Clinical and economic burden associated with cardiovascular events among patients with hyperlipidemia: a retrospective cohort study

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Abstract

Background: Annual direct costs for cardiovascular (CV) diseases in the United States are approximately $195.6 billion, with many high-risk patients remaining at risk for major cardiovascular events (CVE). This study evaluated the direct clinical and economic burden associated with new CVE up to 3 years post-event among patients with hyperlipidemia.

Methods: Hyperlipidemic patients with a primary inpatient claim for new CVE (myocardial infarction, unstable angina, ischemic stroke, transient ischemic attack, coronary artery bypass graft, percutaneous coronary intervention and heart failure) were identified using IMS LifeLink PharMetrics Plus data from January 1, 2006 through June 30, 2012. Patients were stratified by CV risk into history of CVE, modified coronary heart disease risk equivalent, moderate- and low-risk cohorts. Of the eligible patients, propensity score matched 243,640 patients with or without new CVE were included to compare healthcare resource utilization and direct costs ranging from the acute (1-month) phase through 3 years post-CVE date (follow-up period).

Results: Myocardial infarction was the most common CVE in all the risk cohorts. During the acute phase, among patients with new CVE, the average incremental inpatient length of stay and incremental costs ranged from 4.4–6.2 days and $25,666–$30,321, respectively. Acute-phase incremental costs accounted for 61–75 % of first-year costs, but incremental costs also remained high during years 2 and 3 post-CVE.

Conclusions: Among hyperlipidemic patients with new CVE, healthcare utilization and costs incurred were significantly higher than for those without CVE during the acute phase, and remained higher up to 3 years post-event, across all risk cohorts.

Keywords: Hyperlipidemia, Cardiovascular events, Clinical burden, Economic burden

Background

The global cost of cardiovascular disease (CVD) is estimated at $863 billion and is estimated to rise to $1,044 billion in 2030 [1]. The American Heart Association has estimated the direct costs for CVD in the United States at $195.6 billion, approximately 61 % of the total CVD-related healthcare costs [2]. Additionally, hyperlipidemia was among the top 10 costliest medical conditions in 2008 in the US adult population [3]. Presence of hyperlipidemia directly correlates with the risk of developing coronary heart disease (CHD) and future cardiovascular (CV) events [4]. Less than half of adults with elevated low density lipoprotein cholesterol (LDL-C) levels receive treatment or are adequately treated [5, 6] and as a result, high-risk patients continue to remain at risk for new CV events. Almost 44 % of the US population is projected to be diagnosed with some form of CVD by 2030 [2]. These factors result in a substantial clinical
and economic burden in terms of direct healthcare utilization and costs.

While several studies have examined the economic burden of CV events [7–12], to our knowledge contemporary and long-term analyses concerning these event costs incurred by hyperlipidemic patients across a range of CVD risk levels is not available. Previous studies focused on short-term healthcare costs due to CV events [13–17] and investigated patient populations diagnosed with acute coronary syndrome [13, 14], hypertension [15], atherosclerosis [16] or diabetes [17], but not hyperlipidemia. Furthermore, prior studies focused only on the initial CV event and therefore, limited data are available regarding recurrent and subsequent CV event costs. Prior studies have investigated the economic burden of CV events over various time periods [10]; however, incremental costs among hyperlipidemic patients with and without CV events, and in particular, costs stratified by CVD risk level and associated with myocardial infarction (MI), ischemic stroke (IS) unstable angina (UA), coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), heart failure (HF) and transient ischemic attack (TIA), all in one study, have not been previously examined. Therefore, the present study is one of the first to estimate the short-term and long-term (up to 3 years) direct clinical and economic burden of new CV events among hyperlipidemic patients at different CVD risk levels and by specific CV event type.

**Methods**

**Study design**

We conducted a retrospective cohort study including patients with a hyperlipidemia diagnosis who had a new CV event matched to patients without new CV events, using the IMS LifeLink PharMetrics Plus dataset for the study period January 1, 2006 through June 30, 2012. This nationally-representative longitudinal database contains medical and pharmacy claims for over 50 million commercially-insured patients throughout the United States [7, 18, 19]. All claims data were from a limited dataset with de-identified patient information. No patients were directly involved in the study; therefore, this study was exempt from an Institutional Review Board review.

**Study population**

Patients (age ≥18) were included in the study if they had ≥1 medical claims for hyperlipidemia (International Classification of Diseases, 9th Revision Clinical Modifications [ICD-9-CM] code 272) [20] from January 1, 2006 through June 30, 2009. The first diagnosis claim date was designated as the hyperlipidemia diagnosis date. As detailed in Appendix 1, patients were required to have at least one inpatient medical claim for a new CV event (MI, IS, UA, TIA, HF, CABG and PCI) after the hyperlipidemia diagnosis date and during the identification period (January 1, 2007 through June 30, 2009). For hyperlipidemic patients with a new CV event, the earliest inpatient claim date was designated as the index date. If a patient had more than one inpatient claim for a new CV event on the index date, only one CV event was selected, according to the following hierarchy: MI, IS, UA, HF, TIA, CABG and then PCI, based on the clinical importance (e.g. acute/urgency) of CV events and CV-related procedures. The comparison group included patients with no new CV event after the hyperlipidemia diagnosis and through the end of the study period (June 30, 2012). Baseline period of the 12 months prior to the index date was utilized to characterize patients’ CV risk level (e.g. history of CVE or diabetes) and comorbidity status. Patients were followed from the index date through 3 years post-index date to estimate short-term (first 30 days and 1 year) and longer-term (2 years and 3 years) direct costs.

Matching was completed in a two-step approach. The first step was 1:1 match (age, gender, US region) to assign an index date for patients without a new CV event and define the baseline period for quantifying baseline characteristics (CV risk level, comorbidities). These initially matched patients with no new CV event were then assigned the same index date as that of their matched patients who had a new CV event. This assignment of index date to patients with no new CV event provided the same baseline and follow-up time periods for the comparison of outcomes between patients with and without new CV events.

The second step of matching, propensity score matching (PSM) with 0.01 calipers, was applied to control the differences in baseline clinical and demographic factors between patients with and without new CV events within each risk cohort [21, 22]. A standardized difference (STD) of ≥10 % was used to assess significant practical differences in the case–control comparison [23]. The baseline variables adjusted in the model were age group, gender, US region, Charlson comorbidity index (CCI) score, Chronic Disease Score (CDS), individual comorbid conditions (hypertension, arrhythmias, metabolic syndrome, liver disease, obesity, and chronic kidney disease) and number of inpatient admissions per patient per month (PPPM). The methods used in this study have also been published in prior literature [7, 10]. The CCI score is based on ICD-9 codes and CDS uses pharmacy dispensation information for specific drug classes to estimate the burden of comorbidities [24]. The CCI and CDS score have been widely used in many retrospective studies [25–28].

Based on the risk level during the 12-month pre-index (baseline period), the study sample was subdivided into the following CVD risk cohorts: history of CV event, modified CHD risk equivalent (RE), moderate risk and low risk (Fig. 1). Risk levels were defined based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines [29] (Appendix 2).
The history of CV event cohort included patients with MI, UA, CABG, PCI or IS, the modified CHD RE cohort included patients with peripheral arterial disease, abdominal aortic aneurysm, coronary artery disease, diabetes or dyslipidemia. Patients with at least two of the following three risk factors a) hypertension and/or pharmacy claim for blood pressure-lowering medication, b) aged \( \geq 45 \) for men and aged \( \geq 55 \) for women, c) pre-index high-density lipoprotein cholesterol <40 mg/dl were included in the moderate risk cohort, and patients with zero or one risk factor were included in the low risk cohort [see Appendix 2 for detailed ICD-9-CM codes]. Outcome measures included distribution of CV event type, healthcare utilization, and direct incremental costs (obtained from claims) incurred during the acute (first 1 month post-index date), and long-term (1, 2, 3 years post-index date) follow-up periods for hyperlipidemia patients, stratified by CVD risk level. Healthcare utilization included inpatient, outpatient, outpatient office, emergency room and pharmacy visits and direct costs associated with healthcare utilization were computed from health plan- and patient-paid amounts. Total costs included inpatient, outpatient and pharmacy costs. Costs were adjusted to 2012 US dollars using the annual medical care component of the consumer price index (CPI) to reflect inflation.

