

# Two Steps Forward, One Step Back: 50 Years of Societal Value From LDL-C–Lowering Therapies

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**D**espite 70 years of progress due to advances in both prevention and treatment,<sup>1</sup> cardiovascular disease (CVD) remains the leading cause of death and the largest contributor to medical costs in the United States.<sup>2</sup> In 2017, approximately 95 million adults (aged  $\geq 20$  years) in the United States had high cholesterol ( $\geq 200$  mg/dL).<sup>3</sup> Elevated low-density lipoprotein cholesterol (LDL-C) in particular remains a key target for therapy because it is associated with an increased risk of CVD-related events such as nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, and CVD mortality.<sup>4</sup> In 2013–2014, an estimated 30% of adults (aged  $\geq 20$  years) in the United States had high LDL-C ( $\geq 130$  mg/dL).<sup>5,6</sup> Of particular concern, 63% of patients with previous MI exhibited LDL-C levels above the goal of 70 mg/dL despite being on some form of LDL-C–lowering therapy (LLT).<sup>7–11</sup>

In response to continuing unmet need, the LLT landscape has evolved significantly over the past half-century. Statins, which became available in the United States in 1987, are among the world's best studied drugs.<sup>12,13</sup> There is unequivocal evidence on the value of statins in primary and secondary CVD prevention. Based on large outcomes trials and meta-analyses, statins lower CVD event risk by 22% per 38.7 mg/dL (1 mmol/L) reduction in LDL-C.<sup>8,14,15</sup> The West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated a durable survival benefit for long-term ( $\geq 5$  years) statin users.<sup>16</sup>

Additionally, 2 other classes of drugs have yielded positive results in combination with statins by reducing LDL-C: ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.<sup>8–11</sup> However, evidence on their clinical value remains mixed. For PCSK9 inhibitors, the ODYSSEY Outcomes trial demonstrated a survival benefit in the secondary prevention setting,<sup>17</sup> but the FOURIER trial (evolocumab) and subsequent trial meta-analyses did not.<sup>11,18</sup> Although ezetimibe demonstrated a benefit in the composite end point of CV death/myocardial infarction (MI)/hospitalization for unstable angina/coronary revascularization beyond 30 days/stroke, it did not demonstrate a significant protective effect for CV mortality alone.<sup>19</sup> However, some have argued that this is due to the relatively low mean baseline LDL-C levels of trial participants (95 mg/dL in both arms of IMPROVE-IT).<sup>19,20</sup>

## ABSTRACT

**OBJECTIVES:** To assess the evolving landscape of low-density lipoprotein cholesterol–lowering therapies (LLTs) and quantify their effect on cardiovascular disease (CVD)–related mortality and morbidity.

**STUDY DESIGN:** Secondary data came from LLT clinical trials and 1999–2014 National Health and Nutrition Examination Survey (NHANES) data. 1996–2016 Medical Expenditure Panel Survey (MEPS) data were used to estimate LLT spending. Nonfatal CVD events prevented by LLTs were calculated from clinical trials and NHANES. The value of nonfatal events prevented was calculated as the product of event treatment costs and the number of events prevented. The value of mortality reduction was calculated as the product of a value of a life-year and the life expectancy gain from LLTs. This was compared with LLT spending estimated using MEPS.

**METHODS:** Total LLT expenditures were calculated based on MEPS LLT utilization and expenditure data. Values of prevented hospitalizations, prevented CVD events, and other LLT utilization–related outcomes were pulled from the published literature.

**RESULTS:** Combined, statins and ezetimibe prevented 2.8 million nonfatal heart attacks and 1.7 million nonfatal strokes from 1999 to 2014. Statin use generated \$2.6 trillion in societal value through CVD deaths avoided from 1987 to 2014, and 85% accrued to patients.

**CONCLUSIONS:** LLTs have yielded significant societal value, and the majority of this value has accrued to patients.

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Prior literature has established that statins alone have produced value far in excess of their costs. The initial introduction and uptake of statins in 1987 prompted the publication of several cost-effectiveness studies using traditional cost-benefit analysis.<sup>21–23</sup> More recently, Grabowski et al expanded on traditional cost-benefit analysis to approximate the societal value of survival gains generated by statin use<sup>24</sup> and found that statins generate significant value to society, the majority of which accrues to patients. There is also some evidence of societal value from PCSK9 inhibitor drugs. Jena et al estimated that reducing LDL-C by 50% among patients with a high risk of experiencing a CV event who have insufficient response to other LLTs could prevent up to 14.2 million major adverse coronary events (MACEs), including 1.6 million CVD deaths, by 2035.<sup>25</sup>

Given CVD's high disease burden and the evolution of LLT innovation and clinical guidelines, it is informative to update the prior literature by incorporating more recent information on statins and other LLTs.

