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Association of a Combined Measure of Adherence and Treatment Intensity With Cardiovascular Outcomes in Patients With Atherosclerosis or Other Cardiovascular Risk Factors Treated With Statins and/or Ezetimibe

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Abstract

IMPORTANCE Both adherence and treatment intensity can alter the effectiveness of lipid-lowering therapy in routine clinical practice.

OBJECTIVE To evaluate the association of adherence and treatment intensity with cardiovascular outcomes in patients with documented cardiovascular disease (CVD), type 2 diabetes without CVD or chronic kidney disease (CKD), and CKD without CVD.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study using the Clinical Practice Research Datalink from January 2010 through February 2016. United Kingdom primary care was the setting. Participants were newly treated patients who received their first statin and/or ezetimibe prescription between January 1, 2010, and December 31, 2013, plus an additional prescription for statins and/or ezetimibe during the following year.

EXPOSURES Adherence was assessed annually using the proportion of days covered, with adherent defined as a proportion of days covered of 80% or higher. Treatment intensity was classified according to guidelines based on the expected percentage of low-density lipoprotein cholesterol (LDL-C) reduction as low (<30% reduction), moderate (30% to <50% reduction), or high (≥50% reduction). Adherence and treatment intensity were multiplied to create a combined measure, reflecting treatment intensity after accounting for adherence.

MAIN OUTCOMES AND MEASURES Composite end point of cardiovascular death or hospitalization for myocardial infarction, unstable angina, ischemic stroke, heart failure, or revascularization. Hazard ratios (HRs) were estimated against patients not treated for 1 year or longer.

RESULTS Among a total of 29 797 newly treated patients, there were 16 701, 12 422, and 674 patients with documented CVD, type 2 diabetes without CVD or CKD, and CKD without CVD, respectively; mean (SD) ages were 68.3 (13.2), 59.3 (12.4), and 67.3 (15.1) years, and male proportions were 60.6%, 55.0%, and 47.0%. In the documented CVD cohort, patients receiving high-intensity therapy were more likely to be adherent over time (84.1% in year 1 and 72.3% in year 6) than patients receiving low-intensity therapy (57.4% in year 1 and 48.4% in year 6). Using a combined measure of adherence and treatment intensity, a graded association was observed with both LDL-C reduction and CVD outcomes: each 10% increase in the combined measure was associated with a 10% lower risk (HR, 0.90; 95% CI, 0.86-0.94). Adherent patients receiving a high-intensity regimen had the

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Key Points

Question How are adherence and treatment intensity associated with cardiovascular disease (CVD) outcomes in patients newly treated with statins and/or ezetimibe?

Findings This cohort study of 3 groups of patients (16 701 with documented CVD, 12 422 with type 2 diabetes without CVD or or chronic kidney disease, and 674 with chronic kidney disease without CVD) showed a continuous association of the combined measure of adherence and treatment intensity with low-density lipoprotein cholesterol (LDL-C) reduction and with CVD outcomes. The largest reductions in LDL-C and CVD risk were observed among adherent patients receiving high-intensity therapy.

Meaning Improving adherence and the use of high-intensity therapies could achieve greater reductions in LDL-C and reduce CVD risk.

+ **Supplemental content**

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Abstract (continued)

lowest risk (HR, 0.60; 95% CI, 0.54-0.68) vs patients untreated for 1 year or longer. Findings in the other 2 cohorts were similar.

CONCLUSIONS AND RELEVANCE Results of this study demonstrate that the lowest cardiovascular risk was observed among adherent patients receiving high-intensity therapy, and the highest cardiovascular risk was observed among nonadherent patients receiving low-intensity therapy. Strategies that improve adherence and greater use of intensive therapies could substantially improve cardiovascular risk.

Introduction

Cardiovascular disease (CVD) is a major cause of premature death and disability worldwide.[1-3] Medications that decrease low-density lipoprotein cholesterol (LDL-C) levels have been proved to reduce the risk of cardiovascular events, and statins are first-line therapy in global treatment guidelines. Guidelines from the American College of Cardiology/American Heart Association,[4] the National Institute for Health and Care Excellence,[3] the Joint British Societies,[2] and the European Society of Cardiology,[5] among others, have emphasized the importance of aligning the intensity of LDL-C reduction with the risk of future cardiovascular events.