**Statistical analysis**

**Descriptive analysis**

Descriptive analysis was conducted to compare demographic and clinical characteristics between patients with and without a new CV event within each risk cohort. The direct total incremental costs were calculated as the difference in total costs for patients with a new CV event and total costs for patients without a CV event. Negative incremental costs indicate that the total costs were lower for patients with new CV events than for patients without new CV events.

**Multivariate analysis**

The differences in economic outcomes for each risk cohort were compared among PSM cases and controls. Patients...
without new CV events were designated as the reference group (controls). All analyses were performed using SAS® version 9.3 (SAS® Institute Inc., Cary, NC).

**Results**

Among patients with a new CV event, a large proportion had two or more new CV events (65.8 %) during the 3-year follow-up period. Second and subsequent CV events during follow-up were often the same event type as the first event. A total of 451,450 patients were eligible for the study, among which 267,165 patients had a new CV event, and 184,285 patients had no new CV event before 1:1 matching. A total of 184,285 hyperlipidemic patients with new CV events from January 1, 2006 through June 30, 2009 were matched according to age, gender and US region to 184,285 hyperlipidemic patients without a new CV event (Fig. 1).

**Baseline demographic and clinical characteristics**

Baseline demographic and characteristics of unmatched patients with a new CV event (N = 267,165) and patients without a new CV event (N = 184,285) are provided in Appendix 3. Baseline demographic and clinical characteristics for propensity score-matched patients with a new CV event (N = 121,820) and patients without a new CV event (N = 121,820), stratified by CVD risk level, are provided in Table 1. Patients without CV events were well-matched with patients with new CV event within each risk cohort, since the STD was <10 % for all variables included in the PSM. The majority of patients were classified in the modified CHD RE cohort (74.4 %), followed by the history of CV event cohort (8.8 %). Overall, the average age of patients with a new CV event (N = 121,820) ranged from 56 to 72 years; 65–67 % were male; and hypertension was the most common baseline comorbidity (4.7–84.4 %).

**Clinical burden**

MI was more commonly diagnosed than other CV event types among patients in the low-risk, moderate-risk and modified CHD RE cohorts. Frequency of MI, IS and HF was similar among patients in the history of CV event cohort (Fig. 2).

During the 1 month post-index date, among patients with history of a CV event (n = 10,741), the mean inpatient length of stay (LOS) was significantly longer among hyperlipidemic patients with a new CV event compared to those without (6.4 vs. 0.25 days, p < 0.0001, Table 2). This trend was observed across all risk cohorts. The inpatient LOS remained longer during the short- and long-term follow-up periods among patients with a new CV event, compared to those without, for all risk cohorts (e.g. history of CV event cohort inpatient LOS in year 2 = 4.14 vs. 1.50 days, p < 0.0001, and in year 3 = 3.72 vs. 1.38 days, p < 0.0001) (Table 3). During the 1 month post-index date, patients with history of a CV event (n = 10,741) had significantly more outpatient emergency room (ER) visits PPPM compared to patients without a new CV event (0.17 vs. 0.04 visits, p < 0.0001, Table 2). This trend continued across all risk cohorts and during all follow-up periods (Tables 2 & 3). Among hyperlipidemic patients with new CV events, all resource utilization components were highest during the 1-month post-index follow-up phase for all risk cohorts, indicating that the highest healthcare utilization occurred during the first month post-CV event. However, healthcare resource utilization during years 2 and 3 of the follow-up period remained significantly higher for patients with a new CV event than for those without, across all risk cohorts (e.g. history of CV event cohort ER visits PPPM during year 2 = 0.05 vs. 0.03 visits, p < 0.0001; and year 3 = 0.05 vs. 0.03 visits, p < 0.0001).

**Economic burden**

Across all CV event type and risk cohorts, the direct incremental costs ranged from $17,903 to $65,825 in the first year of follow-up period, $474 to $19,617 during the second year post-CV event and $2,598 to $26,982 during the third year post-CV event (Table 4).

Direct incremental costs categorized by CV event type varied in relation to the duration of the follow-up period. The direct incremental costs accrued during the 1-month post-index phase represented approximately 45–90 % of first-year costs (data not shown). During the first year post-CV event, CABG costs were highest ($55,548–$65,825) for all risk cohorts, followed by MI ($47,840–$51,686) and HF ($41,001–$46,890). During years 2 and 3 post-index date, patients diagnosed with HF incurred the highest cost burden (year 2: $11,289–$19,617; year 3: $7,820–$26,982) among all risk cohorts. The direct incremental costs during these years were mainly driven by heart failure. For all CV event types, first-year incremental costs were higher compared to those accrued in the second and third post-CV event years; second- and third-year costs were always higher for hyperlipidemic patients with new CV events than for those matched patients without CV events.

