline characteristics for the database and simulation cohorts

	Database cohort*	Database cohort with mortality information†	Database cohort without mortality information	Simulation cohort‡
	(n = 105,269)	(n = 61,699)	(n = 43,570)	(n = 25,000)
Demographic characteristics				
Age, mean, y	65.1	65.4	64.7	66.5
Age ≥ 75 y, %	23.4	23.1	23.9	26.9
Male, %	57.2	60.7	52.3	54.9
Medicare,§ %	45.9	47.5	43.5	52.6
US Region, %				
South	20.2	24.1	14.6	18.4
Northeast	21.4	3.2	47.1	21.6
Midwest	22.1	28.3	13.3	22.2
West/other	36.4	44.4	25.0	37.7
Baseline clinical characteristics				
Recent ACS, %	5.6	5.6	5.6	5.4
Stable CHD, %	68.4	69.3	67.0	66.3
ICBVD, %	24.5	22.7	27.1	26.6
PAD, %	29.4	29.0	30.0	31.5
DM, %	35.9	36.3	35.3	36.2
Other comorbidities				
Hypertension, %	82.1	81.7	82.5	82.8
Heart failure, %	18.3	18.0	18.7	19.0
CKD, stage III, %	11.3	11.6	11.0	12.4
CKD, stage IV-V,‖ %	4.3	4.3	4.2	4.5
Concomitant medication use				
β-Blockers, %	44.3	44.4	44.3	44.7
ACEI/ARBs, %	46.9	47.7	45.7	47.2
Antiplatelets,¶ %	23.8	23.8	23.8	23.4

ACEI, angiotensin converting enzyme inhibitor; *ACS*, acute coronary syndrome; *ARB*, angiotensin II receptor blocker; *ASCVD*, atherosclerotic cardiovascular disease; *CHD*, coronary heart disease; *CKD*, chronic kidney disease; *DM*, diabetes mellitus; *ICBVD*, ischemic cerebrovascular disease; *PAD*, peripheral arterial disease; *SSA-DMF*, social security administration death master file.

* Database cohort refers to the cohort of patients with ASCVD developed from the claims database.

† Database cohort with mortality information refers to the subset of the database cohort that could be linked to mortality status via the SSA-DMF.

‡ Simulation cohort refers to a cohort of 25,000 patients sampled from the database cohort via bootstrapping. Values for the Simulation cohort represent the median of the 1,000 bootstrap iterations.

§ Represents health plan offered by a private company that contracts with Medicare to provide patients with hospital and medical insurance benefits.

‖ Includes dialysis.

¶ Includes clopidogrel, ticagrelor, and/or prasugrel.

scenario summarizing both the revised logic of intensification under this scenario, as well as the proportion of patients at various intensification steps. This figure represents the situation for patients at time 0, when nonadherence was not yet in effect (it was assumed to take effect at 2.5 years). Nonadherence was incorporated in the background as the patient progressed in the simulation, and its net effect is reflected in the number of events avoided.

Table II summarizes the number of patients and number of events avoided by treatment intensification steps in an ASCVD cohort of 1,000 patients for the ideal and real-world treatment intensification scenarios. As the number of events avoided is impacted by both the number of patients at individual intensification steps and the ARR at that step (see Figure 3 and Supplementary Table SIV for ARR by intensification steps), the progressive decline in number of events avoided in Table II is mainly driven by the incrementally smaller number of patients requiring further intensification. Approximately 813 (809-818) patients required treatment intensification in the ideal scenario. Before treatment intensification, approximately 183 (179-187) events would be expected to occur within 5 years. Treatment intensification resulted in 40 (34-45) of these events being avoided. In the real-world scenario, approximately 818 (813-823) patients required treatment intensification. In these patients, 185 (181-189) events would be expected to occur within 5 years, with 29 (24-34) events that could be avoided through treatment intensification. The treatment-limiting factors added to this scenario impacted both the proportion of patients at each treatment step and the corresponding reduction in risk due to treatment. Their effects on the number of events avoided are described in detail in the "Discussion" section.