However, patients may not derive the intended benefit from the use of lipid-lowering agents for a number of reasons associated with physician-level and patient-level factors. Physician-level factors include limited knowledge about the evidence[6-8] and a real or perceived risk of adverse effects.[9] There is also reluctance among physicians to prescribe high-intensity statin therapy.[10,11] Patient-level factors include poor adherence, either from not taking medication consistently (ie, low compliance) or by discontinuing medication (ie, low persistence).[12,13]

These issues can lead to suboptimal risk reduction in high-risk populations that may benefit from high-intensity therapy. Trial evidence suggests that higher treatment intensity achieves greater reductions in LDL-C and is associated with improved cardiovascular outcomes[14-16]; similarly, observational studies have shown that higher adherence with lipid-lowering therapy is associated with improved cardiovascular outcomes.[16-18] Therefore, the aim of our study was to evaluate the potential contributions of both adherence and treatment intensity jointly over time on cardiovascular outcomes in newly treated patients with important cardiovascular risk factors or documented CVD.[5]

Methods

We conducted a retrospective observational cohort study using linked data from the following sources: Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics, and Office for National Statistics. United Kingdom primary care was the setting. All data were deidentified, so patient consent was not required. The CPRD Division within the Medicines and Healthcare Products Regulatory Agency has received Health Research Authority Research Ethics Committee approval for all observational research using deidentified CPRD data approved by the Independent Scientific Advisory Committee (ISAC). The study was approved by the CPRD ISAC with protocol 17-044. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

The study included newly treated patients with hypercholesterolemia, defined as those who received their first statin and/or ezetimibe prescription between January 1, 2010, and December 31, 2013, and who also received at least 1 additional prescription for statins and/or ezetimibe during the following year. The index date (start of the period at risk for outcomes) was the date of the second prescription. On the first prescription date, patients must have been aged at least 18 years, been

registered in a general practice with at least 2 years of up-to-standard data beforehand, and received no prior lipid-lowering therapy based on their available medical history. Serum LDL-C levels were assessed on or before the first prescription date.

To be included, patients must have had documented CVD, type 2 diabetes, or stage 4 to 5 chronic kidney disease (CKD) at the time of the initial lipid-lowering therapy prescription to reflect very high-risk patients as described in the European Society of Cardiology guidelines.[5] Documented CVD was defined as any of the following: myocardial infarction, unstable angina, ischemic stroke, surgical or percutaneous revascularization, transient ischemic attack, carotid stenosis, peripheral artery disease, abdominal aortic aneurysm, or stable angina.[5] Chronic kidney disease was identified based on diagnoses or estimated glomerular filtration rate values. Type 2 diabetes was based on diagnoses or the use of antidiabetic medication[19] (eMethods in the Supplement).

Patients were analyzed in 3 cohorts. These cohorts included those with documented CVD (CVD cohort), those with type 2 diabetes without CVD or CKD (diabetes cohort), and those with CKD without CVD (CKD cohort).

Exposures and Outcomes

Adherence was measured using the proportion of days covered (PDC).[20,21] In keeping with other studies, we defined patients with a PDC of 80% or higher as adherent.[16] Lipid-lowering regimens were analyzed based on the expected percentage of LDL-C reduction measured in trial data (eTable 1 in the Supplement).[3] According to the American College of Cardiology/American Heart Association guidelines, these agents can be grouped into low intensity (<30% reduction), moderate intensity (30% to <50% reduction), or high intensity (≥50% reduction).[3,4] Ezetimibe monotherapy was considered low intensity (19% expected LDL-C reduction), and combination therapy assumed a 24% LDL-C reduction after applying the statin reduction.[22,23] Individuals who received no treatment during the entire year were included in the reference group for that year using time-varying covariates for adherence and treatment intensity (eFigure 1 in the Supplement).