We build upon and broaden the seminal Grabowski et al study on statins by (1) updating the estimates through 2014, which is the most recently available year of observed data; (2) estimating nonfatal events and hospitalizations avoided; and (3) incorporating other LLTs. To gain further understanding of the relationship between LLT use and reductions in CVD mortality and morbidity, this study utilized a quantitative analysis to calculate the societal benefits and costs of LLTs to patients initiating LLT for primary and secondary prevention from 1987, when statins were introduced, through 2014.

## METHODS

### Study Design Overview

Descriptive analyses of the rates of LLT use and LLT spending over time were conducted using both National Health and Nutrition Examination Survey (NHANES) (1999–2014) and Medical Expenditure Panel Survey (MEPS) (1996–2016) data, and the associations between LDL-C levels and CV mortality and hospitalizations were identified in the literature. The basis for the Grabowski methodology, which we build upon, is the notion that social value estimates ought to begin with real-world data on statin users. NHANES is the only nationally representative health survey with objective data on lipid levels, and MEPS is the only nationally representative database on health care expenditures. These databases were used to estimate the number of statin users (for < 5 years and ≥ 5 years), the number of ezetimibe users, nonfatal MIs and strokes among LLT users, annual expenditures on statins, and annual expenditures on ezetimibe. As with most large-scale surveys, the NHANES and MEPS data have some gaps. For this reason, we relied on the literature to derive estimates of the relative risk of CVD events for statin users vs nonusers. Our approach, however,

## TAKEAWAY POINTS

Low-density lipoprotein cholesterol–lowering therapies (LLTs) have yielded significant value to society through reduced costs for both fatal and nonfatal cardiovascular disease (CVD) events. The vast majority of this value has accrued to patients.

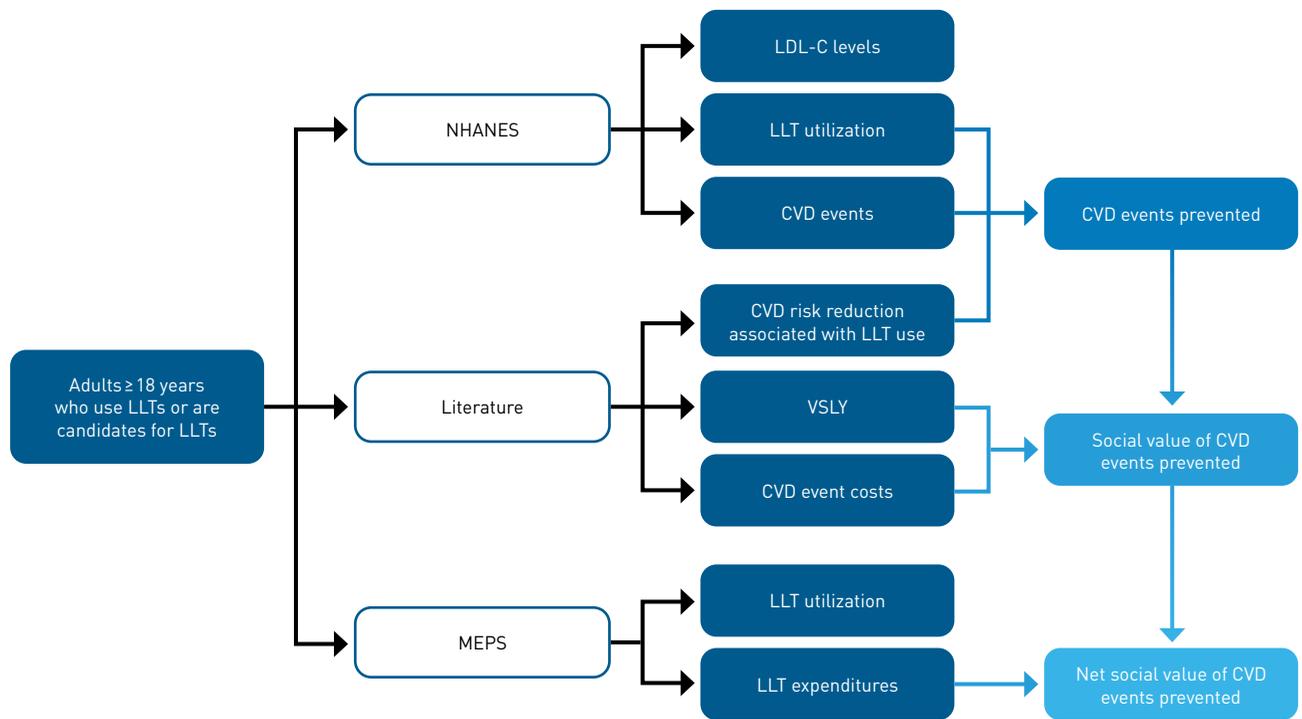
- ▶ This study contributes to the literature on the value of preventive medicine and to the growing body of evidence that LLTs generate significant economic and clinical value to both patients and society as a whole.
- ▶ We demonstrate that statins and ezetimibe have yielded significant value to society through the reduction of costs associated with both fatal and nonfatal CVD events.
- ▶ It is important to understand the value generated by these therapies, as this information can inform the development of treatment guidelines and managed care policy.

