POLICY

Value of Improved Lipid Control in Patients at High Risk for Adverse Cardiac Events

Anupam B. Jena, MD, PhD; Daniel M. Blumenthal, MD, MBA; Warren Stevens, PhD; Jacquelyn W. Chou, MPP, MPL; Thanh G.N. Ton, PhD; and Dana P. Goldman, PhD

ABSTRACT

Objectives: Lipid-lowering therapy (LLT) is suboptimally used in patients with hyperlipidemia in the 2 highest statin benefit groups (SBGs), as categorized by the American College of Cardiology and the American Heart Association. This study estimated the social value of reducing low-density lipoprotein cholesterol (LDL-C) levels by 50% for patients in SBGs 1 and 2 who have been treated with standard LLT but have not reached LDL-C goal, as well as the potential value of PCSK9 inhibitors for patients in these groups.

Study Design: Simulation model.

Methods: We used National Health and Nutrition Examination Surveys (NHANES) and US Census data to project the population of SBGs 1 and 2 in the time period 2015 to 2035. We used insurance claims data to estimate incidence rates of major adverse cardiac events (MACEs), and NHANES with National Vital Statistics data to estimate cardiovascular disease mortality rates. Using established associations between LDL-C and MACE risk, we estimated the value of reducing LDL-C levels by 50%. We incorporated results from a meta-analysis to estimate the value of PSCK9 inhibitors.

Results: Among those treated with LLT with LDL-C >70 mg/dL in SBGs 1 and 2, the cumulative value of reducing LDL-C levels by 50% would be $2.9 trillion from 2015 to 2035, resulting primarily from 1.6 million deaths averted. The cumulative value of PCSK9 inhibitors would range from $3.4 trillion to $5.1 trillion (1.9-2.8 million deaths averted), or $12,000 to $17,000 per patient-year of treatment.

Conclusions: Lowering LDL-C in high-risk patients with hyperlipidemia has enormous potential social value. For patients in these high-risk groups, PCSK9 inhibitors may have considerable net value depending on the final prices payers ultimately select.

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Cardiovascular disease (CVD) remains the leading cause of death, disability, and medical costs in the United States. Nearly 1 in 3 Americans dies of heart disease or stroke, and the annual cost of CVD in the United States exceeds $600 billion.[1] Elevated low-density lipoprotein cholesterol (LDL-C) has been associated with increased risk for CVD events and death.[2-8] Historically, statins have served as first-line lipid-lowering therapy (LLT) for LDL-C reduction, although recent guidelines have questioned the role of specific LDL-C goals in the primary and secondary prevention of CVD events.[3,9]

Despite estimates of the costs of CVD in the United States, little is known about the economic value of reducing the hyperlipidemia burden among those at high risk for CVD who, despite use of standard LLT, do not achieve conventional LDL-C goals (eg, ≤70 mg/dL). The American College of Cardiology (ACC) and American Heart Association (AHA) classify patients as being in the highest-risk statin benefit groups (SBGs) with established atherosclerotic CVD (ASCVD) (SBG 1), LDL-C levels >190 mg/dL (SBG 2), and diabetes (SBG 3).[3] Previous research estimated that up to 75% of high-risk patients treated with statins fail to achieve LDL-C of ≤70 mg/dL.[10] High CVD event rates in this population, coupled with a substantial proportion of patients not at conventional LDL-C goals, suggest potentially large economic value from reducing the burden of hyperlipidemia. Previously, eliminating deaths resulting from CVD has been estimated to be worth nearly $50 trillion in economic value.[11] For those initiating statin therapy between 1997 and 2008 alone, the value of averted deaths and CVD events may exceed $1 trillion.[12]

Members of a novel class of therapies called PCSK9 inhibitors have recently been approved for treatment of hyperlipidemia in patients in SBGs 1 and 2 who do not achieve LDL-C of ≤70 mg/dL despite receiving maximally tolerated LLT. In phase 2 and 3 trials, PCSK9 inhibitors have been shown to reduce LDL-C by between 50% and 77%, on av-

Take-Away Points

Before PCSK9 inhibitors even reached market, their costs to the healthcare system were the subject of much scrutiny. We estimated the social value of PCSK9 inhibitors to place their costs in context with the value they generate for patients and society.

- Our study confirmed what we already knew: reducing lipid levels significantly in high-risk patients can have a considerable health impact.
- Our study suggests that depending on the resulting confirmation of current estimates of effectiveness, PCSK9 inhibitors can provide considerable value when appropriately targeted, even at currently negotiated prices.
- We also show that estimates of the likely budget impact are considerably off the mark when realistic uptake patterns are applied.

erage.[13] Preliminary clinical outcomes from these studies suggest that PCSK9 inhibitors may reduce rates of major adverse cardiac events (MACEs) by up to 50%.[13] Based on these findings, the FDA approved alirocumab and evolocumab for use in adults with heterozygous familial hypercholesterolemia or ASCVD, who require additional LDL-C reduction.[14] Amidst these developments, payers and policy makers have expressed concern that PCSK9 inhibitors' costs—announced at $14,100 and $14,600 annually for evolocumab and alirocumab, respectively—will dramatically increase healthcare spending.[15,16]

In this study, we estimated the economic value to the United States over the next 20 years (2015-2035) of reducing hyperlipidemia burden among those at high risk for MACEs (SBGs 1 and 2) who have not achieved conventional LDL-C goals despite use of standard LLT therapy. As a case study, we estimated the value to the United States of using PCSK9 inhibitors in these patients who are currently on LLT but have not achieved an LDL-C of ≤70 mg/dL.

METHODS

Overview of Approach

Our study had 2 objectives: first, we sought to quantify the clinical and economic values of reducing the burden of hyperlipidemia among patients in the United States at high risk for MACEs or CVD mortality who have been treated with standard LLT but have not achieved conventional LDL-C goals. Second, we sought to project the clinical and economic value of PCSK9 inhibitors in patients at particularly high risk of MACEs or CVD mortality who may be eligible for treatment with these agents—those in SBGs 1 and 2—who have been treated with standard LLT but have not achieved conventional LDL-C goals. We defined conventional LDL-C goals to be ≤70 mg/dL and analyzed the sensitivity to a higher threshold of ≤100 mg/dL.

We used the 2011 to 2012 National Health and Nutrition Examination Study (NHANES)[17] to first estimate the proportion of the US adult population (nonpregnant adults 18 years or older) in SBGs 1 and 2, as outlined by ACC and AHA guidelines[3] (see **eAppendix Tables 1** and **2** [eAppendices available at **www.ajmc.com**]).[3] We then divided each of these groups into 3 risk subgroups based on their use of, and LDL-C response to, LLT: subgroup A—patients on LLT who have not successfully reduced LDL-C to ≤70 mg/dL (or ≤100 mg/dL, in sensitivity analyses); subgroup B—patients at goal LDL-C on LLT; and subgroup C—patients not on LLT.[3,17] We used US Census projections to estimate the size of each these populations from 2015 to 2035.[18] We used the Truven Marketscan insurance claims database to estimate the rates of nonfatal CVD events (ie, unstable angina, myocardial infarction, coronary arterial revascularization, and ischemic stroke) and a combination of the NHANES mortality files and National Vital Statistics Mortality Report (2012) to estimate mortality rates for each of these groups (see **eAppendix Tables 3-5**).[17,19,20]

With projected prevalence of patients not at goal LDL-C despite being on LLT (or who are intolerant to statins), we estimated the number of CVD-related deaths and MACEs averted for subgroup A in the time period 2015 to 2035 if LDL-C levels were hypothetically reduced by 50%, as suggested by the ACC and AHA.[3] To estimate the effects of LDL-C reductions, we used the quantitative relationship between LDL-C and relative risk of CVD events and mortality from the Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis.[9,13] We then quantified the economic value to the United States of averted CVD-related deaths and MACEs using standard health economic valuation approaches.[12,21]

We simulated the effects of PCSK9 inhibitor use for SBGs 1 and 2 in subgroup A patients. We projected the number of CVD-related deaths and MACEs averted in the time period 2015 to 2035, and the associated economic value if these patients were to receive PCSK9 inhibitors for further LDL-C reduction. We estimated the effects of PCSK9 inhibitors in 2 ways. First, we combined the LDL-C–lowering effects from PCSK9 inhibitor trials with the LDL-C relationship from the CTT Collaboration meta-analysis.[9,13] Second, we used data on the effects of PCSK9 inhibitors on CVD-related death and MACEs from a meta-analysis of recent randomized controlled trials of these drugs.[13] For a more detailed description of our methods for population and prevalence projections and event and mortality rate estimates, please see the eAppendix.