We explored continuous measures of adherence and treatment intensity in separate models. For our primary model, we combined adherence and treatment intensity into a single value intended to reflect the treatment intensity of a regimen after accounting for a patient's adherence.[24] This combined measure was created by multiplying adherence (range, 0%-100%) and treatment intensity (range, 0%-66%); as a result, the combined measure ranged from 0% to 66% (ie, 0.66 × 1.0 = 0.66). Because the combined measure is continuous, it was more efficient than using a categorical representation and facilitated estimates in untreated patients (ie, 0% treatment intensity and 0% PDC).

The primary outcome measure was a composite end point of cardiovascular death or hospitalization for myocardial infarction, unstable angina, ischemic stroke, heart failure, or revascularization (eTable 2 in the Supplement). Because heart failure is less commonly used as an outcome measure in lipid-lowering trials but is relevant in health economic evaluations, we excluded heart failure from the composite end point in sensitivity analyses. Hazard ratios (HRs) were estimated against patients not treated for 1 year or longer.

Time at risk for cardiovascular events began after the index date. The baseline period for assessing demographics, comorbidity, and laboratory values was defined as the period before the index date. Measures of adherence and treatment intensity were calculated based on prescriptions during each year of follow-up and were updated annually for each patient. Adherence and treatment intensity calculations for patients who ended follow-up within 1 year were based on the data through the end of follow-up. The follow-up period for the assessment of cardiovascular events continued until death, cardiovascular event of interest, last known up-to-standard CPRD record for the patient in the practice, switch to a therapy other than a statin or ezetimibe, or February 29, 2016, whichever came first.

Statistical Analysis

We used Cox proportional hazards regression models to quantify the association of adherence and treatment intensity with the risk of cardiovascular events. Analyses were conducted separately for each cohort. We initially assessed a continuous measure of adherence and a continuous measure of treatment intensity in 2 separate models, and we then modeled the combined measure of adherence and treatment intensity as our primary analyses. We also present results for specific patient profiles (eg, adherent patients) based on the mean value of the continuous measure for patients with the specific adherence and/or treatment intensity profile.

In all Cox proportional hazards regression models, we used age as the timescale to minimize any association between the event rate and time, particularly for the CVD cohort.[25] Because adherence, treatment intensity, and the combined measure were annual estimates, all were modeled using a 1-year lag to provide a stable PDC estimate; hence, adherence and treatment intensity in 1 year were used to estimate the number of cardiovascular events in the following year. As a result, events occurring during the first year after treatment were attributed to the lack of treatment in the year beforehand (eFigure 1 in the Supplement). Exposure during this period was included in the reference group (defined as untreated for ≥1 year). The adherence and treatment intensity measures, as well as the year of follow-up, were included as time-varying covariates and updated annually. As a result, patients moved into and out of the reference group over time as a function of their time-varying covariates.

We also estimated the residual cardiovascular event risk if all patients in the CVD cohort were to receive and adhere to a high-intensity regimen (optimal adherence and treatment intensity). To do this, we used the information from the fitted Cox proportional hazards regression model to estimate the expected rate of events assuming everyone had a combined measure of 50% (ie, a 50% expected LDL-C reduction after accounting for adherence). We used bootstrapping to estimate the 95% CIs for the estimates.

In addition to analyses for the 3 primary cohorts, we also evaluated a variety of preplanned subgroups in the CVD cohort based on risk factors, comorbidity scores, and polypharmacy. Details are available in eTable 3 and the eMethods in the Supplement.

To assess whether the changes in adherence and treatment intensity were also associated with changes in LDL-C, thus representing a biologically plausible mechanism, we evaluated the association of the combined adherence and treatment intensity measure with the percentage change in LDL-C over time. We included patients with at least 1 pretreatment and 1 posttreatment LDL-C measure within each cohort.

All analyses were conducted using a software program (R, version 3.4.4; R Foundation for Statistical Computing). Additional details are available in the eMethods in the Supplement.