Table II. Number of events avoided due to treatment intensification in an ASCVD cohort of 1,000 patients

	Ideal treatment intensification scenario		Real-world treatment intensification scenario*	
	No. of patients n (95% CI)	No. of events avoided n (95% CI)	No. of patients n (95% CI)	No. of events avoided n (95% CI)
Add atorvastatin 20 mg†	468 (461-474)	20 (17-23)	452 (446-459)	17 (14-20)
Uptitrate to atorvastatin 80 mg	418 (412-424)	9 (6-11)	376 (370-382)	7 (5-10)
Add ezetimibe	299 (293-304)	6 (4-8)	338 (332-344)	7 (5-9)
Alirocumab 75 mg/150 mg uptitration	140 (136-144)	5 (4-5)	88 (84-91)	3 (3-4)
All treatment intensification steps	813 (809-818)	40 (34-45)	818 (813-823)	29 (24-34)
No treatment intensification	187 (182-191)	0	182 (177-187)	0
Any oral LLT	809 (804-813)	35 (30-40)	815 (811-820)	26 (20-31)
PCSK9 inhibitor scenarios‡				
Alirocumab 75 mg/150 mg uptitration	140 (136-144)	5 (4-5)	88 (84-91)	3 (3-4)
Add-on alirocumab 150 mg only	140 (136-144)	5 (5-6)	88 (84-91)	4 (4-5)
Add-on evolocumab	140 (136-144)	3 (2-3)	88 (84-91)	2 (1-2)

ASCVD, atherosclerotic cardiovascular disease; *CI*, confidence interval; *HIS*, high-intensity statin; *LLT*, lipid-lowering therapy; *PCSK9*, proprotein convertase subtilisin/kexin type 9. Events avoided are based on first events. Estimates are based on the median (95% CI) of 1,000 iterations of a simulation of 25,000 patients.

*The real-world treatment intensification scenario incorporates the following factors: patient nonadherence to LLT, full and partial statin intolerance, and payer restrictions to PCSK9 inhibitors.

† This step also includes patients who are downtitrated from HIS due to partial statin intolerance in the real-world treatment intensification scenario.

‡ The clinical benefit of each PCSK9 inhibitor is based on specific outcomes reported in the corresponding outcomes trial (ODYSSEY OUTCOMES or FOURIER).

Figure 3 presents the summary findings of this simulation for the ideal treatment intensification scenario in terms of the more conventional measures of CV risk over 5 years for an overall ASCVD cohort of 1,000 patients. For the 813 (809-818) patients who required treatment intensification, the 5-year CV event risk at baseline was 22.5% (22.0%-23.0%), which was reduced to 17.6% (17.2%-18.1%) with full treatment intensification, thus representing an ARR of 4.9% (4.2%-5.5%), an RRR of 21.6% (19.1%-24.1%), and an NNT of 21 (18-24). Supplementary Figures S4 and S5 summarize the ARRs and NNTs by treatment intensification steps for ASCVD subpopulations. Additional tables describing the results from the ideal treatment intensification scenario can also be found in the supplement. Supplementary Table SIV provides a comprehensive summary of the 5-year CV event risk before and after treatment intensification, and the resulting ARRs, RRRs, and NNTs for ASCVD subpopulations. Supplementary Table SV provides the same measures by CV event types.