Across all PCSK9 inhibitor trials, the mean difference in LDL-C between those receiving LLT plus PCKS9 inhibitors compared with LLT alone was 59% (95% CI, 57%-61%). We used data from the CTT Collaboration meta-analysis (described in the eAppendix) to estimate the effect on clinical outcomes.[9] Using this method, PCSK9 inhibitor use in SBG 1 was associated with a reduction in MACE risk ranging from 43% to 50%, and a 32% reduction in CVD mortality risk, assuming the same baseline LDL-C level as indicated above. In SBG 2, the mortality reduction was 45%. The estimated impact of PCSK9 inhibitors on clinical outcomes in this scenario was termed the "conservative efficacy" treatment scenario. Next, we modeled the impact of PCSK9 inhibitors on MACEs and CVD deaths by using direct outcomes data from a meta-analysis of PCSK9 trials.[13] In the meta-analysis, PCSK9 inhibitor use was associated with a 50% relative risk reduction in rates of MACEs and CVD mortality. We termed this scenario the "high-efficacy" treatment scenario.

It should be noted that the studies in this meta-analysis were not weighted to detect differences in MACE outcomes, but for changes in LDL-C levels. Therefore, these results should be interpreted with caution.

We then modeled 3 uptake scenarios for PCSK9 inhibitors. In each scenario, PCSK9 inhibitor uptake began at 3% of the eligible population in 2015 (the eligible population included patients in SBGs 1 and 2 treated with standard LLT, but with LDL-C >70 mg/dL). Starting in 2016, uptake was assumed to increase linearly by 1%, 2%, or 3% for scenarios 1, 2, and 3, respectively, until 2023, when treatment uptake reached the maximum of 10% (scenario 1), 20% (scenario 2), or 30% (scenario 3) of the eligible population, and then remained constant through 2035.

Translating Clinical Outcomes Into Estimates of Economic Value

We estimated the economic value associated with averted CVD-related deaths and MACEs as follows. First, we identified the number of life-years gained by averting a single CVD-related death to be 14.9 additional life-years.[22] As this number was taken from follow-up data based on a clinical trial, and clinical trials tend to exclude older age groups, we were concerned that this number may overstate the additional life-years after a CVD event. Therefore, we also undertook the same analysis using the mean life-years lost from an ischemic heart disease death from the US Burden of Disease Study[23] (these results are shown in **eAppendix Table A6**). To value the gain in life-years, we used a value of $150,000 per life-year.[21,24] The World Health Organization's report on macroeconomics and health outlined an alternative approach to estimating the social value of lives saved due to healthcare interventions and concluded that healthcare interventions that save 1 life-year at a cost of less than 3 times the gross domestic product per capita (for a given country) are cost-effective.[25]

Second, we assessed the value of reducing CVD-related hospitalizations using a recent review of the incremental costs of these hospitalizations in the United States. We estimated total cost savings from averted CVD hospitalizations by multiplying these unit cost estimates by the number of events averted.[26] The value of life-years gained and savings from reduced CVD hospitalizations were summed to estimate both the total value of reducing residual LDL-C by the ACC/AHA goal of 50%, and the value of PCSK9 inhibitors in SBGs 1 and 2 for each of the 3 uptake scenarios described above. Future costs and benefits were discounted at 3%, using 2015 as the base year.

RESULTS

We estimated that in 2015, 32 million individuals in the United States would fall into ACC/AHA SBGs 1 and 2. Of these, 17.1 million did not receive LLT, 11.8 million were treated with standard LLT but had LDL-C >70 mg/dL, and 6.1 million were treated with standard LLT but had LDL-C >100 mg/dL. We projected that these figures would increase to 21.4 million, 16 million, and 8.1 million individuals, respectively, by 2035, absent changes in LLT use (**Table 1**). In 2015, the largest SBG—SBG 1—was estimated to have 10.1 million individuals with LDL-C >70 mg/dL and 4.4 million with LDL-C >100 mg/dL despite having been treated with LLT. By 2035, these figures were projected to increase to 14.0 million and 6.1 million, respectively.

Value of Averted MACEs and CVD Deaths Associated With a Hypothetical 50% LDL-C Reduction in SBGs 1 and 2

We estimated that by 2020, approximately 3.6 million MACEs would be averted if LDL-C levels were reduced by 50% among those treated with standard LLT but who still had LDL-C levels >70 mg/dL (**Figure 1**). Additionally, we estimated that approximately 1.9 million MACEs would be averted by then if LDL-C levels were reduced by 50% among those treated with standard LLT but who still had LDL-C >100mg/dL. By 2035, these figures were estimated to increase to 14.2 million and 7.5 million, respectively.

We also estimated that by 2020, approximately 400,000 CVD deaths would be averted if LDL-C levels were reduced by 50% among those treated with standard LLT but who still had LDL-C levels >70mg/dL (**eAppendix Figure 1**). Approxi-

Table 1. Projected Distribution of Lipid-Lowering Therapy and LDL-C Goal Achievement by Statin Benefit Group, 2015 and 2035[a]

	2015						2035					
		On Lipid-Lowering Therapy						On Lipid-Lowering Therapy				
		LDL-C Level						LDL-C Level				
	Untreated	≤70 mg/dL[b]	>70 mg/dL	≤100 mg/dL[b]	>100 mg/dL	Total	Untreated	≤70 mg/dL[b]	>70 mg/dL	≤100 mg/dL[b]	>100 mg/dL	Total
SBG 1[c]	8.1 M	3.0 M	10.1 M	8.8 M	4.4 M	21.3 M	11.2 M	4.2 M	14.0 M	12.1 M	6.1 M	29.4 M
SBG 2[d]	9.0 M	–	1.7 M	–	1.7 M	10.7 M	10.2 M	–	2.0 M	–	2.0 M	12.2 M
Total	17.1 M	3.0 M	11.8 M	8.8 M	6.1 M	32.0 M	21.4 M	4.2 M	16.0 M	12.1 M	8.1 M	41.6 M

LDL-C indicates low-density lipoprotein cholesterol; M, million; SBG, statin benefit group.
[a]Patient population projections were estimated with US Census population projections and National Health and Nutrition Examination Surveys proportions of patients in each risk group.
[c]Statin benefit group 1: patients with clinical atherosclerotic cardiovascular disease.
[d]Statin benefit group 2: patients with familial hyperlipidemia, defined as those with LDL-C levels ≥190 mg/dL; no patients reached LDL-C goal in this group.
[b]Goal LDL-C level was defined as ≤70 mg/dL in baseline analysis and ≤100 mg/dL in sensitivity analysis.

mately 230,000 CVD-related deaths would be prevented by 2020 for those with LDL-C >100 mg/dL. These figures increased to 1.6 million and 900,000, respectively, by 2035.

We estimated that by 2035, the cumulative value of averted CVD deaths and MACEs associated with a hypothetical 50% LDL-C reduction would be $2.9 trillion among individuals treated with standard LLT but who still had LDL-C >70mg/dL and $1.6 trillion among individuals with LDL-C >100mg/dL.

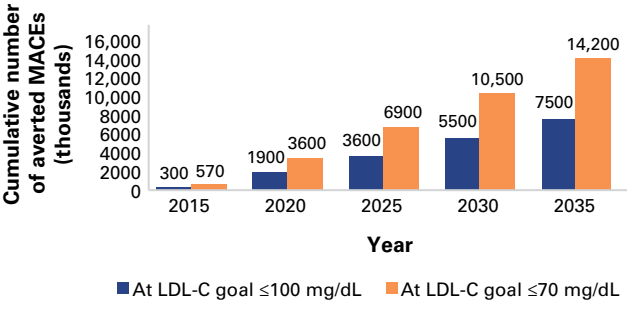
Value of Averted MACEs and CVD Deaths Associated With PCSK9 Inhibitor Use in SBGs 1 and 2

We estimated that by 2035, approximately 17 million MACEs (eAppendix Figure 2) and 2 million CVD deaths (eAppendix Figure 3) would be averted under a conservative PCSK9 inhibitor efficacy scenario if all patients in SBGs 1 and 2 treated with standard LLT, but who still had LDL-C >70 mg/dL, used PCSK9 inhibitors. Under the high-efficacy scenario, which assumed a 50% reduction in CVD mortality with PCSK9 inhibitor use, PCSK9 inhibitor use would prevent approximately 19 million MACEs and 3 million CVD-related deaths. In patients treated with standard LLT, but who still had LDL-C >100 mg/dL, 100% uptake of PCSK9 inhibitors would prevent approximately 9 million MACEs and 1 million CVD-related deaths under the conservative-efficacy scenario, as well as 10 million MACEs and 1.5 million CVD-related deaths under the high-efficacy scenario.

For patients in SBGs 1 and 2 treated with standard LLT but who still had LDL-C >70 mg/dL, we estimated the cumulative value of averted deaths and MACEs by 2035 to be $3.4 trillion under the conservative scenario and $5.1 trillion under the high-efficacy scenario (assuming 100% PCSK9 inhibitor uptake) (Figure 2). For patients in SBGs 1 and 2 treated with standard LLT, but who still had LDL-C >100 mg/dL, we projected the cumulative value of averted deaths and MACEs by 2035 to be $1.9 trillion under the conservative-efficacy scenario and $2.7 trillion under the high-efficacy scenario (again assuming 100% PCSK9 inhibitor uptake).