does not capture reductions in quality of life from drug adverse effects or improvements in quality of life from improved health. In focusing exclusively on survival and costs, we follow the bulk of the existing literature on social value.<sup>26–28</sup> The rationale for this strategy in the literature is that survival gains are more straightforward to monetize than quality-of-life harms and benefits, and they are likely to be more quantitatively meaningful in this context.

The total number of nonfatal CVD events prevented over time was calculated using HRs from published clinical trials and NHANES data on the number of LLT users and frequency of self-reported nonfatal CVD events among these users. Events avoided were calculated as the difference between real-world CVD events observed among LLT users and events that would have occurred in the absence of LLT use. The latter was calculated by taking the real-world CVD events among LLT users in NHANES and deducting the difference in events between treated and untreated patients in LLT trials. This yields an estimate of total nonfatal CVD events prevented. We then multiply by prior estimates of nonfatal CVD event costs<sup>3,29</sup> to construct the value of prevention. The value of mortality reduction was calculated as the product of the value of a statistical life-year (VSLY; \$150,000) and the life expectancy gain from the WOSCOPS clinical trials for statins (for primary prevention), respectively.<sup>16</sup> The life expectancy gains for those using statins for at least 5 years estimated from WOSCOPS equaled 0.145 years per user. The life expectancy gains for those using statins for 4 or fewer years was estimated at 0.03 years based on the WOSCOPS trial data, as in Grabowski et al.<sup>24</sup> We do not include survival benefits for PCSK9 inhibitors because the trial evidence is mixed on PCSK9 inhibitor survival benefits.<sup>19,20</sup> Further details are illustrated in **Figure 1** and described below.

A targeted literature review was conducted to identify studies on the relationship between LLT use and (1) CVD morbidity (eg, heart attack, stroke), (2) CVD event hospitalizations, and (3) CVD mortality. The goals of the literature review were to provide context for the study, identify relevant parameters for quantifying the reductions in CVD mortality and hospitalizations attributable to LLTs through reductions in LDL-C, and inform comparisons of the relative degree of innovativeness of a particular LLT or category of LLTs. Search strategies were implemented using Google Scholar, PubMed, and the Cochrane Library. Reviewers screened the titles

FIGURE 1. Study Design



CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; LLT, LDL-C-lowering therapy; MEPS, Medical Expenditure Panel Survey; NHANES, National Health and Nutrition Examination Survey; VSLY, value of a statistical life-year.

and abstracts to identify publications that appeared to capture the relevant information in accordance with the selection criteria.

**Statistical Analysis**

Descriptive analyses of the rates of LLT utilization and LDL-C levels, as well as all other patient characteristics (age, race, blood pressure readings, weight, height, smoking status, physical activity, prescription drug use, and relevant medical conditions), were conducted using data from all continuous NHANES survey cycles (eg, 1999-2000 to 2013-2014). The unadjusted number and percentage of Americans 18 years and older using LLTs by LLT type and American College of Cardiology/American Heart Association statin benefit group and across study years were calculated. The number of users from 2015 to 2030 was projected based on the linear time trend estimated from observed number of statin users in 1999-2014. The Guideline on the Assessment of CVD Risk<sup>30</sup> was used to estimate individuals' 10-year atherosclerotic CVD risk, where 10-year risk of 7.5% or greater is considered elevated risk.<sup>30</sup> We conducted 2 sensitivity analyses: (1) We explored the effect of halving the estimated growth of statin use from 2015 to 2030, and (2) we explored the use of predicted values for statin utilization and statin costs from nonlinear regressions and generated CIs around these estimates. The sensitivity analysis methods are described in the **eAppendix** materials (eAppendix available at [ajmc.com](http://ajmc.com)).