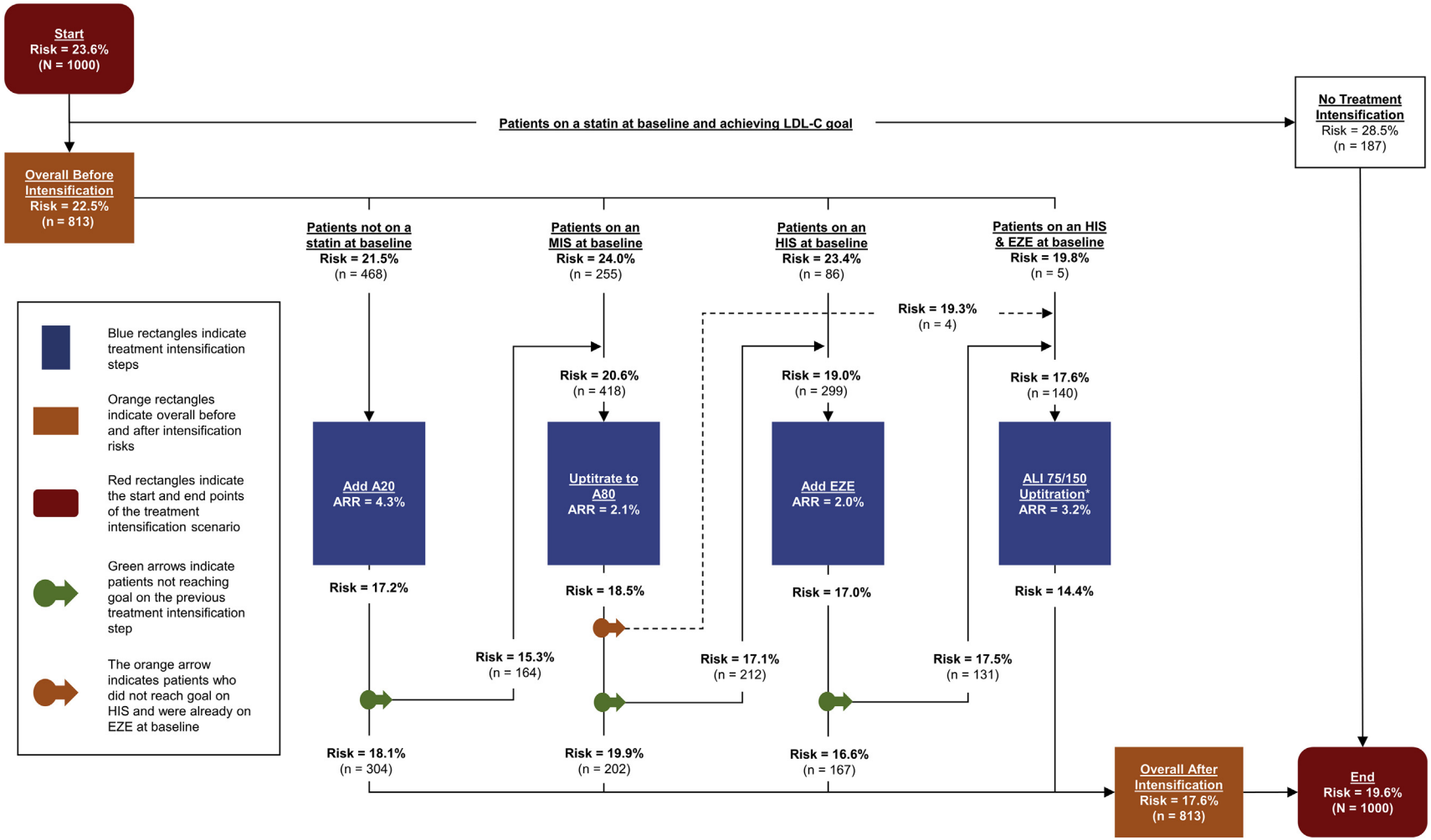
Discussion

Our study found that a substantial number of CV events could be prevented with the adoption of a stepwise approach to LLT intensification. We estimated that in a representative cohort of 1,000 patients with ASCVD, LLT would not need to be intensified in 187 patients (as it was already optimized per guidelines). In the remaining 813 patients, 183 (179-187) first events can be expected to occur within 5 years, indicating an opportunity for further CV risk reduction. Through ideal LLT intensification, 40 of these events can be avoided. This summary measure provides an appreciation of the potential CV burden that can be addressed in an ASCVD population. Real-world factors tend to reduce this clinical benefit. A real-world scenario that we investigated indicated that a more realistic estimate could be 29 events avoided (out of 185 [181-189] events) over 5 years with LLT intensification in 818 patients. Our simulation focused only on first events avoided, but insights from recent clinical trials indicate that the total number of events avoided by LLT is nearly double the number of first events avoided.[17,18] Our estimates thus represent approximately half of the true potential number of events avoided by LLT intensification.