Results

Of the 29 797 newly treated patients, there were 16 701 (56.0%) in the CVD cohort, 12 422 (41.7%) in the diabetes cohort, and 674 (2.3%) in the CKD cohort (eFigure 2 in the Supplement). The mean (SD) age was similar in the CVD cohort and the CKD cohort (68.3 [13.2] and 67.3 [15.1] years, respectively) but was lower in the diabetes cohort (59.3 [12.4] years). The CVD cohort had a higher proportion of men (60.6%) than the diabetes cohort (55.0%) and the CKD cohort (47.0%). Baseline LDL-C (for 64.5% of patients with available data) was 128 mg/dL for the CVD cohort, 135 mg/dL for the diabetes cohort, and 143 mg/dL for the CKD cohort (to convert cholesterol level to millimoles per liter, multiply by 0.0259). In the CVD cohort, 79.0% had been diagnosed as having a cardiovascular condition in the year before initiating therapy. The mean duration of follow-up was approximately 3 years for each cohort (**Table 1**).

The initial lipid-lowering therapy was a high-intensity statin for 23.4% of the CVD cohort compared with 1.1% of the diabetes cohort and 3.1% of the CKD cohort. Most patients received moderate-intensity statins (74.0% for the CVD cohort, 94.5% for the diabetes cohort, and 87.1% for

the CKD cohort). Initial use of ezetimibe alone, with or without a statin, was rare at both the initial and last prescriptions (<1% for all cohorts) (Table 1). At the end of follow-up for each person, moderate-intensity regimens were still the most common. Between 33.3% and 42.9% of patients, depending on the cohort, did not have an active prescription at the end of follow-up.

Adherence, as measured by the PDC, varied by cohort and by treatment intensity and generally declined after the first year. In the CVD cohort, patients receiving high-intensity therapy were more likely to be adherent over time (84.1% in year 1 and 72.3% in year 6) than patients receiving

Table 1. Baseline Characteristics of the 3 Cohorts

Variable	Documented CVD (n = 16 701)	Type 2 Diabetes Without CVD (n = 12 422)	CKD Without CVD (n = 674)
Age, mean (SD), y	68.3 (13.2)	59.3 (12.4)	67.3 (15.1)
Male, No. (%)	10 117 (60.6)	6832 (55.0)	317 (47.0)
BMI, mean (SD)[a]	27.6 (5.4)	32.3 (6.6)	29.3 (6.2)
Follow-up time, mean (SD), y	2.9 (1.5)	3.1 (1.5)	3.2 (1.6)
Smoking, No. (%)			
Current	3246 (19.4)	2210 (17.8)	103 (15.3)
Former	6384 (38.2)	3990 (32.1)	228 (33.8)
Never	7071 (42.3)	6222 (50.1)	343 (50.9)
Charlson Comorbidity Index, No. (%)			
0	4040 (24.2)	68 (0.5)	141 (20.9)
1	6531 (39.1)	7646 (61.6)	87 (12.9)
≥2	6130 (36.7)	4708 (37.9)	446 (66.2)
Risk factors, No. (%)			
Hypertension	14 455 (86.5)	8605 (69.3)	581 (86.2)
Type 2 diabetes	1043 (6.2)	12 422 (100)	126 (18.7)
Potential familial hypercholesterolemia[b]	15 (0.1)	13 (0.1)	1 (0.1)
Stage 4-5 CKD	286 (1.7)	0	674 (100)
Antihypertensive drug	12 833 (76.8)	6420 (51.7)	509 (75.5)
Antithrombotic drug	14 114 (84.5)	1614 (13.0)	226 (33.5)
Antidiabetic drug	726 (4.3)	8159 (65.7)	104 (15.4)
Atrial fibrillation	1584 (9.5)	373 (3.0)	62 (9.2)
Blood pressure, mean (SD), mm Hg[a]			
Systolic	138 (15.7)	139 (14.0)	139 (15.6)
Diastolic	79 (8.8)	82 (8.3)	79 (8.7)
Chronic disease medications (multimorbidity/polypharmacy), mean (SD), No.[c]	5.7 (3.8)	4.8 (3.6)	6.6 (4.2)
Cholesterol measures, mean (SD), mg/dL[a]			
LDL-C	128 (39)	135 (35)	143 (39)
Total	205 (46)	220 (43)	228 (50)
HDL-C	54 (15)	46 (12)	54 (15)
Initial prescription, No. (%)			
High-intensity statin	3916 (23.4)	140 (1.1)	21 (3.1)
Moderate-intensity statin	12 364 (74.0)	11 743 (94.5)	587 (87.1)
Low-intensity statin	388 (2.3)	514 (4.1)	61 (9.1)
Statin with ezetimibe	5 (0.0)	6 (0.0)	2 (0.3)
Ezetimibe alone	28 (0.2)	19 (0.2)	3 (0.4)
Last prescription, No. (%)[d]			
High-intensity statin	3050 (18.3)	586 (4.7)	23 (3.4)
Moderate-intensity statin	7653 (45.8)	6870 (55.3)	320 (47.5)
Low-intensity statin	345 (2.1)	376 (3.0)	38 (5.6)
Statin with ezetimibe	22 (0.1)	14 (0.1)	0
Ezetimibe alone	73 (0.4)	56 (0.5)	4 (0.6)
None	5558 (33.3)	4520 (36.4)	289 (42.9)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CKD, chronic kidney disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factor: To convert cholesterol level to millimoles per liter, multiply by 0.0259.