Mean annual expenditures on LLTs were calculated based on LLT utilization and expenditures from MEPS. All expenditure outcomes were inflated to 2018 Q1 US\$ using the all-urban US Bureau of Labor Statistics Consumer Price Index.<sup>31</sup> All statistics were estimated using the appropriate survey weights and variance primary sampling unit to account for the complex survey design and to produce nationally representative estimates.

Information on cardiac revascularizations is not available in NHANES; thus, we could not estimate the number of revascularizations prevented among LLT users. Nonfatal events prevented (EP) by year and LLT type (ie, statins and ezetimibe) were calculated as the difference between the number of CVD events we would expect to see in LLT users if they did not use LLTs (E<sub>1</sub>) and the number of events we see in LLT users when they do use LLTs (E<sub>2</sub>) (ie, EP = E<sub>1</sub> - E<sub>2</sub>). We estimated E<sub>1</sub> based on the relative risk of CVD events in clinical trials for statins and ezetimibe<sup>16,19</sup> (HR<sub>CT</sub>) and the observed frequency of CVD events (ie, MI or stroke) among LLT users in NHANES in the previous 12 months, Pr(E<sub>2</sub>). Events prevented were calculated as:

$$EP = n_{LLT} [Pr(E_1) - Pr(E_2)] = n_{LLT} \left[ \frac{Pr(E_2)}{HR_{CT}} - Pr(E_2) \right],$$

where n<sub>LLT</sub> denotes the number of individuals using an LLT in a given year. Utilization of LLTs and frequency of nonfatal MIs and strokes

among LLT users by LLT type were estimated in the NHANES data.

The expected life-years gained from LLT use (ie, reduction in CVD mortality) were estimated from the hazard/survival curves reported in the key LLT clinical trial WOSCOPS (statins).<sup>16</sup> The survival curve coordinates were extracted for both trial arms and used to estimate the life expectancy for each curve. Life expectancy was estimated as the integral of the survival curve. Mean life expectancy gain was calculated as the difference between the trial treatment and control arms.

The value of prevented hospitalizations for nonfatal MI and nonfatal stroke was calculated using the estimated number of nonfatal events prevented by LLT and mean costs for these events from the literature.<sup>30-41</sup> Mortality reductions were valued based on widely used estimates of the VSLY (\$150,000)<sup>42-44</sup> and the expected life-years gained from LLT use that were estimated from the hazard/survival curves reported in WOSCOPS for statins.<sup>16,17</sup> Health gains were discounted at 3% per year. Annual social value was calculated as:

$$V_t = 150,000 \times 0.145 \times \exp(-0.03[t-2018]) \times n_t^{5+} + 150,000 \times 0.03 \times \exp(-0.03[t-2018]) \times n_t^{<5}$$

where  $n_t^{5+}$  is the incidence of 5-year statin use and  $n_t^{<5}$  is the prevalence of 0 to 4 years of statin use.

## RESULTS

### LLT Costs, LDL-C Levels, CVD Events, and Life-Years Saved

Mean annual expenditures on LLTs hovered around \$900 per treated patient per year from 1999 to 2008, then fell sharply after several statin patent expirations in the mid- to late 2000s. In 2016, annual expenditures on LLTs averaged \$517 per treated patient.

Mean LDL-C levels among LLT users fell sharply between 1999 and 2006, from approximately 120 mg/dL to 100 mg/dL, and remained at approximately 100 mg/dL through 2014. Mean LDL-C levels among LLT candidates (ie, those in a statin benefit group not using an LLT) had mean LDL-C level of approximately 130 mg/dL from 1999 to 2014.