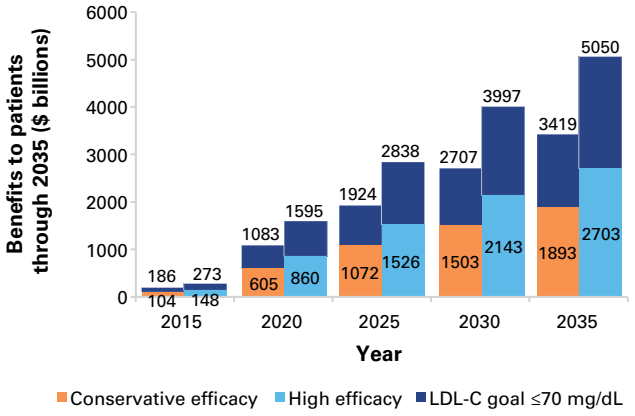
We modeled how varying PCSK9 inhibitor uptake influenced our projections. In our low-uptake scenario (in which a maximum of 10% of eligible patients use PCSK9 inhibitors by 2035), we estimated the value of averted MACEs and CVD-related deaths by 2035 to be $300 billion in the conservative-efficacy PCSK9 inhibitor scenario

Figure 1. Cumulative Averted MACEs[a] Associated With a Hypothetical 50% LDL-C Reduction by LDL-C in SBGs 1 and 2, 2015-2035[b]



LDL-C indicates low-density lipoprotein cholesterol; MACE, major adverse cardiac event; SBG, statin benefit group.
[a]MACEs include myocardial infarction, ischemic stroke, unstable angina, coronary artery bypass graft surgery, percutaneous coronary intervention, and cardiovascular death.
[b]Two LDL-C "at-goal" thresholds were modeled: 1) ≤70 mg/dL; 2) ≤100 mg/dL. The efficacy scenarios modeled assume a hypothetical goal of reducing LDL-C levels by 50% in all patients receiving treatment but not yet at goal LDL-C.

Figure 2. Cumulative Value Associated With PCSK9 Inhibitor Use in SBGs 1 and 2, 2015-2035[a]



LDL-C indicates low-density lipoprotein cholesterol; SBG, statin benefit group.
[a]In the conservative-efficacy PCSK9 inhibitor scenario, PCSK9 inhibitors were assumed to reduce LDL-C by 59%; associated reductions in major adverse cardiac events (MACEs) and cardiovascular disease (CVD) deaths were then estimated from established associations between LDL-C levels and CVD event rates. In the high-efficacy PCSK9 inhibitor scenario, PCSK9 inhibitors were assumed to result in a 50% reduction in MACEs. Both conservative- and high-efficacy PCSK9 inhibitor scenarios were modeled under 2 "at-goal" thresholds: an LDL-C goal of ≤100 mg/dL (orange and blue bars) and an LDL-C goal of ≤70 mg/dL (dark blue bars). The value of health benefits included cost savings from averted MACEs. Generally, cost offsets account for approximately 10% to 15% of the total value.

and $430 billion in the high-efficacy scenario (Figure 3). In contrast, in a high-uptake scenario (in which a maximum of 30% of eligible patients by 2035 use PCSK9 inhibitors), we estimated the value of averted MACEs and CVD-related deaths by 2035 to be $830 billion in the conservative-efficacy PCSK9 scenario and $1.2 trillion in the high-efficacy scenario.

Per-Person Value of Averted MACE and CVD Deaths Associated With PCSK9 Inhibitor Treatment

In addition to estimating MACEs, CVD-related deaths, and the potential value of averted events associated with PCSK9 inhibitor use at the population level, we estimated the value per person-year of treatment with a PCSK9 inhibitor for patients in SBGs 1 and 2 (Table 2). For patients treated with standard LLT but who still had LDL-C >70 mg/dL, we projected the value per person-year of treatment to be $11,600 in the conservative-efficacy scenario and $17,100 in the high-efficacy scenario. At a goal LDL-C of ≤100 mg/dL, the estimated value per person-year of treatment with PCSK9 inhibitors was $12,600 in the conservative-efficacy scenario and $18,000 in the high-efficacy scenario. These estimates illustrate the potential range of social value per eligible patient treated with PCSK9 inhibitors.

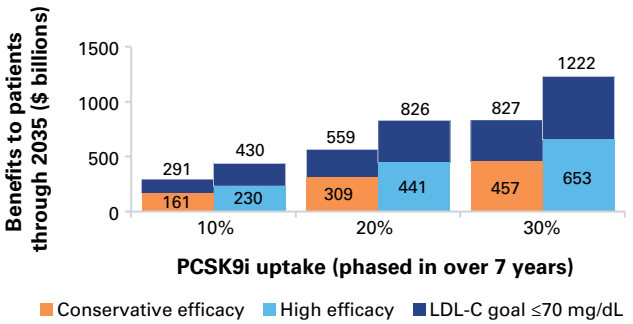
DISCUSSION

We estimated the economic value to the United States over the next 20 years of reducing the burden of hyperlipidemia among patients in the highest ACC and AHA SBGs.[3] We estimated that reducing LDL-C by 50% in SBG 1 and 2 patients who have been treated with standard LLT but still have LDL-C levels >70 mg/dL could avert approximately 14.2 million MACEs, including 1.6 million CVD-related deaths, by 2035.

Our study complements previous estimates of the economic value of LLT, including statin therapy, in the United States.[12] Our estimates of the value of PCSK9 inhibitors are lower than the previously estimated social value of statins of approximately $51,000 per patient (in 2015 dollars).[12] One factor that may partly explain this difference is that the growing use of percutaneous coronary intervention, P2Y12 inhibitors, angiotensin-converting enzyme inhibitors, aldosterone antagonists, and implantable cardiac defibrillators has led to dramatic improvements in CVD outcomes since statins were introduced.[27-34] It is also possible that new CVD treatments produce smaller absolute benefits compared with those projected for statins, simply because overall morbidity and mortality for CVD were higher 20 years ago than today.

Although PCSK9 inhibitors may lower LDL-C and improve health outcomes for high-risk populations, policy

Figure 3. Cumulative Value Associated With PCSK9 Inhibitor Use in SBGs 1 and 2 Under Various Drug Uptake Scenarios, 2015-2035[a]



LDL-C indicates low-density lipoprotein cholesterol; SBG, statin benefit group.
[a]In the conservative-efficacy PCSK9 inhibitor scenario, PCSK9 inhibitors were assumed to reduce LDL-C by 59%; associated reductions in major adverse cardiac events (MACEs) and cardiovascular disease (CVD) deaths were then estimated from established associations between LDL-C levels and CVD event rates. In the high-efficacy PCSK9 inhibitor scenario, PCSK9 inhibitors were assumed to result in a 50% reduction in MACEs. Both conservative- and high-efficacy PCSK9 inhibitor scenarios were modeled under 2 "at-goal" thresholds: an LDL-C goal of ≤100 mg/dL (orange and blue bars) and an LDL-C goal of ≤70 mg/dL (dark blue bars). The value of health benefits included cost savings from averted MACEs. Generally, cost offsets account for approximately 10% to 15% of the total value.

Table 2. Value per Person-Year for Those Treated With PCSK9 Inhibitors in SBGs 1 and 2, 2015-2035

	Conservative PCSK9 Inhibitor Efficacy Scenario[a]					High PCSK9 Inhibitor Efficacy Scenario[b]				
	2015	2020	2025	2030	2035	2015	2020	2025	2030	2035
A. Treatment of patients in SBGs 1 and 2 with PCSK9 inhibitors, assuming goal LDL-C ≤70 mg/dL										
Number of averted events (thousands)										
MACE	670	4200	8000	12,300	16,800	760	4800	9200	14,000	19,100
CVD deaths	75	470	900	1400	1900	110	710	1400	2100	2800
Value from averted events ($ billions)										
MACE	$19	$110	$200	$280	$350	$21	$120	$215	$300	$380
CVD deaths	$170	$970	$1700	$2400	$3100	$250	$1500	$2600	$3700	$4700
Value per person-year, treated ($)										
Cost offsets			$1200					$1300		
Life-years			$10,400					$15,800		
Total social value			$11,600					$17,100		
B. Treatment of patients in SBGs 1 and 2 with PCSK9 inhibitors, assuming goal LDL-C ≤100 mg/dL										
Number of averted events (thousands)										
MACE	360	2200	4300	6500	8800	400	2500	4900	7400	10,000
CVD deaths	42	260	500	760	1000	61	380	740	1100	1500
Value from averted events ($ billions)										
MACE	$10	$58	$100	$150	$180	$11	$64	$110	$160	$200
CVD deaths	$94	$550	$970	$1400	$1700	$140	$800	$1400	$2000	$2500
Value per person-year, treated ($)										
Cost offsets			$1200					$1300		
Life-years			$11,400					$16,600		
Total social value			$12,600					$18,000		