**Discussion**

Our study showed that the long-term clinical and economic burden associated with CV events among hyperlipidemic patients was substantial across all risk cohorts, but especially among high-risk cohorts (i.e. patients with history of a CV event and prior CHD RE diagnosis). Our mean healthcare resource
| History of CV event cohort | Modified CHD RE Cohort | Moderate risk cohort | Low risk cohort |
|---------------------------|------------------------|---------------------|----------------|
| Without CV events | With CV events | Without CV events | With CV events | Without CV events | With CV events | Without CV events | With CV events |
| (N = 10741) | (N = 10741) | (N = 90614) | (N = 90614) | (N = 7938) | (N = 7938) | (N = 12527) | (N = 12527) |
| Mean (%/SD) | Mean (%/SD) | P-value<sup>a</sup> STD | Mean (%/SD) | Mean (%/SD) | P-value<sup>a</sup> STD | Mean (%/SD) | Mean (%/SD) | P-value<sup>a</sup> STD |
| Age | 73.66(13.15) | 71.76(12.18) | <0.0001 | 65.32(12.95) | 64.69(12.75) | <0.0001 | 65.58(11.93) | 65.45(12.11) | 0.503 | 56.18(11.24) | 55.86(10.92) | 0.022 |
| 18–24 | [0.0 %] | [0.0 %] | N/A | 0.0 | [0.0 %] | [0.0 %] | 0.336 | 0.5 | [0.0 %] | [0.0 %] | N/A | 0.0 | [0.1 %] | [0.1 %] | 0.683 | 0.5 |
| 25–34 | [0.1 %] | [0.1 %] | 0.781 | 0.4 | [0.3 %] | [0.3 %] | 0.189 | 0.6 | [0.0 %] | [0.0 %] | N/A | 0.0 | [1.1 %] | [1.1 %] | 0.952 | 0.1 |
| 35–54 | [7.0 %] | [6.0 %] | 0.006 | 3.8 | [19.0 %] | [19.7 %] | <0.0001 | 1.9 | [14.6 %] | [14.5 %] | 0.946 | 0.1 | [45.6 %] | [45.6 %] | 0.970 | 0.1 |
| 55–64 | [22.1 %] | [20.9 %] | 0.043 | 2.8 | [36.7 %] | [36.4 %] | 0.1 | 0.8 | [43.9 %] | [43.8 %] | 0.949 | 0.1 | [36.9 %] | [36.9 %] | 0.990 | 0.0 |
| ≥65 | [70.9 %] | [73.0 %] | 0.001 | 4.6 | [44.0 %] | [43.6 %] | 0.129 | 0.7 | [41.6 %] | [41.7 %] | 0.910 | 0.2 | [16.3 %] | [16.3 %] | 0.932 | 0.1 |
| Male | [66.6 %] | [65.2 %] | 0.029 | 3.0 | [65.3 %] | [65.2 %] | 0.657 | 0.2 | [66.7 %] | [66.7 %] | 0.946 | 0.1 | [64.7 %] | [64.7 %] | 0.926 | 0.1 |
| US geographic region | | | | | | | | | | | | | | |
| Northeast | [39.3 %] | [39.5 %] | 0.769 | 0.4 | [35.5 %] | [35.3 %] | 0.366 | 0.4 | [32.1 %] | [32.1 %] | 0.973 | 0.1 | [35.2 %] | [35.3 %] | 0.874 | 0.2 |
| Midwest | [22.1 %] | [23.3 %] | 0.040 | 2.8 | [25.9 %] | [26.0 %] | 0.351 | 0.4 | [28.2 %] | [28.3 %] | 0.930 | 0.1 | [26.5 %] | [26.5 %] | 0.989 | 0.0 |
| South | [24.4 %] | [22.6 %] | 0.002 | 4.3 | [27.6 %] | [27.6 %] | 0.992 | 0.0 | [28.3 %] | [28.1 %] | 0.874 | 0.3 | [28.9 %] | [28.8 %] | 0.933 | 0.1 |
| West | [14.2 %] | [14.7 %] | 0.351 | 1.3 | [11.1 %] | [11.1 %] | 0.929 | 0.0 | [11.4 %] | [11.5 %] | 0.960 | 0.1 | [9.4 %] | [9.3 %] | 0.914 | 0.1 |
| Baseline comorbid condition | CCI Score | 2.72(2.15) | 2.82(2.14) | <0.001 | 4.9 | 1.23(1.54) | 1.21(1.47) | <0.001 | 1.7 | 0.32(0.77) | 0.31(0.75) | 0.876 | 0.3 | 0.14(0.5) | 0.14(0.49) | 0.848 | 0.2 |
| Chronic disease score | 5.29(4.06) | 5.49(4.19) | <0.001 | 5.0 | 4.58(3.62) | 4.57(3.65) | 0.716 | 0.2 | 3.99(2.86) | 3.99(2.87) | 0.892 | 0.2 | 0.97(1.74) | 0.97(1.74) | 0.957 | 0.1 |
| Baseline number of inpatient visits PPPM | 0.19(0.49) | 0.2(0.45) | 0.193 | 1.8 | 0.04(0.19) | 0.04(0.18) | 0.007 | 1.3 | 0.01(0.05) | 0.01(0.05) | 0.817 | 0.4 | 0.0(0.03) | 0.0(0.03) | 0.654 | 0.6 |

<sup>a</sup>Chi-square tests were used to evaluate the statistical significance of differences in categorical variables; student t-tests were used for the continuous variables.

Propensity score matching was applied for each cardiovascular disease risk cohort using covariates: age group, gender, US region, baseline Charlson comorbidity index score, Chronic Disease Score, comorbidities (hypertension, arrhythmias, metabolic syndrome, liver disease, obesity and chronic kidney disease) and number of inpatient admissions per patient per month.

CHD RE coronary heart disease risk equivalent, SD standard deviation, STD standardized difference, CV cardiovascular, CVD cardiovascular disease, PPPM per patient per month, PSM propensity score matching.

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utilization analysis demonstrated that during the acute follow-up period, hyperlipidemic patients with new CV events had an additional +4.4 to +6.2 (days) inpatient LOS and +2.6 to +3.6 outpatient visits PPPM, compared to patients without CV events. The clinical burden remained over the long-term, and was substantial for patients with a new CV event (year 2 incremental inpatient LOS: +0.5 to +2.6, outpatient visits PPPM: +0.2 to +0.3; year 3 incremental inpatient LOS: +0.4 to +2.3, outpatient visits PPPM: +0.1 to +0.3). The pattern of long term healthcare resource utilization among patients with new CV events may be attributable to the higher long term HF costs. Our study also reported that a large proportion (65.8 %) of patients with a new CV event had more than one new CV event during the follow-up period, adding to the long-term clinical burden of CV events on hyperlipidemic patients. These are only the direct medical costs of care; total costs would be larger if other indirect costs associated with CVE were accounted for. A prior study did show that new CVE were associated with increased indirect costs [30].

Previous studies have reported that inpatient hospital stays and ER visits are expensive, resource intensive and impose a great clinical burden on patients [31, 32]. Higher healthcare resource utilization is a major component of increased healthcare costs. Healthcare costs were higher among hyperlipidemic patients with a new CV event in the acute phase, compared to patients without a new CV event. Our results are similar to the Chapman et al. study, which concluded that patients with new CV events incurred the highest follow-up costs during the acute phase, and acute phase costs were much higher than those in years 2 and 3 [7]. However, our study also determined that incremental costs remained higher through 3 years of follow-up (year 1: $39,869 to $41,648 higher; year 2: $5,900 to $9,436 higher; year 3: $4,704 to $11,400 higher), for all risk cohorts of hyperlipidemic patients with a new CV event, compared to those without, emphasizing a sustained economic burden. Compared with the Chapman et al. [7] study with cost estimates from 2001–2006, the present study also provides more recent estimates for healthcare resource utilization and costs across the CVD risk spectrum (history of CV events through low risk) rather than excluding the highest risk cohort (i.e. patients with a history of CV events) as in the Chapman et al. study. Our study also captures the cost of care for multiple CV events thereby providing a more accurate estimate of the direct cost of care for patients experiencing new CV events rather than estimating the cost for each
Table 2  PSM-adjusted follow-up (short and long-term) healthcare utilization for hyperlipidemic patients with and without new CV events, categorized by CVD risk level

| History of CV event cohort | Modified CHD RE cohort | Moderate risk cohort | Low risk cohort |
|---------------------------|------------------------|----------------------|-----------------|
| Without CV events | With CV events | Without CV events | With CV events | Without CV events | With CV events | Without CV events | With CV events |
| (N = 10741) | (N = 10741) | (N = 90614) | (N = 90614) | (N = 7938) | (N = 7938) | (N = 12527) | (N = 12527) |
| N/Mean [N %]/(SD) | N/Mean [N %]/(SD) | N/Mean [N %]/(SD) | N/Mean [N %]/(SD) | N/Mean [N %]/(SD) | N/Mean [N %]/(SD) | N/Mean [N %]/(SD) | N/Mean [N %]/(SD) |
| P-value | P-value | P-value | P-value |

All-cause healthcare utilization 1 month (acute phase) post-index date

| Number of continuous enrollment patients | 10577(98.5 %) | 10282(95.7 %) | <0.0001 | 89539(98.8 %) | 88196(97.3 %) | <0.0001 | 7845(98.8 %) | 7727(97.3 %) | <0.0001 |
| Inpatient LOS (days) | 0.25(1.94) | 6.43(6.94) | <0.0001 | 0.07(0.90) | 5.22(5.39) | <0.0001 | 0.04(0.61) | 4.97(4.91) | <0.0001 |
| Number of patients with Inpatient Visits | 346(3.3 %) | 10282(100.0 %) | <0.0001 | 1102(1.2 %) | 88196(100.0 %) | <0.0001 | 59(0.8 %) | 7727(100.0 %) | <0.0001 |
| Number of patients with Outpatient ER Visits | 387(3.7 %) | 1503(14.6 %) | <0.0001 | 1674(19.1 %) | 15425(17.5 %) | <0.0001 | 124(1.6 %) | 1663(21.5 %) | <0.0001 |
| Number of patients with Outpatient Office Visits | 543(51.3 %) | 714(69.5 %) | <0.0001 | 39109(43.8 %) | 67063(76.0 %) | <0.0001 | 2857(36.4 %) | 5654(73.2 %) | <0.0001 |
| Number of patients with Outpatient Pharmacy Visits | 6842(64.7 %) | 7296(70.5 %) | <0.0001 | 56480(63.1 %) | 67216(76.2 %) | <0.0001 | 3616(46.1 %) | 7078(91.6 %) | <0.0001 |