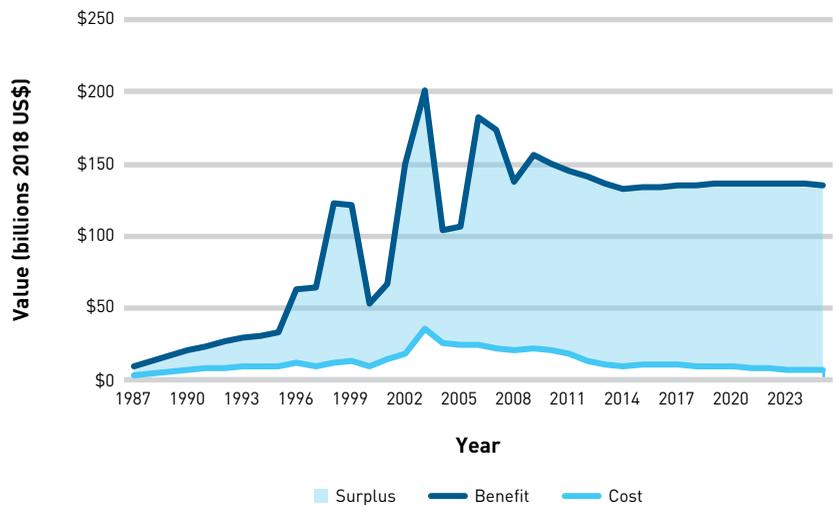
Using the NHANES data, we estimated that statins and ezetimibe prevented a combined 2.8 million nonfatal heart attacks and 1.7 million nonfatal strokes from 1999 to 2014. Note that we predicted zero events prevented by ezetimibe for some years because no

nonfatal strokes or MIs were observed among the small number of ezetimibe users in those years.

### Social Value

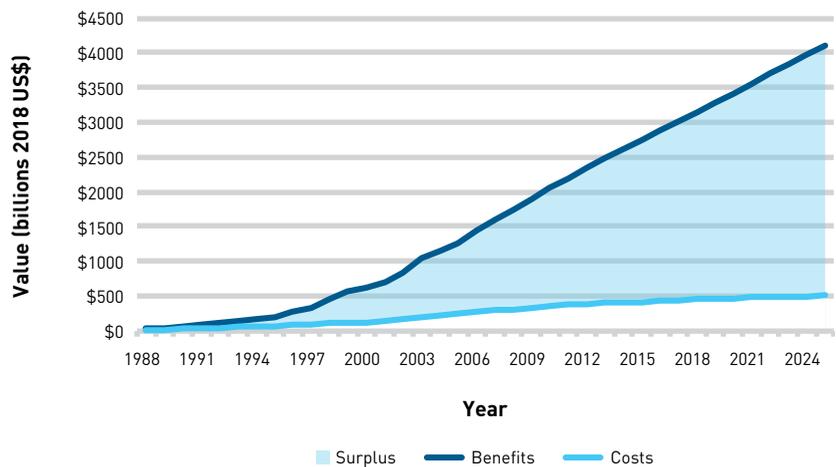
In the United States alone, we estimate that statin use generated \$2.6 trillion (2018 US\$) in cumulative social value in prevented CVD deaths from 1987 to 2014 and that patients retained 85% (\$2.2 trillion of \$2.6 trillion) of this value. Assuming a VSLY of \$150,000, the cost to society of each life-year gained by statin users equals \$18,500 (Figure 2 and Figure 3). Even at a more modest VSLY of \$50,000, statin use generated \$869 billion (2018 US\$) in cumulative social

**FIGURE 2.** Annual Social Value of Statin Use From Reductions in CVD Mortality



CVD, cardiovascular disease.

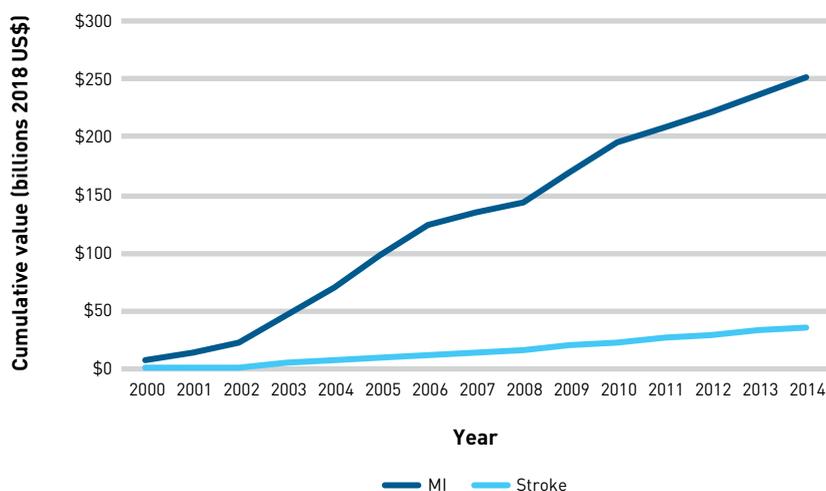
**FIGURE 3.** Cumulative Social Value of Statin Use From Reductions in CVD Mortality



CVD, cardiovascular disease.