CVD indicates cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac event; SBG, statin benefit group.
[a]In the conservative-efficacy PCSK9 inhibitor scenario, PCSK9 inhibitors were assumed to reduce LDL-C by 59%; associated reductions in MACEs and CVD deaths were then estimated from established associations between LDL-C levels and CVD event rates.
[b]In the high-efficacy PCSK9 inhibitor scenario, PCSK9 inhibitors were assumed to result in a 50% reduction in MACEs.

makers and clinicians have raised concerns about the cost of these drugs to the healthcare system.[16] The prices per patient-year of treatment were set recently at $14,100 and $14,600 per year for evolocumab and alirocumab, respectively. Some have estimated that systemwide costs for these drugs could be $150 billion annually.[35] A critical question for patients and payers will be whether the value of PCSK9 inhibitor benefits outweighs their expense. Our estimates suggest that whether PCSK9 inhibitors deliver net social value (ie, generate benefits in excess of costs) depends on the assumptions about drug efficacy, the economic value of mortality improvements, which patient populations receive PCSK9 inhibitors, and the ultimate prices paid for these drugs. PCSK9 inhibitors would generate net positive social value for the average patients in SBGs 1 and 2, as long as the annual net price falls below $18,000 in a high-efficiency scenario or $12,000 in a conservative-efficiency scenario. According to a recent report, the average reported rebates for branded pharmaceutical drugs are around 30%,[36] which would mean an average cost per year for PCSK9 inhibitors of around $10,000. Because our estimates do not include any benefits from increases in health-related quality of life from treatments or events avoided, our estimates may be conservative.

Our findings also add to our understanding of the size of the populations likely to receive PCSK9 inhibitors initially. Several current estimates assume that a majority of the 70 million patients in the 4 ACC/AHA SBGs (only 3 of which were included in this study) will eventually receive PCSK9 inhibitors, which may overestimate the actual societal cost of PCSK9 inhibitors if they are instead primarily prescribed to high-risk patients with poorly controlled LDL-C despite LLT—a small subset of all patients in these 4 SBGs. Our models for patients in the 2 highest SBGs (patients with ASCVD or LDL-C >190 mg/dL) were designed to reflect the reality that clinicians and payers are likely to focus initially on

the smaller subset of patients who have up-titrated to maximal statins, but have still failed to achieve LDL-C reduction. For this reason, our projections of the potential benefits and value of PCSK9 inhibitors over the next 3 to 5 years may be more accurate than previous estimates. Nonetheless, even if PCSK9 inhibitors are prescribed only to patients in SBGs 1 and 2 who have been treated with standard LLTs but have not reached the LDL-C goal, some estimates suggest that healthcare spending on LLTs may increase by $10 billion annually over the next 2 decades.[15]

Limitations

Our study has several limitations. First, our estimated clinical impacts rely on epidemiologic models and evidence from studies of statins of the association among LDL-C levels, MACEs, and CVD-related deaths, which may differ in patients receiving PCSK9 inhibitors. Our estimated impacts assume a linear relationship among the levels of LDL-C reduction and MACEs and CVD-related deaths, which may not be the case at the lower levels of resulting LDL-C simulated in our model. In addition, our analysis of PCSK9 inhibitors used early clinical outcomes data for these drugs; relative risk reductions estimated from larger patient populations may differ from current estimates. Although existing studies suggest that PCSK9 inhibitors are associated with reduced MACEs and deaths, definitive evidence will not be available for several years. Furthermore, even definitive trial evidence may differ from real-world outcomes. Real-world efficacy patterns will be affected by patient treatment heterogeneity and physician decision making.

Second, we estimated the value of PCSK9 inhibitors among patients in the 2 highest SBGs who had been treated but were not at goal LDL-C, assuming that these patients would be the relevant treatment population who had been up-titrated to maximally tolerated doses for statins or other LLTs. In reality, many patients on LLT are not at maximally tolerated doses or are nonadherent with LLT even if they do not experience side effects from these agents.[37] Optimizing LLT may reduce the size of the prevalent population who could potentially benefit from PCSK9 inhibitors, since the number of patients failing to achieve LDL-C goals would fall. Our estimates may therefore be an upper bound of the value of PCSK9 inhibitors in these populations because we assumed that LLT rates would remain at their current levels and not rise due to payer pressures. In addition, patients who are nonadherent with LLT may not be candidates for PCSK9 inhibitors even if their LDL-C is >70 mg/dL.

Third, we relied on parameter assumptions and outcomes data to estimate the impacts of LDL-C reduction and PCSK9 inhibitors. The Truven Marketscan database had inconsistent information across variables, particularly with regard to risk factors and cardiovascular events, and lacked information on blood pressure. We therefore may have underestimated cardiovascular events. In addition, the NHANES data used for mortality estimates lacked information on heart failure and transient ischemic attacks, leading us to potentially underestimate overall CVD burden. In our PCSK9 inhibitor analysis, we also assumed that the mean difference in LDL-C between those receiving LLT plus PCKS9 inhibitors versus LLT alone was 59%.[13] We did not conduct a separate sensitivity analysis using the bounds of this confidence interval. Rather, we reported a broad range of estimates based on assumptions of conservative versus high efficacy of PCSK9 inhibitors.

Fourth, we did not account for growing efforts to prescribe high-intensity statins, which may increase the proportion of high-risk patients who achieve target LDL-C goals, potentially reducing demand for PCSK9 inhibitors. Indeed, as of 2009, more than 70% of patients with indications for high-intensity statins—including patients hospitalized for acute coronary syndrome—did not receive statin prescriptions.[10,38]

Finally, while we defined an LDL-C goal of ≤70 mg/dL, current cholesterol treatment guidelines do not recommend treating to a specific LDL-C goal because some have argued that the data to support this practice is not sufficiently robust.[3] However, existing evidence indicates that statins reduce MACEs when the baseline LDL-C level is >70 mg/dL.[3] Moreover, in many countries, ≤70 mg/dL remains an important LDL-C treatment goal for high-risk patients.[39] Nonetheless, our definition of the PCSK9 inhibitor–eligible population as all high-risk patients with LDL-C >70 mg/dL could have led us to overestimate the size of the patient population that stands to benefit from these drugs.

CONCLUSIONS

The population burden of CVD continues to grow despite improvements in CVD treatment. Among those at high risk for CVD who do not achieve sufficient LDL-C reduction despite LLT, we estimated substantial economic value associated with reducing the burden of hyperlipidemia by the ACC/AHA goal of 50%. Moreover, although at an early stage, early clinical studies suggest that PCSK9 inhibitors may substantially reduce MACEs and CVD-related deaths. Although our estimates suggest that these drugs may generate significant value for society, PCSK9 inhibitors' net impact will depend on the final costs of these therapies and on pending results of trials evaluating

their clinical outcomes. The number of individuals initially prescribed PCSK9 inhibitors is likely to be significantly lower than that suggested by previous estimates.

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Author Affiliations: Harvard Medical School (ABJ and DMB), Boston, MA; Massachusetts General Hospital (ABJ and DMB), Boston, MA; Precision Health Economics (WS, TGNT, JWC), Oakland, CA; University of Southern California (DPG), Los Angeles, CA.

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Address correspondence to: Anupam B. Jena, MD, PhD, Harvard Medical School, Department of Health Care Policy, 180 Longwood Ave, Boston, MA 02115-5899. E-mail: Jena@hcp.med.harvard.edu.

REFERENCES

1. Heidenreich PA, Trogdon JG, Khavjou OA, et al; American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation*. 2011;123(8):933-944. doi: 10.1161/CIR.0b013e31820a55f5.

2. Jackson R, Lawes CM, Bennett DA, Milne RJ, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. *Lancet*. 2005;365(9457):434-441.

3. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25, pt B):2889-2934. doi: 10.1016/j.jacc.2013.11.002.

4. Go AS, Mozaffarian D, Roger VL, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013;127(1):e6-e245. doi: 10.1161/CIR.0b013e31828124ad.

5. Prevention of cardiovascular disease: guidelines for assessment and management of cardivascular risk. World Health Organization website. http://www.who.int/cardiovascular_diseases/guidelines/Full%20text.pdf. Published 2007. Accessed January 18, 2016.

6. Hajifathalian K, Ueda P, Lu Y, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. *Lancet Diabetes Endocrinol*. 2015;3(5):339-355. doi: 10.1016/S2213-8587(15)00081-9.

7. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. National Institute for Health and Care Excellence website. https://www.nice.org.uk/guidance/cg67. Published May 2008. Accessed January 18, 2016.

8. Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681. doi: 10.1016/S0140-6736(10)61350-5.

9. Mihaylova B, Emberson J, Blackwell L, et al; Cholesterol Treatment Trialists Collaboration. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380(9841):581-590. doi: 10.1016/S0140-6736(12)60367-5.

10. Rodriguez F, Olufade T, Heithoff K, Friedman HS, Navaratnam P, Foody JM. Frequency of high-risk patients not receiving high-potency statin (from a large managed care database). *Am J Cardiol*. 2015;115(2):190-195. doi: 10.1016/j.amjcard.2014.10.021.

11. Murphy KM, Topel RH. The economic value of medical research. In: Murphy KM, Topel RH, eds. *Measuring the Gains from Medical Research: An Economic Approach*. Chicago, IL: University of Chicago Press; 2003.

12. Grabowski DC, Lakdawalla DN, Goldman DP, et al. The large social value resulting from use of statins warrants steps to improve adherence and broaden treatment. *Health Aff (Millwood)*. 2012;31(10):2276-2285. doi: 10.1377/hlthaff.2011.1120.

13. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;163(1):40-51. doi: 10.7326/M14-2957.

14. FDA approves Praluent to treat certain patients with high cholesterolcholesterol [press release]. Silver Spring, MD: FDA; July 24, 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455883.htm. Accessed August 24, 2015.

15. Pollack A. New drug sharply lowers cholesterol, but it's costly. *The New York Times* website. Published July 24, 2015. Accessed January 18, 2016.

16. Shrank W, Lotvin A, Singh S, Brennan T. In the debate about cost and efficacy, PCSK9 inhibitors may be the biggest challenge yet. *Health Affairs* website. http://healthaffairs.org/blog/2015/02/17/in-the-debate-about-cost-and-efficacy-pcsk9-inhibitors-may-be-the-biggest-challenge-yet/. Published February 17, 2015. Accessed January 18, 2016.

17. National Health and Nutrition Examination Survey data. CDC website. http://www.cdc.gov/nchs/nhanes/. Accessed January 18, 2016.

18. Methodology and assumptions for the 2012 national projections. US Census Bureau website. http://www.census.gov/population/projections/files/methodology/methodstatement12.pdf. Accessed August 4, 2014.

19. Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. *Natl Vital Stat Rep*. 2013;61(4):1-117.

20. Comercial claims and encounters Medicare Supplemental. Truven Health website. http://truvenhealth.com/markets/life-sciences/products/data-tools/marketscan-databases. Accessed January 18, 2016.

21. Viscusi WK, Aldy J. The value of a statistical life: a critical review of market estimates throughout the world. *J Risk Uncertain*. 2003;27(1):5-76.

22. Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM. Long-term follow-up of the West of Scotland Coronary Prevention Study. *N Engl J Med*. 2007;357(15):1477-1486.

23. Murray CJ, Atkinson C, Bhalla K, et al; US Burden of Disease Collaborators. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA*. 2013;310(6):591-608. doi: 10.1001/jama.2013.13805.

24. Miller TR. Variations between countries in values of statistical life. *JTEP*. 2000;34(2):169-188.

25. Commission on Macroeconomics and Health. Macroeconomics and health: investing in health for economic development. World Health Organization website. http://apps.who.int/iris/bitstream/10665/42435/1/924154550X.pdf. Published December 20, 2001. Accessed January 18, 2016.

26. O'Sullivan AK, Rubin J, Nyambose J, Kuznik A, Cohen DJ, Thompson D. Cost estimation of cardiovascular disease events in the US. *Pharmacoeconomics*. 2011;29(8):693-704. doi: 10.2165/11584620-000000000-00000.

27. Mauri L, Kereiakes DJ, Yeh RW, et al; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371(23):2155-2166. doi: 10.1056/NEJMoa1409312.

28. Wald DS, Morris JK, Wald NJ, et al; PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med*. 2013;369(12):1115-1123. doi: 10.1056/NEJMoa1305520.

29. Wallentin L, Becker RC, Budaj A, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057. doi: 10.1056/NEJMoa0904327.

30. Myerburg RJ. Implantable cardioverter–defibrillators after

myocardial infarction. *N Engl J Med*. 2008;359(21):2245-2253. doi: 10.1056/NEJMra0803409.

31. Keeley EC, Hillis LD. Primary PCI for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2007;356(1):47-54.

32. Pitt B, Remme W, Zannad F, et al; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348(14):1309-1321.

33. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342(3):145-153.

34. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet*. 2006;368(9535):581-588.

35. Kolata G. Federal panel backs approval of new drug to fight heart attacks. *The New York Times* website. Published June 9, 2015. Accessed January 18, 2016.

36. Global pharma. Credit Suisse website. https://doc.research-and-analytics.csfb.com/docView?language=ENG&format=PDF&source_id=csplusresearchcp&document_id=1047911451&serialid=hfXhzuK6sK6xRrBsMZzLqZ96QTl7v2YM0kkwWJRGRVU%3D. Published May 1, 2015. Accessed January 18, 2016.

37. Hirsh BJ, Smilowitz NR, Rosenson RS, Fuster V, Sperling LS. Utilization of and adherence to guideline-recommended lipid-lowering therapy after acute coronary syndrome: opportunities for improvement. *J Am Coll Cardiol*. 2015;66(2):184-192. doi: 10.1016/j.jacc.2015.05.030.

38. Rosenson RS, Kent ST, Brown TM, et al. Underutilization of high-intensity statin therapy after hospitalization for coronary heart disease. *J Am Coll Cardiol*. 2015;65(3):270-277. doi: 10.1016/j.jacc.2014.09.088.

39. Blom DJ, Hala T, Bolognese M, et al; DESCARTES Investigators. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med*. 2014;370(19):1809-1819. ■

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eAppendix

Detailed methods

Projecting national estimates of the number of patients in SBGs 1&2 who despite LLT are not at goal LDL-C

Within each SBG, we modeled (1) the proportion of patients currently on LLT and (2) the proportion of these treated patients who had LDL-C below 70 mg/dL (i.e., at conventional goal). To estimate these proportions we used multivariate logistic models that incorporated NHANES survey weights and adjusted for age groups (18-24, 25-64, 65+), sex, and race (black and white/others). Final models were used to predict three sets of prevalence estimates. First, we predicted the distribution of SBGs across age, sex, and race strata (set 1), for the ultimate purpose of projecting national estimates of these risk groups using Census population data. Second, we predicted the proportion of patients treated with LLT within each SBG (set 2). Third, we predicted the proportion of patients within each SBG treated with LLT who were at goal LDL-C (set 3). Specific LDL values were obtained from NHANES,[1] which is described in detail below and in the supplementary materials.

In order to predict national estimates of SBGs, projected population counts for each year from 2015 to 2035 were obtained from the U.S. Census resident population across age, sex, and race strata. These projections were generated by the U.S. Census Bureau based on the U.S. population on July 1, 2011, using a cohort-component method and assumptions about future births, deaths, and net international migration.[2] These population projections served as the denominator for age, sex, and race strata in our analysis.

To estimate the number of adults in each SBG nationally for future years, we multiplied age-, sex-, and race-specific prevalence estimates obtained from NHANES (set 1) to U.S. population projections for the same age, sex, and race strata. This stratification by age, sex, and race allowed the size of SBGs to grow over time as the size of each age/sex/race strata group grew, although within age/sex/race strata prevalence estimates were assumed to stay constant from 2011-2012 through 2035. Because we assumed that within each age/sex/strata group the percent prevalence of each SBG would not change over time, this is likely a conservative estimate of overall growth in risk groups over time.

To estimate the number of individuals treated with LLT within each SBG nationally, we multiplied the projected number of adults in each risk group nationally (described above) by the predicted proportion of individuals receiving LLT within each risk group (set 2). This was done by year.

Finally, to estimate the national number of adults treated with LLT who were expected to reach LDL-C levels less than 70 mg/dL for each future year, we multiplied the estimated number of treated adults in each SBG (obtained above) by the proportion reaching LDL-C targets from the NHANES 2011-12 survey (set 3). By using one set of prevalence estimates, we assumed that the proportion of treated individuals who reached goal LDL-C remained constant from 2011-2012 through 2035.

Estimating MACE rates

We estimated MACE rates in each SBG using administrative insurance claims data with linked laboratory data from the Truven Marketscan database.[3] The database is a large-scale sample of claims for the commercially insured U.S. population, patients with Medicare Supplemental insurance, and patients covered by privately administered Medicaid. Linked laboratory results are available for a subset of patients in the database.[4] Details on the assembly of the patient sample, including inclusion and exclusion criteria, are available in this manuscript's supplementary material (Table A5.).