Implications for ARR and NNT

The ARRs were influenced by a combination of factors representing patients' baseline CV risk, baseline LDL-C, LLT type, and where the LLT was introduced in the sequence of treatment intensification. When looking at intensification steps under the ideal treatment intensification scenario, the estimated ARR for simply adding atorvastatin 20 mg to those not initially on a statin was 4.3% (3.6%-5.0%). This large effect was in part due to an initial high baseline LDL-C level and the resultant larger absolute reduction in LDL-C in those not on statin. The ARRs for statin uptitration and add-on ezetimibe were somewhat smaller at 2.1% (1.4%-2.7%) and 1.9% (1.3%-2.5%), respectively, owing to the incrementally smaller impact on percent LDL-C reduction due to these steps and the fact that the baseline LDL-C levels in this subgroup were already lowered by the initial addition of atorvastatin 20 mg. The ARR for the subgroup requiring PCSK9 inhibitor (alirocumab 75/150 mg uptitration

Figure 3



Five-year CV event risk based on events for the ideal treatment intensification scenario. Number (n) of patients is based on an overall ASCVD cohort of 1,000 patients. Risk denotes the 5-year CV event risk based on first events. Estimates are based on the median of 1,000 iterations of a simulation of 25,000 patients. CIs are not reported for clarity but are available for most of the measures in Table II and Supplementary Table SIV. Green arrows indicate patients who did not reach goal on previous intensification steps and who are moving on to the next treatment. The patients exiting at the orange arrow indicate those that were already on ezetimibe at baseline but did not reach goal on statins and ezetimibe, and therefore will be receiving ALI 75/150. *The reduction in risk due to these steps is combined for figure simplicity. A20, atorvastatin 20 mg; A80, atorvastatin 80 mg; ALI 75, alirocumab 75 mg; ALI 150, alirocumab 150 mg; ARR, absolute risk reduction; ASCVD, atherosclerotic cardiovascular disease; *CI*, confidence interval; CV, cardiovascular; EZE, ezetimibe; HIS, high-intensity statin; MIS, moderate- to low-intensity statin.

strategy) was still relatively high at 3.2% (2.7%-3.9%), despite this population already being on optimal-intensity statin and ezetimibe, because of the relatively large impact on percent LDL-C reduction.

The ARRs were also influenced by where the intensification step was placed in the sequence of treatment. For example, the ARR due to add-on alirocumab represented a population already on optimal-intensity statin and ezetimibe. When alirocumab was added immediately after statin uptitration (omitting the addition of ezetimibe; with an uptitration strategy for alirocumab), the ARR increased from 3.2% (2.7%-3.9%) to 3.6% (3.0%-4.2%). The increase in ARR due to add-on alirocumab (with the omission of ezetimibe) was observed across all subpopulations (Supplementary Table SVI) and was caused by the higher percent LDL-C reduction with alirocumab as compared with ezetimibe. However, the number of patients requiring alirocumab increased from 14.0% (13.6%-14.4%) to 30.7% (30.2%-31.2%). Furthermore, when we examined a population already on optimal-intensity statin and ezetimibe and not at LDL-C goals, the ARR was 3.9% (3.3%-4.5%) with alirocumab 150 mg only (instead of uptitrating from alirocumab 75 mg) and 1.9% (1.3%-2.5%) for patients receiving evolocumab only. The difference in the estimated ARRs for the 2 PCSK9 inhibitor agents was due to the differences in risk reduction per unit LDL-C reduction by individual CV end points (especially CV death) as reported in the ODYSSEY OUTCOMES and FOURIER trials.[3,4] When looking at ASCVD subpopulations, the ARR for a given treatment intensification step (eg, adding atorvastatin 20 mg) was highest for those with the highest baseline CV event risk, such as the recent ACS population.