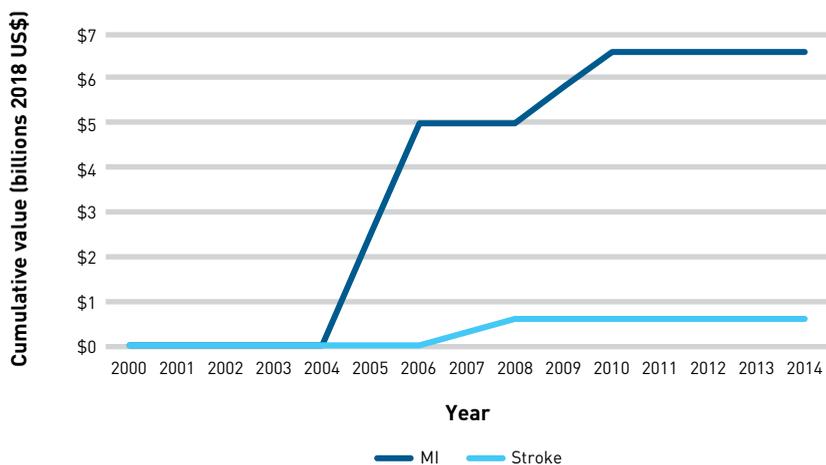
## METHODS

**FIGURE 4.** Cumulative Value of Nonfatal CVD Events Prevented by Statins, 1999-2014



CVD, cardiovascular disease; MI, myocardial infarction.

**FIGURE 5.** Cumulative Value of Nonfatal CVD Events Prevented by Ezetimibe, 1999-2014



CVD, cardiovascular disease; MI, myocardial infarction.

value in prevented CVD deaths from 1987 to 2014, and patients retained \$463 billion of this value. From 2015 to 2030, the analysis predicts that statin use will generate an additional \$1.5 trillion (2018 US\$) in cumulative social value in prevented CVD deaths and that patients will retain 93% (\$1.4 trillion of \$1.5 trillion) of this value. The societal value of these innovations is greatest late in the product life cycle, as the number of treated patients and the duration of treatment increases and as patents expire.

The first sensitivity analysis, where we reduced the predicted growth in statin utilization from 2015 to 2030 by half, resulted in a modest decrease in the aggregate benefits of statin use, from

\$4.1 trillion to \$3.7 trillion over the period 1987 to 2030. In this scenario, the vast majority (87%) of the benefits still accrue to patients, and the cost per life-year gained remains well under conventional methods that typically use a threshold of \$50,000 for high-value services. In the second sensitivity analysis, designed to produce CIs, the cumulative benefits and costs from 1987 to 2030 are both lower, at \$3.2 trillion (95% CI, \$2.9 trillion–\$3.5 trillion) and \$299 billion (95% CI, \$269 billion–\$330 billion), respectively. However, the proportion accruing to patients is a bit higher, 93% vs 87%, in the baseline analysis (see [eAppendix Figure](#)).

In terms of morbidity, statins and ezetimibe have prevented a combined 2.8 million nonfatal heart attacks between 1999 and 2014, which would have cost society \$258 billion to treat. Statins and ezetimibe have prevented a combined 1.7 million nonfatal strokes over the same period, which would have cost society \$37 billion to treat ([eAppendix Table, Figure 4, and Figure 5](#)).

In sum, about 88% (\$2.16 trillion) of total LLT value was accrued as mortality reduction from 1999 to 2014, and about 12% was accrued through reductions in morbidity.

## DISCUSSION

Over time, new LLTs are developed and brought to market, and long-term outcomes are studied in the real-world setting. As the LLT landscape evolves, so too do treatment guidelines. Given the immense clinical and economic burden of CVD, it is informative and meaningful to better understand the societal value generated by LLTs.