We identified a sample of 73,206 patients who met our inclusion and exclusion criteria, and had been followed over an average of 7.0 years. We calculated incidence rates for each of several outcomes (unstable angina, myocardial infarction (MI), coronary arterial revascularization, and ischemic stroke) using a Poisson regression model with robust standard errors and an offset of log-transformed person-years. We calculated the incidence rate for each outcome for those treated with LLT and untreated, adjusting for age, sex, smoking status, pre-treatment LDL-C (for those who received LLT), and use of antihypertensive medications (binary indicator). We used the final models to predict adjusted incidence rates for each outcome for those treated with LLT but not at goal LDL-C.

Estimating mortality rates

Due to the limited number of CVD deaths in the 2011-2012 NHANES database, we used multiple waves of NHANES (2004-2012) to obtain a sufficient sample of cardiovascular deaths to effectively allocate across SBGs. Even with this expanded data, we were limited to deaths in people under 85 years of age available in NHANES. As such we imputed the population-wide distribution of cardiovascular deaths from the National Vital Statistics Mortality Report from 2012 to ensure the total deaths for the base year matched the total number of deaths for 2012 in the model.[5]

In addition to this approach of estimating baseline mortality rates in each SBG, we assessed the sensitivity of our findings to literature-based sources of baseline mortality for each SBG, as well as insurance claims-based sources (described in supplementary materials).

Estimating impact on MACE and CVD death of 50% reduction in LDL-C

We estimated the impact on MACE and CVD death in SBGs 1&2 of reducing LDL-C by 50%, a target that is consistent with the latest ACC/AHA guidelines. This calculation relied on our baseline estimates of MACE and CVD mortality risk for patients in each SBG who were not at goal LDL-C despite LLT. We used data from the CTT Collaboration meta-analysis of RCTs of intensive statin regimens to estimate the benefits of reducing LDL-C by 50%.[6] In this meta-analysis, a 50% LDL-C reduction was associated with 36-42% reduction in risk of MACE and 27% reduction in CVD mortality in risk group 1, assuming a baseline LDL-C level of 134 mg/dL. In risk group 2, with a baseline LDL-C level of 209 mg/dL, the corresponding mortality reduction was 42%.

Estimating impact of PCSK9 inhibitors on MACE and CVD death in SBGs 1-2

We estimated the impact on MACE and CVD death of using PCSK9 inhibitors in SBGs 1-2. Although PCSK9 inhibitors are approved for patients with ASCVD and heterozygous familial hyperlipidemia (FH) who do not achieve sufficient LDL-C reduction (e.g., LDL-C < 70mg/dL) with maximally tolerant statins,[7] we modeled their use only among the subset of patients who fail to achieve LDL-C reduction while on LLT. That is, we excluded from our analyses all patients in SBGs 1-2 who were not receiving LLT. Moreover, while PCSK9 inhibitors are approved in FH, we projected use, and the effects of use, among the larger cohort of patients with LDL-C levels greater than 190mg/dl despite LLT, as there currently exists no ICD-9 code for heterozygous familial hyperlipidemia. This cohort likely includes patients both with and without FH; recent estimates suggest the condition is diagnosed in less than 10% of cases.[8]

Estimating event rates for dyslipidemia risk groups

We used the Truven Marketscan database to estimate major cardiovascular event rates for unstable angina, myocardial infarction (MI), coronary or arterial revascularizations, and ischemic stroke.[3] Truven MarketScan databases are a large-scale convenience sample of claims for the commercially insured, patients with Medicare Supplemental insurance, and patients covered by Medicaid. Linked laboratory results are available for a subset of patients in the database.[4]

Pre-Baseline "Clean Period": We established a pre-baseline period defined as the time between January 1, 2005, and December 31, 2006, as the "clean period" for enrollment of our study population, implemented inclusion and exclusion criteria, screened for prevalent conditions to be excluded at baseline, and evaluated patients regarding their treatment and achievement status.

Inclusion Criteria: Patients eligible for the study were required to have 24 months of continuous enrollment during the "clean period" and at least one observed LDL-C value. Patients had to meet American College of Cardiology and the American Heart Association (ACC/AHA) risk-group criteria to be eligible for study enrollment.

Exclusion Criteria: All patients with evidence of pregnancy during this time were excluded as they can skew the untreated population because of pregnancy-related medication restrictions. All without at least one day of follow up after the "clean period" were excluded.

Defining Risk Groups in Claims Data: Table 2 provides a summary of how the ACC/AHA risk-group definitions were implemented in the Truven Marketscan data. Any patient with evidence of atherosclerotic cardiovascular disease (ASCVD) during the "clean period" was categorized into Group 1. ASCVD was defined as evidence of having ≥1 inpatient claim or ≥2 outpatient claims between January 1, 2005, and December 31, 2006, for any of the following conditions: unstable angina, stable angina, MI, coronary or arterial revascularizations, ischemic stroke, transient ischemic stroke (TIA), peripheral arterial disease, ischemic heart disease, abdominal aortic aneurysm, congestive heart failure, and carotid artery disease. Patients without any ASCVD during the "clean period" but with a pre-treated LDL-C value ≥190 were categorized into Group 2. For those treated during the "clean period," we calculated pre-treatment values using a published algorithm that incorporates observed LDL-C levels, type of medication the patient was

taking, and the specific dose of that medication [9]. For untreated individuals during the "clean period," we used their observed LDL-C values to define their risk-group eligibility.

Treatment Groups: We defined treatment groups as those with at least one prescription for LLTs during the "clean period." Treatment group was defined as a dichotomous variable (yes/no).

Table 1. Implementation of ACC/AHA Risk Group Definitions in NHANES

Statin-Benefit Risk Group	2013 ACC/AHA Definition	Definition in NHANES
Group 1	With clinical ASCVD	Has a doctor or other health profession ever told you had: • Coronary heart disease • Angina pectoris • Heart attack (also called myocardial infarction) • Stroke *Coronary or arterial revascularizations, TIA, and peripheral arterial disease were not assessed in NHANES.*
Group 2	No ASCVD	No positive answers to clinical ASCVD questions
	LDL-C≥190 mg/dL	Lab measurements

Table 2. Implementation of ACC/AHA Definitions in Truven Marketscan Database

Statin-Benefit Risk Group	2013 ACC/AHA Definition	Definition in Truven MarketScan Database (ICD-9 code)
Group 1	With clinical ASCVD	
	Unstable angina/acute coronary syndrome	411.1X, 411.8X
	Stable angina	413.XX
	Myocardial infarction (MI)	410.XX
	Coronary artery bypass graft (CABG)	ICD-9 Procedure Codes: 36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.17, 36.19
		CPT Codes: 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33521, 33522, 33523, 33530, 33533, 33534, 33535, 33536
		HCPCS: S2205, S2206, S2207, S2208, S2209
	Percutaneous coronary intervention (PCI)	ICD-9 Procedure Codes: 00.66, 36.06, 36.07, 17.55, 00.45, 00.46, 00.47, 00.48
		CPT Codes: 92973, 92980, 92981, 92982, 92984, 92995, 92996, 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944
		HCPCS: G0290, G0291, C9600, C9601, C9602, C9603, C9604, C9605, C9606, C9607, C9608
	Ischemic stroke	433.X1, 434.X1
	Transient ischemic attack (TIA)	435.0X, 435.1X, 435.8X, 435.9X
	Peripheral arterial disease	440.0X, 440.1X, 440.2X, 440.3X, 440.4X, 440.8X, 440.9X, 443.81, 443.9X, 444.XX, 445.XX
	Ischemic heart disease	414.XX
	Abdominal aortic aneurysm	441.3X, 441.4X
	Congestive heart failure (CHF)	428.XX
	Carotid artery disease	433,10, 433.11
Group 2	No ASCVD condition	No ASCVD in clean period
	LDL ≥ 190	

Cross validation of estimates of SBG-specific CVD mortality rates

We estimated deaths from CVD across multiple NHANES surveys death files (2004-2012) and then used survey specific weightings to translate that to a hypothetical distribution of CVD deaths by SBG from ages 35-84 across these years, and the total across the population as a whole. We then used total CVD deaths from National Vital Statistics Report 2012, to estimate how that distribution translates to total CVD deaths across SBGs in 2012. We then assumed that the deaths in those aged 85 and above was distributed across SBGs at the same rate.

Using the estimation of total population size from NHANES from the earlier part of the study, we then translated these into SBG specific death rates as in the table below.

Table 3. CVD mortality rate estimates with NHANES surveys and the National Vital Statistics Report

	NHANES surveys pooled (2004-2012)			2012 NVSR[5]	2012 NHANES	[2012[5]]
	35-84 years			All ages		CVD mortality
	heart disease deaths					rate
	sample	Sample weighted	share	CVD deaths	population	(per 100,000)
All ASCVD	33	124,349	0.431	334,459	15,498,274	2,158
All LDL> 190	41	55,597	0.193	149,538	9,445,500	1,583
All pop	94	288,803		776,788	166,514,805	466

To cross validate these estimates we used both the literature on estimates of the standardized mortality ratios between SBGs and the general population, for CVD death and we estimated the same ratios from the limited mortality data we have from the Truven Marketscan data set. Both these and the NHANES estimates are shown in the table below. All three sources were in the same general range which we took to be a validation of sorts.