All-cause Healthcare Utilizations 1 year (31–365 days) post-index date

| Number of continuous enrollment patients | 8447(78.6 %) | 7808(72.7 %) | <0.0001 | 75203(83.0 %) | 70525(77.8 %) | <0.0001 | 6588(83.0 %) | 6165(77.7 %) | <0.0001 |
| Inpatient LOS (days) | 2.06(13.01) | 6.61(20.85) | <0.0001 | 1.35(20.5) | 4.29(41.1) | <0.0001 | 1.00(167) | 4.17(408) | <0.0001 |
| Number of patients with Inpatient Visits | 1304(15.4 %) | 2916(37.3 %) | <0.0001 | 445(68.6 %) | 18316(26.0 %) | <0.0001 | 1.21(140) | 2.28(176) | <0.0001 |
| Number of patients with Outpatient ER Visits | 7297(69.0 %) | 9296(90.4 %) | <0.0001 | 50185(56.0 %) | 81329(92.2 %) | <0.0001 | 3616(46.1 %) | 7078(91.6 %) | <0.0001 |
| Number of patients with Outpatient Pharmacy Visits | 6842(64.7 %) | 7253(70.5 %) | <0.0001 | 56480(63.1 %) | 67216(76.2 %) | <0.0001 | 3500(28.2 %) | 9242(75.0 %) | <0.0001 |
Table 2  PSM-adjusted follow-up (short and long-term) healthcare utilization for hyperlipidemic patients with and without new CV events, categorized by CVD risk level (Continued)

|                               | Number of patients with | Number of visits PPPM | p-value               | Number of patients with | Number of visits PPPM | p-value               | Number of patients with | Number of visits PPPM | p-value               | Number of patients with | Number of visits PPPM | p-value               |
|--------------------------------|-------------------------|-----------------------|-----------------------|-------------------------|-----------------------|-----------------------|-------------------------|-----------------------|-----------------------|-------------------------|-----------------------|-----------------------|
| Number of patients with       |                         |                       |                       |                         |                       |                       |                         |                       |                       |                         |                       |                       |
| Outpatient Pharmacy Visits    | 6685[79.1 %]            | 6397[81.9 %]          | <0.0001               | 5440[82.6 %]            | 5111[87.8 %]          | <0.0001               | 8281[82.1 %]            | <0.0001               |                       |                         |                       |                       |
| Inpatient stays               | 0.02(0.06)              | 0.06(0.11)            | <0.0001               | 0.01(0.04)              | 0.04(0.09)            | <0.0001               | 0.01(0.03)              | 0.03(0.07)            | <0.0001               | 0.00(0.02)              | 0.02(0.06)            | <0.0001               |
| Outpatient Visits b           | 1.81(1.71)              | 2.62(2.20)            | <0.0001               | 1.28(1.33)              | 2.13(1.86)            | <0.0001               | 0.95(1.09)              | 1.74(1.62)            | <0.0001               | 0.65(0.88)              | 1.50(1.47)            | <0.0001               |
| Outpatient ER Visits          | 0.04(0.08)              | 0.06(0.14)            | <0.0001               | 0.02(0.06)              | 0.04(0.10)            | <0.0001               | 0.02(0.05)              | 0.04(0.09)            | <0.0001               | 0.01(0.04)              | 0.03(0.08)            | <0.0001               |
| Outpatient Pharmacy Visits    | 1.66(1.53)              | 2.05(1.69)            | <0.0001               | 1.37(1.28)              | 1.87(1.48)            | <0.0001               | 1.18(1.12)              | 1.80(1.32)            | <0.0001               | 0.50(0.75)              | 1.29(1.11)            | <0.0001               |
| Outpatient Office Visits      | 0.90(0.88)              | 1.10(0.99)            | <0.0001               | 0.73(0.79)              | 0.98(0.87)            | <0.0001               | 0.57(0.71)              | 0.80(0.80)            | <0.0001               | 0.42(0.64)              | 0.68(0.73)            | <0.0001               |
| All-cause healthcare utilization 2 years post-index date |                       |                       |                       |                         |                       |                       |                         |                       |                       |                         |                       |                       |
| Number of patients with       | 848[14.3 %]             | 1660[29.8 %]          | <0.0001               | 5208[8.8 %]             | 11020[20.7 %]         | <0.0001               | 394[7.7 %]              | 856[18.4 %]            | <0.0001               | 391[4.4 %]              | 915[11.7 %]           | <0.0001               |
| Inpatient Visits              |                         |                       |                       |                         |                       |                       |                         |                       |                       |                         |                       |                       |
| Number of patients with       | 1455[24.5 %]            | 1845[33.1 %]          | <0.0001               | 9514[16.1 %]            | 13799[25.9 %]         | <0.0001               | 759[14.9 %]             | 1134[24.3 %]          | <0.0001               | 963[10.9 %]             | 1583[20.2 %]          | <0.0001               |
| Outpatient ER Visits          | 5371[90.6 %]            | 5084[91.2 %]          | 0.286                 | 5407[91.8 %]            | 4975[93.5 %]          | <0.0001               | 4433[87.0 %]             | 4213[90.4 %]          | <0.0001               | 6969[78.8 %]             | 6944[88.8 %]          | <0.0001               |
| Outpatient Pharmacy Visits    | 5668[95.6 %]            | 5352[96.0 %]          | 0.325                 | 5588[94.9 %]            | 5139[96.6 %]          | <0.0001               | 4669[91.6 %]             | 4445[95.3 %]          | <0.0001               | 7377[83.4 %]             | 7286[93.1 %]          | <0.0001               |
| Outpatient Office Visits      | 4720[79.6 %]            | 4549[81.6 %]          | 0.008                 | 4832[82.0 %]            | 4459[83.8 %]          | <0.0001               | 4228[83.0 %]             | 4015[86.1 %]          | <0.0001               | 5886[66.6 %]             | 6324[80.8 %]          | <0.0001               |
| All-cause healthcare utilization 3 years post-index date |                       |                       |                       |                         |                       |                       |                         |                       |                       |                         |                       |                       |
| Number of patients with       | 563[14.1 %]             | 961[27.2 %]           | <0.0001               | 3941[8.8 %]             | 7146[18.6 %]          | <0.0001               | 288[7.4 %]              | 590[16.9 %]            | <0.0001               | 325[4.5 %]              | 617[10.3 %]           | <0.0001               |
| Inpatient Visits              |                         |                       |                       |                         |                       |                       |                         |                       |                       |                         |                       |                       |
| Number of patients with       | 965[24.2 %]             | 1173[33.2 %]          | <0.0001               | 7049[15.8 %]            | 9683[25.2 %]          | <0.0001               | 503[12.9 %]             | 817[23.4 %]           | <0.0001               | 804[11.2 %]             | 1187[19.9 %]          | <0.0001               |
| Outpatient ER Visits          | 3569[89.4 %]            | 3150[89.2 %]          | 0.78                  | 4063[91.0 %]            | 3541[92.0 %]          | <0.0001               | 3420[87.6 %]             | 3095[88.8 %]          | 0.115                | 5871[81.7 %]             | 5209[87.2 %]          | <0.0001               |
| Outpatient Office Visits      | 3775[94.5 %]            | 3335[94.4 %]          | 0.819                 | 4213[94.4 %]            | 3676[95.5 %]          | <0.0001               | 3587[91.9 %]             | 3272[93.9 %]          | 0.001                | 6194[86.2 %]             | 5468[91.6 %]          | <0.0001               |
| Number of patients with       | 3216[80.5 %]            | 2908[82.3 %]          | 0.047                 | 3643[81.6 %]            | 3231[84.0 %]          | <0.0001               | 3221[82.5 %]             | 2958[84.9 %]          | 0.006                | 4991[69.4 %]             | 4804[80.5 %]          | <0.0001               |
| Outpatient Pharmacy Visits    |                         |                       |                       |                         |                       |                       |                         |                       |                       |                         |                       |                       |