When we considered the relatively hard clinical end point comprised only of MI, ischemic stroke, and CV death, the ARR for atorvastatin 20 mg initiation was 3.4% (2.9%-4.0%), atorvastatin 80 mg uptitration was 1.7% (1.1%-2.3%), add-on ezetimibe was 1.5% (0.9%-2.1%), and add-on PCSK9 inhibitor was 2.4% (1.8%-3.0%), with an overall ARR of 3.1% (2.5%-3.7%) across all intensification steps. The relatively hard clinical end point represented a relatively high proportion (approximately 73%) of the overall clinical benefit represented in our analyses, which also included UA hospitalization and coronary revascularization.

Prior studies have suggested that an NNT of 50 is an acceptable threshold by clinicians for initiating treatment.[19] All treatment intensification steps for all ASCVD subpopulations in our ideal treatment intensification scenario had an NNT $\leq$50, with the exceptions of add-on ezetimibe in the overall cohort, statin uptitration and add-on ezetimibe in the PAD-only group (eg, patients with PAD without concomitant coronary or cerebrovascular conditions), and add-on ezetimibe in the stable CHD group (Supplementary Figure S5 and Table SIV).

Implications of real-world factors

Implementation of treatment-limiting factors into the real-world treatment intensification scenario reduced the estimated overall number of events avoided as compared with the ideal treatment intensification scenario (Table II). For the addition of atorvastatin 20 mg and uptitration to atorvastatin 80 mg, the number of events avoided decreased due to nonadherence and the fact that a lower number of patients received statins because of statin intolerance status. For the addition of ezetimibe, the number of events avoided increased. Although nonadherence reduced the number of patients receiving ezetimibe, the incorporation of statin intolerance made more patients eligible to receive this treatment. The net effect was more patients receiving ezetimibe and therefore more events avoided. For the addition of PCSK9 inhibitors, the number of events avoided decreased. Although the number of patients eligible for PCSK9 inhibitors increased because of statin intolerance, there were 2 factors that caused the number of patients receiving this treatment to decrease. These included the incorporation of nonadherence and an assumption that an additional 50% of patients would not receive treatment owing to payer restrictions and access considerations.[16]

Applications of findings

Our study illustrates the development and application of a novel method for assessing the population-level implications of a wider adoption of therapies. The basic approach relies on Monte Carlo simulation of individual patients in which their outcomes (CV events in current study) are simulated probabilistically over time as a function of an individual's baseline demographic and clinical characteristics, and their treatment status. Criteria influencing the treatment status, such as the stepwise treatment intensification algorithm in the current study, or additional criteria such as the real-world factors explored in our study, can be translated into an algorithm and applied to individual patients as they progress in the simulation. Patient-level simulations with and without change in therapy can be aggregated over large numbers of patients in a cohort (with potentially multiple replications per patient) for informing population-level implications of changes in treatment uptake. We used this approach to assess the impact on CV events due to LLT intensification in accordance with consensus statements and guidelines. The general framework is flexible and should be applicable to similar questions in other populations and therapies.

As we demonstrate in our study, the simulation-based approach can help identify subpopulations and treatment strategies that result in a relatively higher absolute clinical benefit as measured by ARRs, NNTs, and CV events avoided. Our summary findings on these measures can be useful for decision-makers (eg, countries, payers, and

providers) who may wish to determine which patients might benefit most from treatment intensification with oral LLTs and add-on PCSK9 inhibitors.[20] In addition, the simulation-based approach is flexible and can incorporate in a systematic manner key real-world factors of interest to stakeholders, such as adherence, intolerance, and payer restrictions. In summary, our study provides an appreciation for the potential clinical benefit that can be realized with widespread use of a stepwise approach to LLT intensification in a representative population. Its use of individual-level data reflecting demographics of actual patients, combined with a simulation model, is a research technique that has the potential to explore population-level interventions prior to widespread implementation. Development of such methods could help reduce costs and maximize benefits of population-wide CV health efforts.