Table 4. Cross-validation of NHANES-based mortality rates

Method	ASCVD (1)	FH (2)
NHANES MR	**2158**	**1583**
Truven Marketscan SMR	2,717	N/A*
Lit-based SMR	2450[10]	1,512[11]
Average	***2442***	***1548***

Table 5. Major Adverse Cardiovascular Event (MACE) Rates from Longitudinal Claims Data (Truven)

A. Major Adverse Cardiovascular Event (MACE) rates per 100,000 person years assuming goal of LDL-C of <70 mg/DL								
Baseline event Rates - LDL-C 70	**Statin Benefit Group 1: ASCVD**				**Statin Benefit Group 2: Familial Hyperlipidemia**			
	Untreated[1]	**Treated and uncontrolled (>=70)[2]**	**50% LDL-C Reduction**	**59% LDL-C Reduction**	**Untreated[1]**	**Treated and uncontrolled (>=70)[2]**	**50% LDL-C Reduction**	**59% LDL-C Reduction**
Myocardial Infarction	2,872	2,326	1,483	1,331	1,464	1,185	756	678
Ischemic Stroke	2,632	2,069	1,319	1,184	1,479	1,163	741	665
Unstable Angina	4,937	4,157	2,546	2,256	2,244	1,890	1,157	1,026
Revascularization[3]	3,772	3,250	1,869	1,620	1,819	1,553	893	774
CVD Mortality	2,412	2,003	1,466	1,369	1,629	1,346	784	739
B. Major Adverse Cardiovascular Event (MACE) rates per 100,000 person years assuming goal of LDL-C of <100 mg/DL								
Baseline event Rates - LDL-C 100	**Statin Benefit Group 1: ASCVD**				**Statin Benefit Group 2: Familial Hyperlipidemia**			
	Untreated[1]	**Treated and uncontrolled (>=100)[2]**	**50% LDL-C Reduction**	**59% LDL-C Reduction**	**Untreated[1]**	**Treated and uncontrolled (>=100)[2]**	**50% LDL-C Reduction**	**59% LDL-C Reduction**
Myocardial Infarction	2,969	2,670	1,702	1,528	1,503	1,352	862	774
Ischemic Stroke	2,697	2,247	1,432	1,286	1,511	1,258	802	720
Unstable Angina	4,967	4,601	2,818	2,497	2,250	2,084	1,276	1,131
Revascularization[3]	3,783	3,545	2,039	1,767	1,817	1,680	966	837
CVD Mortality	2,442	2,212	1,619	1,513	1,609	1,448	843	795

1. Are not currently on lipid control medication
2. Currently on lipid control medication but have not reached goal LDL-C level (<70 or < 100 mg/DL)
3. Revascularization includes CABG and PCI

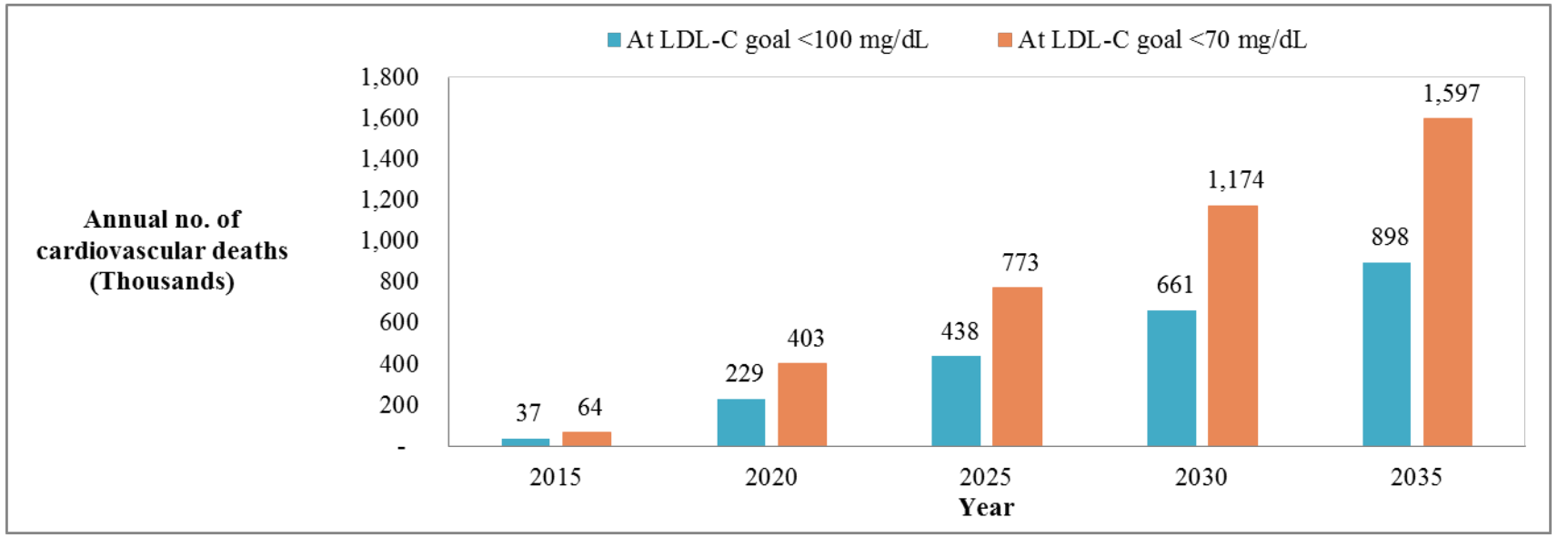
Table 6. Value per person-year treated with PCSK9 inhibitors in SBGs 1-2, 2015-2035 ***[Assuming 12.7 life years lost to CVD deaths estimated from Murray et al 2013 [12]]***

A. Treatment of patients in SBGs 1-2 with PCSK9 inhibitors, assuming goal LDL-C < 70mg/dl										
	Conservative PCSK9i Efficacy Scenario					**High PCSK9i Efficacy Scenario**				
	2015	2020	2025	2030	2035	2015	2020	2025	2030	2035
Number of averted events (thousands)										
MACE	670	4,200	8,000	12,300	16,800	760	4,800	9,200	14,000	19,100
CVD deaths	75	470	900	1,400	1,900	110	710	1,400	2,100	2,800
Value from averted events ($ billions)										
MACE	$19	$110	$200	$280	$350	$21	$120	$215	$300	$380
CVD deaths	**$140**	**$830**	**$1,500**	**$2,000**	**$2,600**	**$215**	**$1,300**	**$2,200**	**$3,200**	**$4,000**
Value per person-year treated ($)										
Cost-offsets	$1,200					$1,300				
Life years	**$8,900**					**$13,500**				
Total social value	**$10,000**					**$14,800**				

B. Treatment of patients in SBGs 1-2 with PCSK9 inhibitors, assuming goal LDL-C < 100mg/dl										
Number of averted events (thousands)										
MACE	360	2,200	4,300	6,500	8,800	400	2,500	4,900	7,400	10,000
CVD deaths	42	260	500	760	1,000	61	380	740	1,100	1,500
Value from averted events ($ billions)										
MACE	$10	$58	$100	$150	$180	$11	$64	$110	$160	$200
CVD deaths	**$80**	**$470**	**$830**	**$1,200**	**$1,500**	**$120**	**$680**	**$1,200**	**$1,700**	**$2,100**
Value per person-year treated ($)										
Cost-offsets	$1,200					$1,300				
Life years	**$9,700**					**$14,200**				
Total social value	**$11,000**					**$15,500**				