Refer to Table 3 for length of stay and number of visits per patient per month during years 2 and 3 of the follow-up period

PSM propensity score matching, CVD cardiovascular disease, CV cardiovascular, CHD RE coronary heart disease risk equivalent, SD standard deviation, LOS length of stay, PPPM per patient per month, ER emergency room

bChi-square tests were used to evaluate the statistical significance of differences in categorical variables; student t-tests were used for the continuous variables

Outpatient visits included emergency room, laboratory/pathology, radiology, outpatient surgical or diagnostic procedure and office visits
|                    | History of CV event cohort | Modified CHD RE cohort | Moderate-risk cohort | Low-risk cohort |
|--------------------|---------------------------|------------------------|---------------------|----------------|
|                    | Without CV events (N = 10,741) | With CV events (N = 10,741) | Without CV events (N = 90,614) | With CV events (N = 90,614) | Without CV events (N = 7,938) | With CV events (N = 7,938) | Without CV events (N = 12,527) | With CV events (N = 12,527) |
| N/mean (SD)        |                             |                        |                      |                             |                             |                        |                      |                             |
|                    | N/mean (%)                  | P-value                 | N/mean (%)          | P-value                  | N/mean (%)                  | P-value                  | N/mean (%)          | P-value                  |
| All-cause Healthcare Utilization 2 Years Post-index Date |
| Number of Continuous Enrollment Patients | 5928(55.2 %) | 5576(51.9 %) | <0.0001 | 5891(65.0 %) | 53212(58.7 %) | <0.0001 | 5096(64.2 %) | 4662(58.7 %) | <0.0001 | 8844(70.6 %) | 7822(62.4 %) | <0.0001 |
| Inpatient LOS (days) | 1.50(7.21) | 4.14(16.22) | <0.0001 | 0.71(4.81) | 2.10(9.46) | <0.0001 | 0.60(4.09) | 1.78(9.78) | <0.0001 | 0.24(1.70) | 0.76(4.36) | <0.0001 |
| Number of Visits (PPPM) |
| Inpatient stays | 0.02(0.05) | 0.04(0.09) | <0.0001 | 0.01(0.04) | 0.03(0.07) | <0.0001 | 0.01(0.03) | 0.02(0.06) | <0.0001 | 0.00(0.02) | 0.01(0.04) | <0.0001 |
| Outpatient Visits | 1.72(1.70) | 2.07(2.01) | <0.0001 | 1.26(1.36) | 1.63(1.65) | <0.0001 | 0.97(1.09) | 1.27(1.31) | <0.0001 | 0.73(0.95) | 0.97(1.13) | <0.0001 |
| Outpatient ER Visits | 0.03(0.08) | 0.05(0.13) | <0.0001 | 0.02(0.06) | 0.04(0.09) | <0.0001 | 0.02(0.05) | 0.03(0.08) | <0.0001 | 0.01(0.04) | 0.02(0.07) | <0.0001 |
| Outpatient Pharmacy Visits | 1.63(1.52) | 1.96(1.70) | <0.0001 | 1.36(1.28) | 1.78(1.49) | <0.0001 | 1.22(1.15) | 1.67(1.34) | <0.0001 | 0.62(0.87) | 1.22(1.14) | <0.0001 |
| Outpatient Office Visits | 0.86(0.86) | 0.94(0.94) | <0.0001 | 0.71(0.78) | 0.83(0.82) | <0.0001 | 0.56(0.67) | 0.67(0.74) | <0.0001 | 0.46(0.67) | 0.53(0.64) | <0.0001 |
| All-cause Healthcare Utilization 3 Years Post-index Date |
| Number of Continuous Enrollment Patients | 3994(37.2 %) | 3533(32.9 %) | <0.0001 | 4465(49.3 %) | 3848(42.5 %) | <0.0001 | 3903(49.2 %) | 3485(43.9 %) | <0.0001 | 7188(70.5 %) | 5971(47.7 %) | <0.0001 |
| Inpatient LOS (days) | 1.38(7.05) | 3.72(14.25) | <0.0001 | 0.69(4.98) | 1.77(8.28) | <0.0001 | 0.72(5.43) | 1.68(8.17) | <0.0001 | 0.29(2.57) | 0.72(5.57) | <0.0001 |
| Number of visits (PPPM) |
| Inpatient stays | 0.02(0.05) | 0.04(0.09) | <0.0001 | 0.01(0.04) | 0.02(0.07) | <0.0001 | 0.01(0.03) | 0.02(0.07) | <0.0001 | 0.00(0.02) | 0.01(0.04) | <0.0001 |
| Outpatient Visits | 1.64(1.74) | 1.97(2.14) | <0.0001 | 1.24(1.41) | 1.55(1.65) | <0.0001 | 0.96(1.18) | 1.22(1.35) | <0.0001 | 0.77(0.95) | 0.91(1.16) | <0.0001 |
| Outpatient ER Visits | 0.03(0.08) | 0.05(0.11) | <0.0001 | 0.02(0.05) | 0.03(0.10) | <0.0001 | 0.01(0.04) | 0.02(0.09) | <0.0001 | 0.01(0.04) | 0.02(0.06) | <0.0001 |
| Outpatient Pharmacy Visits | 1.62(1.49) | 1.94(1.70) | <0.0001 | 1.36(1.29) | 1.75(1.49) | <0.0001 | 1.22(1.15) | 1.60(1.31) | <0.0001 | 0.69(0.91) | 1.20(1.15) | <0.0001 |
| Outpatient Office Visits | 0.83(0.86) | 0.87(0.89) | 0.043 | 0.70(0.78) | 0.79(0.81) | <0.0001 | 0.55(0.66) | 0.65(0.75) | <0.0001 | 0.48(0.69) | 0.51(0.63) | <0.0001 |

**PSM** propensity score matching, **CVD** cardiovascular disease, **CV** cardiovascular, **CHD RE** coronary heart disease risk equivalent, **SD** standard deviation, **LOS** length of stay, **PPPM** per patient per month, **ER** emergency room

*a*Chi-square tests were used to evaluate the statistical significance of differences in categorical variables; student t-tests were used for the continuous variables