This study contributes to the literature on the value of preventive medicine<sup>45,46</sup> and to a growing body of evidence that LLTs generate significant clinical and economic value to

society.<sup>24,25,47</sup> The cost to society of each life-year gained by statin users was \$18,500, which would be considered cost-effective by conventional methods that typically use a threshold of \$50,000 for high-value services<sup>48</sup> and commonly used thresholds of \$100,000 to \$150,000 per quality-adjusted life-year.<sup>49</sup> We demonstrate that statins and ezetimibe have yielded significant value to society through the reduction of costs associated with both fatal and nonfatal CVD events. In the United States alone, statin use generated \$2.6 trillion in cumulative social value in prevented CVD deaths from 1987 to 2014, and patients retained 85% of this value. Expressed in 2008 US\$, our estimates of the social value of statin use for 1987 to 2008 are very

similar to those of Grabowski et al: \$1.29 trillion vs \$1.25 trillion. In a similar study, Jena et al estimated that PCSK9 inhibitor use among high-risk individuals with inadequate response to other LLTs in the United States could prevent an additional 14.2 million MACes, including 1.6 million CVD deaths, between 2015 and 2035 and generate \$2.9 trillion in cumulative value.<sup>25</sup>

Between 1999 and 2014, statins and ezetimibe prevented a combined 2.8 million nonfatal heart attacks, which would have cost society \$258 billion to treat. Over the same period, statins and ezetimibe prevented a combined 1.7 million nonfatal strokes, which would have cost society \$37 billion to treat. These findings are consistent with a recent study by Cutler et al, which found that use of medications for hypertension, high cholesterol (ie, LLTs), and diabetes contributed significantly to the slowing of Medicare expenditure growth between 1999 and 2012.<sup>47</sup>

Many LLTs have been investigated over the previous 40 years, yet only a few have gone on to generate value to patients and the returns to innovators that finance the large number of unsuccessful LLT trials. The societal value of these innovations is greatest late in product life cycle, after patent expiry.

## Limitations

This study has some limitations. First, we do not observe LDL-C, LLT use, and expenditures on LLTs for the same individuals, and we therefore use data from multiple data sources (ie, NHANES and MEPS).

Second, to the extent that the frequency of nonfatal stroke and MI among LLT users, and ezetimibe users in particular, is underestimated in the NHANES data, the estimated number and value of nonfatal events prevented by LLTs use are understated. Also, as discussed earlier, we did not attribute a mortality benefit to ezetimibe use. Therefore, our estimated benefits of ezetimibe use are understated to the extent that there is a mortality benefit from ezetimibe use in the real world (eg, in patients with LDL-C > 100 mg/dL).

Third, our estimates do not include any benefits from increases in health-related quality of life attributable to LLTs or costs from decreases in health-related quality of life attributable to adverse effects. Fourth, our methodological framework does not adequately capture considerations from a cost perspective that may be incurred by patients upon initiating novel LLTs. Fifth, as discussed above, we did not attribute a mortality benefit to PCSK9 inhibitor use. Thus, our estimated benefits of LLT use are understated in regard to the mortality benefit gained from PCSK9 inhibitor use in the real world (eg, among patients who achieve LDL-C < 70 mg/dL with the addition of a PCSK9 inhibitor).

Finally, as with other social value studies, it is difficult to rigorously quantify every source of uncertainty and its implications for the variability of our estimates. For example, real-world clinical benefits may depart from clinical trial benefits. Utilization projections introduce uncertainty above and beyond the variability in the underlying data sets. For these reasons, we follow prior literature by presenting mean estimated effects and transparently documenting

our approach to constructing them. Also following prior studies, we avoid presenting CIs in the main analyses because it is difficult to capture in full all the potential sources of uncertainty possible.<sup>24</sup> However, for completeness, we construct them in a sensitivity analysis, which yields qualitatively similar conclusions and appears in the eAppendix material.

## CONCLUSIONS

Meaningful social value has accrued from innovation in the LLT landscape through the reduction of costs associated with both fatal and nonfatal CVD events. Most of this value was generated by statins, ezetimibe, and PCSK9 inhibitors. ■

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**Authorship Information:** Concept and design (JPM, LL, DL, FS, DNL); acquisition of data (JPM, KE); analysis and interpretation of data (JPM, KE, LL, DL, DNL); drafting of the manuscript (JPM, LMZ); critical revision of the manuscript for important intellectual content (JPM, LMZ, LL, DL, DNL); statistical analysis (JPM); provision of patients or study materials (JPM); obtaining funding (JPM, LL); administrative, technical, or logistic support (JPM, LMZ, LL, FS); supervision (JPM, FS, DNL); and programming (KE).