Limitations

We used a claims database for developing the simulation cohort, which may limit generalizability because the population was fully insured. However, the adjusted sampling methodology helped ensure that the summary characteristics of the simulation cohort were broadly similar to representative ASCVD populations in the United States (eg, from NHANES and PINNACLE; see Supplementary Table SVII).[21,22] With regard to comparison with recent LLT trials (ODYSSEY OUTCOMES, FOURIER, and IMPROVE-IT),[2-4] the summary characteristics were again broadly similar, with the exception of proportion female, which was relatively higher for the simulation cohort. At baseline, we estimated LLT medication use from evidence of filled prescriptions at a point in time, although it was not possible to ascertain from the claims database whether patients took their medications as prescribed.

The estimation of baseline CV event risk was based on a subset of the ASCVD cohort (baseline risk analysis subset). Summary characteristics of this subpopulation were found to be broadly comparable to the remaining population (Table I). Although we validated the baseline CV event risk model by comparing the estimated risk with KM estimates for various ASCVD subpopulations (Supplementary Figures S1 and S2), our model for estimating the baseline CV event risk has not been validated externally. CV deaths in the outpatient setting were expected to be incomplete based on the data source (SSA-DMF). We estimated and applied an adjustment factor to account for this incompleteness (Supplementary Methods). Sensitivity analysis indicated that this adjustment had a relatively small impact on our overall findings (Supplementary Table SII; estimated overall ARRs [95% CI] of 4.9% [4.2%-5.5%] and 4.7% [4.1%-5.3%] with and without adjustment, respectively), as a vast majority of events occurred in the inpatient setting where data are expected to be complete.

For statins and ezetimibe, we used the summary relationship between LDL-C lowering and CV event risk reduction from the CTT meta-analysis. In the CTT meta-analysis, the CIs on the magnitude of CV event risk reduction per unit LDL-C reduction are relatively narrower than the corresponding CIs at the level of individual trials. This is due to the fact that the overall results from the CTT meta-analysis represent aggregation across trials.[1] The CIs reported in our results thus are likely to be underestimated as compared with a scenario in which they reflect uncertainty represented at the level of an individual trial. For PCSK9 inhibitors, we used CIs directly from ODYSSEY OUTCOMES and FOURIER trials. As such, this consideration is likely to be mitigated for PCSK9 inhibitor treatment-related results in our simulation.

The reported estimates for ARRs and NNTs in our study are based on the ideal treatment intensification scenario and effectively represent an on-treatment–based definition. We have not provided estimates for ARRs and NNTs for the real-world intensification scenario because our primary measure to compare these scenarios is the number of events avoided in a cohort of 1,000 patients with ASCVD (Table II). For both the scenarios, the ARRs were estimated as on-treatment–based definitions and multiplied by the number of patients receiving treatment intensification to yield the number of events avoided.

Conclusions

In a cohort of 1,000 patients with ASCVD based on a generalizable ASCVD population in the United States, approximately 813 (809-818) required treatment intensification with LLT under an ideal treatment intensification scenario, resulting in 40 (34-45) events avoided over 5 years. About 818 (813-823) patients required treatment intensification with LLT under a real-world treatment intensification scenario, resulting in 29 (24-34) events avoided over 5 years. Our study provides an appreciation for the potential clinical benefit that can be realized with widespread use of a stepwise approach to LLT intensification as recommended by consensus statements and guidelines. This simulation-based study demonstrates a research technique that can explore the potential benefits of new population-level interventions prior to widespread implementation.

Disclosure information

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Sanofi. I. K. is an employee and stockholder of Sanofi. A. C. K. was an employee of Axtria during the initial creation of the manuscript and has stayed on as an author while an employee of Sarepta. R. B. D'A. has received consulting fees from Sanofi. M. R. R. has received consulting fees from Sanofi. R. J. S. and W. J. S. are employees and stockholders of Regeneron Pharmaceuticals, Inc. J. M. M. has no financial relationships to disclose. No other disclosures were reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.06.005.

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