*b*Outpatient visits included emergency room, laboratory/pathology, radiology, outpatient surgical or diagnostic procedure and office visits
### Table 4: Total annual incremental costs for hyperlipidemic patients with new CV events categorized by post-event periods

| CV event type | 1st year post-CV event | 2 Years post-CV event | 3 Years post-CV event |
|---------------|------------------------|-----------------------|-----------------------|
|               | History of CV event cohort | Modified CHD RE cohort | Moderate-risk cohort | Low-risk cohort | History of CV event cohort | Modified CHD RE cohort | Moderate-risk cohort | Low-risk cohort |
|               | Mean [CI] | Mean [CI] | Mean [CI] | Mean [CI] | Mean [CI] | Mean [CI] | Mean [CI] | Mean [CI] |
| Any CV event  | $41,168 [39,130, 43,206] | $41,648 [41,126, 42,171] | $40,500 [39,039, 40,960] | $39,869 [38,768, 40,971] | $9,436 [7,547, 11,324] | $8,301 [7,850, 8,753] | $6,622 [5,267, 7,976] | $5,900 [5,103, 6,698] |
| MI            | $51,686 [46,728, 56,645] | $52,671 [51,515, 54,530] | $49,383 [46,131, 53,826] | $53,358 [47,247, 59,465] | $10,596 [9,536, 11,656] | $8,105 [7,199, 9,010] | $4,935 [3,249, 6,214] | $5,131 [4,210, 6,052] |
| IS            | $36,572 [31,751, 41,394] | $36,560 [34,951, 38,168] | $34,511 [30,796, 38,227] | $33,791 [30,996, 36,586] | $7,691 [6,400, 8,958] | $7,679 [6,423, 8,623] | $5,437 [3,369, 7,505] | $4,403 [2,879, 6,910] |
| UA            | $34,874 [30,297, 39,451] | $31,627 [30,649, 34,377] | $31,737 [28,737, 34,737] | $28,659 [26,689, 30,629] | $7,018 [5,350, 8,686] | $6,339 [5,047, 7,671] | $6,015 [3,666, 8,364] | $7,504 [5,759, 9,275] |
| PCI           | $32,263 [28,260, 36,266] | $36,231 [33,392, 40,663] | $37,246 [32,773, 40,929] | $38,259 [35,589, 40,463] | $6,910 [5,874, 7,938] | $7,583 [6,734, 8,437] | $10,203 [6,274, 14,131] | $7,972 [5,877, 10,435] |
| CABG          | $55,548 [50,438, 60,657] | $65,296 [63,447, 70,794] | $65,015 [59,236, 71,680] | $65,825 [59,970, 70,943] | $583 [3,375, 4,400] | $3,380 [2,269, 4,940] | $6,414 [5,862, 7,751] | $5,081 [2,598, 7,902] |
| HF            | $46,890 [40,421, 53,358] | $45,514 [43,687, 47,342] | $43,064 [36,834, 49,293] | $41,001 [34,370, 47,633] | $19,617 [13,899, 25,335] | $17,525 [15,454, 19,507] | $11,897 [8,682, 18,213] | $11,974 [8,773, 17,484] |
| TIA           | $23,900 [18,738, 29,062] | $19,055 [17,835, 20,275] | $17,903 [14,265, 21,540] | $18,054 [15,167, 20,940] | $11,557 [6,392, 16,722] | $5,181 [3,933, 6,429] | $4,440 [3,142, 5,747] | $3,941 [2,177, 5,748] |

CI: Confidence interval, CV: cardiovascular, CHD: coronary heart disease, RE: risk equivalent, MI: myocardial infarction, IS: ischemic stroke, UA: unstable angina, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, HF: heart failure, TIA: transient ischemic attack.
specific CV event type. Setting potentially arbitrary time cut-points to distinguish between different CV events among patients with multiple events may produce artificial cost results, as some CV events may occur with little time gap and the cost of one event is entwined with the cost of the next event.

Our study also brings to light the noteworthy clinical and economic burden among patients in the high-risk cohorts (i.e., history of CV event and modified CHD RE cohorts). Inpatient LOS was, on average, 0.09 to 4.89 days longer among patients with history of a CV event or modified CHD RE, compared to those at moderate or lower risk, during all follow-up time periods, suggesting that high-risk patients have greater healthcare resource needs. During the long-term post-CV event periods (1, 2 and 3 years follow-up), patients with a new CV event in the higher risk cohorts utilized more incremental ER visits PPPM, compared to those in the moderate- and low-risk cohorts, demonstrating the potential for a higher healthcare cost burden during the longer-term post-CV event periods. Future research is warranted to more specifically determine the underlying reasons for the sustained difference in clinical and economic burden between high-risk hyperlipidemic patients with a CV event and those without a CV event.

Our study results were similar to a study done by Karan et al., indicating similarity in findings that CVD had more outpatient and inpatients stays and economic burden of CVD is large [33]. However, this study utilized a national survey of households in India and focused on out-of-pocket spending and non-medical spending for CVD, whereas our present study focused on a patient-level perspective of direct medical costs for new CV events. Although previous studies provide a general frame of reference, the cost estimates are not directly comparable to the incremental direct costs in the present study since the studies differed in study design (matched cohorts versus survey sample) [34] and composition of the study population (US hyperlipidemia patients versus hypertension or solely acute coronary syndrome patients including those residing in developing countries) [33, 34], sample size (n = 10,741 vs. 4,669) [10], CVD risk level (low through high CV risk vs. exclusion of high secondary prevention patients) [7, 8] and contemporaneous cost estimates (2009–2013 vs. 2001–2006) [7]. Due to considerable variation in costs by CV event type, the results of our analysis strengthen the importance of evaluating total and individual CV event costs, as this specific information may be essential for secondary prevention and treatment decisions for high-risk patients.

Our present study demonstrated the sustained high economic and clinical burden associated with the occurrence of CV events among hyperlipidemic patients. In patients who have already experienced or who are at high risk for experiencing a CV event, lifestyle intervention strategies alone may not be sufficient to maximally reduce CVD risk [35, 36]. Current US treatment guidelines recommend lipid-lowering therapy in addition to lifestyle modifications to lower LDL-C levels for primary and secondary prevention for high-risk individuals [37]. Although statins are widely prescribed for elevated LDL-C levels, 9 %–20 % of treated patients, especially high-risk patients, continue to have elevated LDL-C and remain at risk for new CV events [38]. Potential new pharmacological treatments (e.g. anti-proprotein convertase subtilisin/kexin type 9 [PCSK9] monoclonal antibodies) aimed at significantly lowering LDL-C beyond that of current available treatment options [39], could potentially help to reduce the substantial clinical and economic burden.

Limitations

Our study limitations were primarily related to the retrospective use of claims data [7, 15]. Misclassification of CV risk, although it cannot be quantified, is likely to be low since the ICD-9-CM codes utilized to capture history of CVD included codes for old MI, stroke sequelae, etc. that would include a history of CVD beyond the baseline period. Similarly, important patient information, including blood pressure, smoking history and family history was not available in the claims data to more accurately classify patients within the CHD RE cohort. Also, administrative claims data do not offer information on whether an elective procedure (CABG, PCI) was planned, thus planned procedures could not be completely excluded from the study. Nevertheless, utilization of the PSM method reduced the differences between patients with and without new CV events and created a balanced study cohort, such that healthcare utilization and incremental costs were more accurately compared.

Conclusion

Substantial incremental costs and healthcare resource utilization 1 month up to 3 years post-CV event highlight the short- and long-term economic and clinical burden especially on high-risk hyperlipidemic patients and the US healthcare system. Interventions used to prevent or reduce the occurrence of CV events among patients with hyperlipidemia may result in substantial cost savings and reduce the clinical burden in the United States.
Appendix 1

Table 5 Cardiovascular event identification codes

| Cardiovascular events                      | Diagnosis/Procedure codes |
|-------------------------------------------|---------------------------|
| Myocardial Infarction                     | ICD-9-CM: 410.xx          |
| Unstable Angina                           | ICD-9-CM: 411.1x, 411.8x  |
| Ischemic Stroke                           | ICD-9-CM: 433.x1, 434.x1  |
| Coronary Artery By pass Graft             | CPT: 33510-33514, 33516-33519, 33521-33523, 33530, 33533-33536 |
|                                          | HCPCS: S2205-S2209        |
|                                          | ICD-9-CM: 36.10-36.17, 36.19 |
| Percutaneous Coronary Intervention        | ICD-9-CM: 00.66, 36.06, 36.07, 17.55 |
|                                          | CPT: 92980, 92981, 92982, 92984-92996, 92973 |
|                                          | HCPCS: G0290, G0291       |
| Transient Ischemic Attack                 | ICD-9-CM: 435.0x, 435.1x, 435.8x, 435.9x |
| Heart Failure                             | ICD-9-CM: 428.xx          |