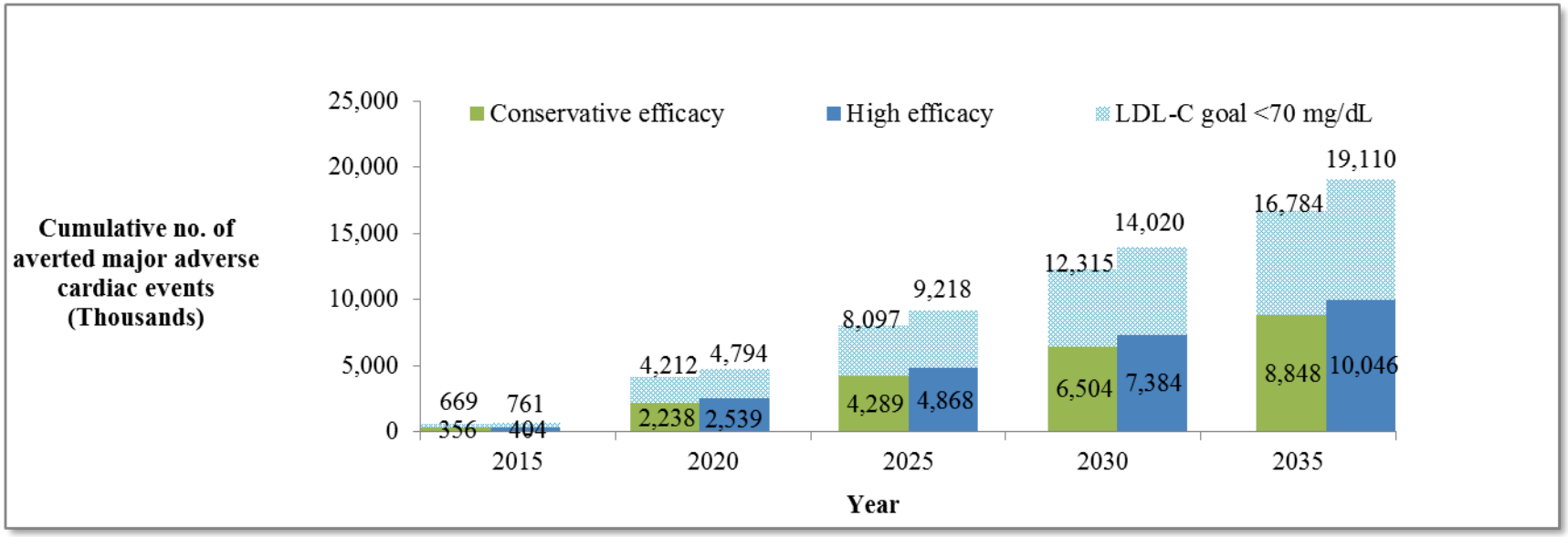
Notes: In the conservative-efficacy PCSK9 inhibitor scenario, PCSK9 inhibitors were assumed to reduce LDL-C by 59%; associated reductions in MACE and CVD deaths were then estimated from established associations between LDL-C levels and CVD event rates. In the high-efficacy PCSK9 inhibitor scenario, PCSK9 inhibitors were assumed to result in a 50% reduction in MACE. The value of health benefits included cost savings from averted MACE. Both conservative- and high-efficacy PCSK9 inhibitor scenarios were modeled under two "at-goal" thresholds: an LDL-C goal of <100 mg/dL and an LDL-C goal of <70 mg/dL.

Figure 1. Cumulative averted CVD deaths associated with a hypothetical 50% LDL-C reduction by LDL-C in SBGs 1 and 2, 2015-2035



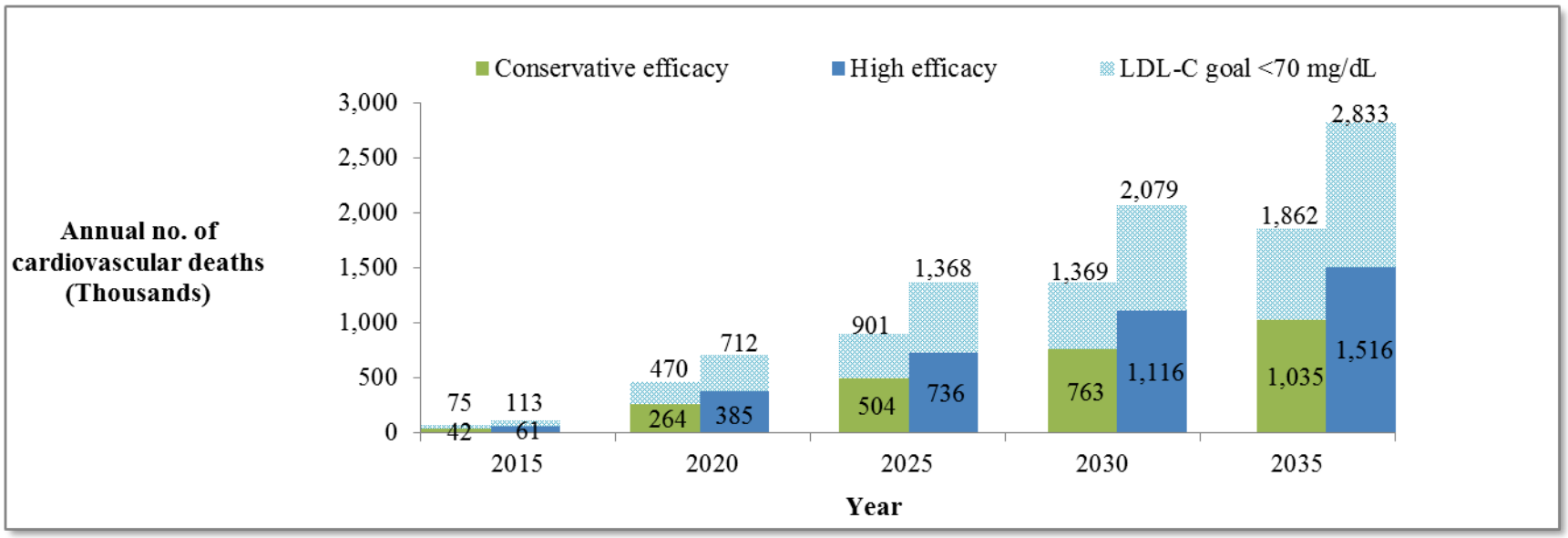
Notes: Two LDL-C "at-goal" thresholds were modeled: 1) <70 mg/dL; 2) <100 mg/dL. The efficacy scenarios modeled assumes a hypothetical goal of reducing LDL-C levels by 50% in the entire treated, not-at-goal population.

Figure 2. Cumulative averted major adverse cardiac events associated with PCSK9 inhibitor use in SBGs 1 and 2, 2015-2035



Notes: In the conservative-efficacy PCSK9 inhibitor scenario, PCSK9 inhibitors were assumed to reduce LDL-C by 59%; associated reductions in MACE and CVD deaths were then estimated from established associations between LDL-C levels and CVD event rates. In the high-efficacy PCSK9 inhibitor scenario, PCSK9 inhibitors were assumed to results in a 50% reduction in MACE. Both conservative- and high-efficacy PCSK9 inhibitor scenarios were modeled under two "at-goal" thresholds: an LDL-C goal of <100 mg/dL (solid bars) and an LDL-C goal of <70 mg/dL (hatched bars).

Figure 3. Cumulative averted CVD deaths associated with PCSK9 inhibitor use in SBGs 1 and 2, 2015-2035



Notes: In the conservative-efficacy PCSK9 inhibitor scenario, PCSK9 inhibitors were assumed to reduce LDL-C by 59%; associated reductions in MACE and CVD deaths were then estimated from established associations between LDL-C levels and CVD event rates. In the high-efficacy PCSK9 inhibitor scenario, PCSK9 inhibitors were assumed to results in a 50% reduction in MACE. Both conservative- and high-efficacy PCSK9 inhibitor scenarios were modeled under two "at-goal" thresholds: an LDL-C goal of <100 mg/dL (solid bars) and an LDL-C goal of <70 mg/dL (hatched bars).

eAppendix References

1. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey Data. In: Statistics NCfH, ed. Hyattsville, MD: U.S. Department of Health & Human Services, Centers for Disease Control and Prevention; 2014.
2. US Census Bureau. Methodology and Assumptions for the 2012 National Projections. 2012; http://www.census.gov/population/projections/files/methodology/methodstatement12.pdf. Accessed August 4, 2014.
3. Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. *Journal of the American College of Cardiology.* 2008;51(7):701-707.
4. Truven Health. Comercial Claims and Encouters Medcaire Supplemental. In: Health T, ed2013.
5. Murphy SL, Xu J, Kochanek KD, Division of Vital Statistics. Deaths: Final data for 2010. *National Vital Statistics Reports.* 2013;61(4).
6. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet.* 2012;380(9841):581-590.
7. U.S. Food and Drug Administration. FDA approves Repatha to treat certain patients with high cholesterol. 2015; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm460082.htm. Accessed August 31, 2015.
8. Knowles JW, O'Brien EC, Greendale K, et al. Reducing the burden of disease and death from familial hypercholesterolemia: A call to action. *American heart journal.* 2014;168(6):807-811.
9. Besseling J, Kindt I, Hof M, Kastelein JJ, Hutten BA, Hovingh GK. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. *Atherosclerosis.* 2014;233(1):219-223.
10. Kavousi M, Leening MJ, Nanchen D, et al. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. *JAMA : the journal of the American Medical Association.* 2014;311(14):1416-1423.
11. Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. *European heart journal.* 2008;29(21):2625-2633.
12. Murray CJ, Atkinson C, Bhalla K, al. e. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA : the journal of the American Medical Association.* 2013;310(6):591-608.