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## eAppendix Material: Sensitivity Analysis

### Methods

As a sensitivity analysis we used non-linear regression to predict statin utilization and costs over the full study window (1987–2030) and then used these predicted values to calculate social value. Utilization ( $u_t$ ) was estimated and predicted using non-linear regression assuming a logistic functional form for the number of statin users over time/by year ( $y_t$ ). That is, we estimated:

$$u_t = \beta_1 / [1 + \exp\{-\beta_2(y_t - \beta_3)\}] + \epsilon_t$$

Similarly, annual statin costs ( $c_t$ ) were estimated and predicted using non-linear regression assuming an exponential functional form:

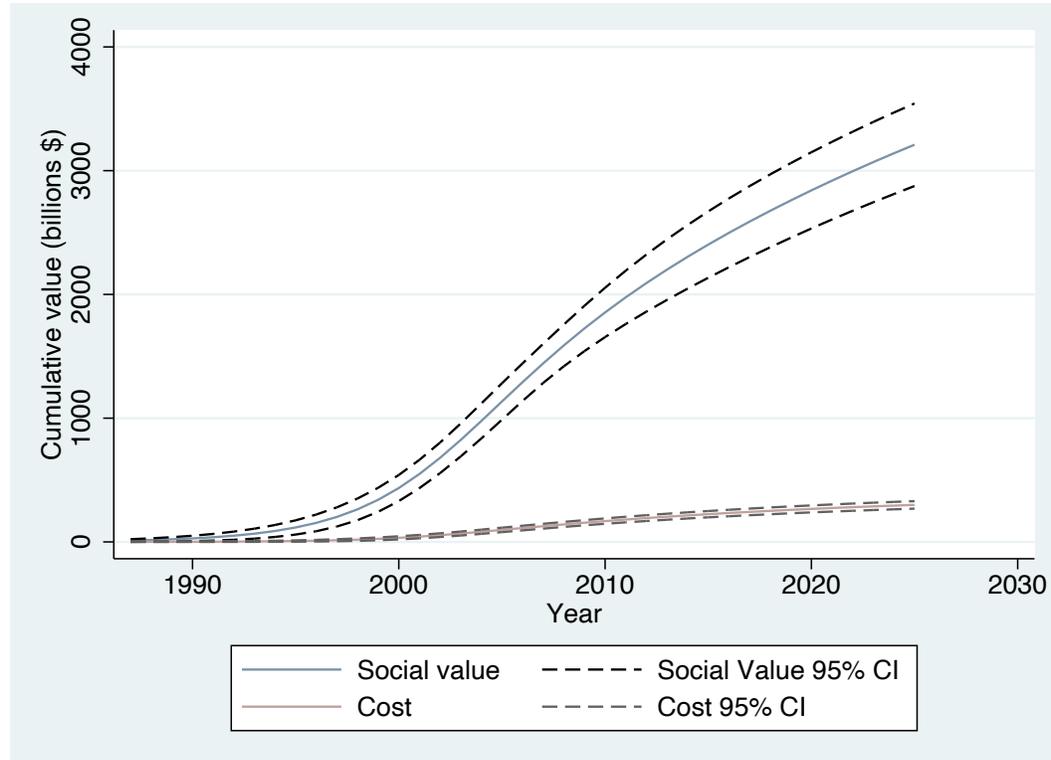
$$c_t = \beta_1 \beta_2^{y_t} + \epsilon_t$$

The predicted values and confidence intervals from these regressions were then used to calculate social value and the proportion accruing to patients.

### Results

In this analysis cumulative benefits and costs from 1987-2030 are both lower than in the main analysis, \$3.2T (95%CI: \$2.9T–\$3.5T) and \$299B (95%CI: \$269B–\$330B), respectively (see figure below). However, the proportion accruing to patients is a bit higher, 93%, versus 87% in the baseline analysis.

eAppendix Figure.



**eAppendix Table.** Estimated Life Years Gained and Non-Fatal CVD Events Prevented from Statin and Ezetimibe Use

	<b>CUMULATIVE LIFE YEARS GAINED 1987-2014</b>	<b>CUMULATIVE NON-FATAL MI 1999-2014</b>	<b>CUMULATIVE NON- FATAL STROKES 1999-2014</b>
<b>STATINS</b>	17,381,412	2,738,904	1,688,744
<b>EZETIMIBE</b>		69,871	28,328