CPT Current Procedural Terminology, HCPCS Healthcare Common Procedural Coding System, ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification

Appendix 2

Table 6 Cardiovascular risk levels and codes, modified based on NCEP ATP III guidelines

| Risk Level                     | Code                                                                 |
|--------------------------------|----------------------------------------------------------------------|
| History of CV event            | ICD-9-CM: 410, 412                                                   |
| Myocardial Infarction          | ICD-9-CM: 411.1, 411.81, 411.89                                       |
| Unstable angina                | CPT-4: 33503-33545                                                   |
| Coronary artery bypass graft   |                                                                         |
| Percutaneous coronary intervention | ICD-9 Procedure: 00.66, 36.09                                     |
| Ischemic Stroke                | ICD-9 CM: 434, 436, 437.0, 437.1, 438, 997.02                        |
| Modified CHD RE                | ICD-9-CM: 440.0x-440.4x, 440.8x-440.9x, 443.81, 443.9x               |
| Peripheral arterial disease    |                                                                         |
| Abdominal aortic aneurysm      | ICD-9-CM: 441.3x-441.4x                                             |
| Coronary artery disease        | ICD-9-CM: 433.1x                                                     |
| Diabetes                       | ICD-9-CM: 249.xx-250.xx                                             |
| Dyslipidemia                   | ICD-9-CM: 272.0x-272.4x                                             |
| Moderate risk                  | Hypertension: ICD-9-CM codes 401.1-401.9, 642.00-642.04, 401.0, 437.2, 402.00-405.99, 642.10-642.24, 642.70-642.94 |
| At least two of the following three risk factors identifiable from administrative claims data: | |
| a) hypertension (ICD-9-CM code or pharmacy claim for a blood pressure-lowering agent), | |
| b) age 45 years or older for men and 55 years or older for women, pre-index high-density lipoprotein (HDL) cholesterol below 40 mg/dl. | |
| Low risk                       | Zero or one risk factor                                              |

CHD RE coronary heart disease risk equivalent, CV cardiovascular, ICD-9-CM International Classifications of Diseases, 9th Revision Clinical Modifications, CPT Current Procedural Terminology, NCEPATP III National Cholesterol Education Program Adult Treatment Panel III

Appendix 3
Table 7 12-month Pre-index demographic and clinical characteristics for hyperlipidemic patients with and without new CV events before matching

|                                | History of CV event cohort | Modified CHD RE cohort | Moderate risk cohort | Low risk cohort |
|--------------------------------|---------------------------|------------------------|---------------------|----------------|
|                                | Without CV events         | With CV events         | Without CV events   | With CV events |
|                                | (N = 10744)               | (N = 77163)            | (N = 145642)        | (N = 156793)   |
| Mean (SD) Age                  | 73.66 (13.15)             | 66.41 (13.65)          | <0.0001             | STD 65.28 (13.16)       | 65.17 (13.17)       | 0.0189             | STD 67.83 (12.63)       | 65.83 (12.83)       | <0.0001 |
| Mean (SD) 18-24                | [0.0 %]                   | [0.0 %]                | 0.04                | STD [0.03 %]         | [0.05 %]         | 0.0018             | STD [0.00 %]         | [0.00 %]         | N/A    | 0.0 |
| Mean (SD) 25-34                | [0.1 %]                   | [0.4 %]                | <0.0001             | STD [0.3 %]         | [0.4 %]         | 0.0002             | STD [0.00 %]         | [0.00 %]         | N/A    | 0.0 |
| Mean (SD) 35-54                | [6.9 %]                   | [18.4 %]               | <0.0001             | STD [34.8 %]         | [19.6 %]         | 0.6784             | STD [0.2 %]         | [11.7 %]         | [16.7 %] | <0.0001 |
| Mean (SD) 55-64                | [22.1 %]                  | [32.1 %]               | <0.0001             | STD [22.7 %]         | [35.7 %]         | 0.0122             | STD [0.9 %]         | [38.0 %]         | [41.2 %] | <0.0001 |
| Mean (SD) ≥65                  | [70.9 %]                  | [49.2 %]               | <0.0001             | STD [45.6 %]         | [44.4 %]         | 0.1341             | STD [0.5 %]         | [50.3 %]         | [42.1 %] | <0.0001 |
| Mean (SD) Male                  | [66.6 %]                  | [63.0 %]               | <0.0001             | STD [7.7]           | [62.2 %]         | <0.0001             | STD [2.4]           | [62.4 %]         | [65.2 %] | <0.0001 |
| Mean (SD) US geographic region |                           |                        |                     |                  |                  |                     |                     |                  |                  |       |
| Northeast                       | [39.3 %]                  | [36.0 %]               | <0.0001             | STD [6.8]           | [35.3 %]         | 0.0398             | STD [0.7]           | [33.1 %]         | [31.0 %] | 0.0003 |
| Midwest                        | [22.1 %]                  | [25.5 %]               | <0.0001             | STD [8.0]           | [26.2 %]         | 0.2635             | STD [0.4]           | [27.2 %]         | [28.2 %] | 0.0671 |
| South                          | [24.4 %]                  | [26.3 %]               | <0.0001             | STD [4.4]           | [26.8 %]         | 0.0006             | STD [1.3]           | [26.0 %]         | [28.3 %] | <0.0001 |
| West                           | [14.2 %]                  | [12.2 %]               | <0.0001             | STD [5.9]           | [11.5 %]         | 0.864              | STD [0.1]           | [13.7 %]         | [12.5 %] | 0.004  |
| Baseline comorbid condition    |                           |                        |                     |                  |                  |                     |                     |                  |                  |       |
| Charlson comorbidity index (CCI)| [2.72(2.15)]             | [3.30(2.65)]           | <0.0001             | STD [2.43]         | [0.99(1.49)]     | 2.10(2.27)         | <0.0001             | STD [57.6]        | [0.53(1.23)]     | 0.92(1.69) | <0.0001 |
| Chronic disease score          | [5.28(4.06)]             | [6.01(4.44)]           | <0.0001             | STD [17.0]         | [3.91(3.48)]     | 5.70(4.24)         | <0.0001             | STD [46.2]        | [4.17(3.04)]     | 4.70(3.40) | <0.0001 |
| Baseline number of inpatient visits PPPM | [0.19(0.49)] | [0.39(0.84)]           | <0.0001             | STD [28.8]         | [0.04(0.19)]     | 0.18(0.52)         | <0.0001             | STD [36.1]        | [0.03(0.19)]     | 0.10(0.35) | <0.0001 |

CHD RE coronary heart disease risk equivalent, SD standard deviation, STD standardized difference, CV cardiovascular, CVD cardiovascular disease, PPPM per patient per month

*Chi-square tests were used to evaluate the statistical significance of differences in categorical variables; student t-tests were used for the continuous variables
Competing interests
The current study was sponsored by Amgen Inc. RG.W.Q. and S.R.G. are employees of Amgen, Inc. L.W., L.L. and O.B. are employees of STATinMED Research, which is a paid consultant to Amgen Inc. K.M.F. is an independent consultant who received research funds from Amgen, Inc.

Authors’ contributions
RGW.Q and S.R.G are employees of Amgen Inc. and participated in the study design, and provided data interpretation and critical review of the study results and manuscript. L.W, O.B and L.L are employees of STATinMED Research, which is a paid consultant to Amgen Inc, and participated in the design of the study, interpretation of data, drafting of the manuscript, and performed the statistical analysis. KMF received research funds from Amgen Inc. and participated in the study design, data interpretation, and critical review of the study results and manuscript. All authors read and approved the final manuscript.

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References
1. Bloom DE, Caillero ET, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, Fatima S, et al, editors. The Global Economic Burden of Non-communicable Diseases. Geneva: World Economic Forum. 2011. http://www.hspiharvard.edu/program-on-the-global-demography-of-aging/WorkingPapers/2012/PGDA_WF_08.pdf. Accessed 14 July 2015.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, et al. American Heart Association Statistics Committee and Stroke Subcommittee: Heart disease and stroke statistics—2015 update: A report from the American Heart Association. Circulation. 2015;131:e29–e322.
3. Soni A. Top 10 most costly condition among men and women 2008: estimates for the U.S. civilian noninstitutionalized adult population, age 18 and older. Medical Expenditure Panel Survey. Statistical Brief #813. http://meps.ahiq.gov/mepsweb/data_files/publications/st813/st813.html. Accessed 14 July 2014.
4. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation. 2004;109(10 Suppl I):I–10–I–12.
5. American Heart Association: Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2014;130:e28–e342.
6. Centers for Disease Control and Prevention: High Cholesterol Facts. http://www.cdc.gov/cholesterol/cholesterol.facts.htm. Accessed 14 July 2014.
7. Chapman RH, Liu LZ, Girase PG, Strak RJ. Determining initial and follow-up costs of cardiovascular events in a US managed care population. BMC Cardiovasc Disord. 2011;11:11. doi:10.1186/1471-2261-11-11.
8. Grover SA, Ho V, Lavoie F, Coupal L, Zowall H, Pilote L. The importance of indirect costs in primary cardiovascular disease prevention: can we save lives and money with statins? Arch Intern Med. 2003;163(3):333–9.
9. Trogdon JG, Finkielstein EA, Nwaise IA, Tangka FK, Orenstein D. The economic burden of chronic cardiovascular disease for major insurers. Health Promot Pract. 2007;8(3):234–42.
10. O’Sullivan AK, Rubins J, Nyambose J, Kuznik A, Cohen DJ, Thompson D. Cost estimation of cardiovascular disease events in the US. Pharmacoeconomics. 2011;28(6):693–704.
11. Engeland WM, Karen A, Mahal A. The economic impact of non-communicable diseases on households in India. Global Health. 2012;8:9. doi:10.1186/1744-8603-8-9.
12. Leeder S, Raymond S, Greenberg H, Liu H, Esson K. A Race against Time: The Challenge of Cardiovascular Disease in Developing Countries. New York: Columbia University Press; 2004.
13. Eisenstein EL, Shaw LK, Anstrom KJ, Nelson CL, Hakim Z, Hasselblad V, et al. Assessing the clinical and economic burden of coronary artery disease: 1986–1998. Med Care. 2001;39(8):824–35.
14. Etemad LR, McCollam PL. Total first-year costs of acute coronary syndrome in a managed care setting. J Manag Care Pharm. 2005;11(4):300–6.
15. Duh MS, Fulcher NM, White LA, Jayawant SS, Ramamurthy P, Moyer E, et al. Costs associated with cardiovascular events in patients with hypertension in US managed care settings. J Am Soc Hypertens. 2009;3(6):403–15.
16. Onsfeldt RL, Gandhi SK, Fox KM, Bullano MF, Davidson M. Medical and cost burden of atherothrombosis among patients treated in routine clinical practice. J Med Econ. 2010;13(3):500–7.
17. Straka RJ, Liu LZ, Girase PS, DeLorenzo A, Chapman RH. Incremental cardiovascular costs and resource use associated with diabetes: an assessment of 29,863 patients in the US managed-care setting. Cardiovasc Diabetol. 2009;8:53. doi:10.1186/1475-2840-8-53.
18. Steihlorn R, Cingilco C, Sengupta N. Risk of cardiovascular and major bleeding event rehospitalizations and cost of care among ACS patients in the US. Circ Cardiovasc Qual Outcomes. 2012;5:A318.
19. Vachopoulos CV, Terentes-Printzios DG, Loakeimidis NK, Aznaouridis KA, Stefanidis CI. Prediction of cardiovascular events and all-cause mortality with erectile dysfunction. Circ Cardiovasc Qual Outcomes. 2013;6(1):99–109.
20. Chuang CS, Yang Y, Mau OH, Su H, Sung F, Rao C. Hyperlipidemia, statin use and the risk of developing depression: a nationwide retrospective cohort study. General Hospital Psychiatry. 2014;36:497–501.
21. Parsons LS, Ovation Research Group, Seattle, WA. Reducing bias in a propensity score method matched-pair sampling using greedy matching techniques. Paper 214–26. http://www.2sas.com/proceedings/sug12/p214-26.pdf. Accessed 14 July 2014.
22. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46(3):399–424.
23. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: A matched analysis using propensity scores. J Clin Epidemiol. 2001;54(4):387–98.
24. Asche CV, Kim J, Kulkarni AS, Chakravarti P, Andersen KE. Assessment of association of increased heart rates to cardiovascular events among healthy subjects in the United States: Analysis of a primary care electronic medical records database. Cardiology. 2011;2011;924343. doi:10.5402/2011/924343.
25. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. J Clin Epidemiol. 2006;61(12):1238–40.
26. Petersen LA, Preet K, Woodward LD, Byrne M. Comparison of the predictive validity of diagnosis-based risk adjusters for clinical outcomes. Med Care. 2005;43(1):161–7.
27. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol. 1992;45(2):197–203.
28. McGregor JC, Kim PW, Perencevich EN, et al. Utility of the Chronic Disease Score and Charlson Comorbidity Index as comorbidity measures for use in epidemiologic studies of antibiotic-resistant organisms. Am J Epidemiol. 2005;161(5):483–493.
29. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2451–63.
30. Song X, Quek RG, Gandara SR, Cappell KA, Fowler R, Cong Z. Productivity loss and indirect costs in primary cardiovascular disease prevention: can we save lives and money with statins? Arch Intern Med. 2003;163(3):333–9.
31. Weiss AJ, Barrett ML, Steiner CA. Trends and projections in inpatient hospital costs and utilization, 2003–2013. Healthcare Cost and Utilization Project (HCUP) Statistical Brief #175. July 2014. Agency for Healthcare Research and Quality, Rockville, MD. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb175-Hospital-Cost-Utilization-Projections-2013.pdf. Accessed 14 July 2014.
32. Caldwell N, Srebotnjak T, Wang T, Hsia R. How much will I get charged for this? Patient charges for top ten diagnoses in the emergency department. PLoS One. 2013;8(2):e55491.
33. Karan A, Engelgau M, Mahal A. The household level economic burden of heart disease in India. Trop Med Int Health. 2014;19(5):581–91.
34. Mahal M, Karan A, Engelgau M. The economic implications for non-communicable disease in India. HNP Discussion Paper, World Bank, January, 2010. http://siteresources.worldbank.org/HEALTHNUTRITIONANDPOPULATION/Resources/201627-1096698140167/EconomicImplicationsofNCDsforIndia.pdf. Accessed 14 January 2015
35. Bouillon K, Singh-Manoux A, Jokela M, Shipley MJ, Batty GD, Brunner EJ, et al. Decline in low-density lipoprotein cholesterol concentration: lipid-lowering drugs, diet, or physical activity? Evidence from the Whitehall II study. Heart. 2011;97(11):923–30.
36. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 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. Circulation. 2014;129:1–45.
37. National Cholesterol Education Program. Detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). http://www.nhlbi.nih.gov/files/docs/guidelines/atp3xsum.pdf. Accessed 17 June 2014.
38. Sampson UK, Fazio S, Linton MF. Residual cardiovascular risk despite optimal LDL-cholesterol reduction with statins: The evidence, etiology and therapeutic challenges. Curr Atheroscler Rep. 2010;12(1):1–10.
39. Dadu RT, Ballantyne CM. Lipid lowering with PCSK9 inhibitors. Nat Rev Cardiol. 2014;11(10):563–75.