[a] Laboratory measures were only available on a subset of the population.

[b] Potential familial hypercholesterolemia was identified using the Dutch Lipid Clinic score[26] (retrospectively) and/or familial hypercholesterolemia–specific Read codes.

[c] Unique medication count excludes lipid-lowering therapies.

[d] Last prescription refers to the prescription at the end of observation for each person. Patients without an active prescription on this date were included as "none."

low-intensity therapy (57.4% in year 1 and 48.4% in year 6). Adherence was generally similar across treatment intensity groups for the diabetes cohort and the CKD cohort (**Figure 1**).

Cardiovascular event rates varied by cohort. The CVD cohort had the highest mean event rate (72.1 events per 1000 person-years of follow-up). This rate was highest during the first year at 136 and was lower afterward, ranging from a minimum of 30 to a maximum of 46. The decrease in rates is most likely due to the consequences of treatment. The mean event rate in the diabetes cohort was 13 and ranged from 10 to 20; the mean event rate in the CKD cohort was 38 and ranged from 20 to 52 (eTable 4 and eTable 5 in the Supplement).

Association of Adherence and Treatment Intensity With Outcomes

Higher adherence and higher treatment intensity were each associated with a lower risk of cardiovascular events in separate adjusted regression models. The associations were graded and consistent across all 3 cohorts (**Table 2**). In particular, the HR in the CVD cohort for each 10% increase in adherence (eg, 70% to 80%) was 0.95 (95% CI, 0.94-0.97). Based on the mean PDC for all adherent patients, the HR was 0.65 (95% CI, 0.60-0.70). Similarly, for each 10% increase in treatment intensity (eg, 30% to 40%), the HR was 0.90 (95% CI, 0.86-0.95). Based on the mean treatment intensity for patients receiving high-intensity therapy, the HR was 0.60 (95% CI, 0.52-0.68). Results were similar for the diabetes cohort and the CKD cohort. The reference group for all analyses was defined as patients untreated for at least 1 year (eTable 6 in the Supplement).

The association between the combined measure of adherence and treatment intensity with outcomes was also graded (**Figure 2**). For example, in the CVD cohort, each 10% increase in the combined measure (eg, from 40% to 50%) was associated with a lower risk of cardiovascular events by 10% (HR, 0.90; 95% CI, 0.86-0.94). As a particular example, in the CVD cohort, adherent patients who were receiving a high-intensity regimen had a 40% lower cardiovascular event risk than patients who were untreated for at least 1 year (the reference group) (HR, 0.60; 95% CI, 0.54-0.68). In contrast, nonadherent patients receiving a low-intensity regimen had a 5% lower risk. Results were similar for the diabetes cohort and the CKD cohort (Figure 2).

We conducted additional subgroup and sensitivity analyses within the CVD cohort (**Figure 3**). The associated risk reduction for each 10% increase in the combined measure appeared more marked among high-risk subgroups, including those with diabetes (HR, 0.70; 95% CI, 0.60-0.82) and those with both multiple cardiovascular events in their history and LDL-C of 135 mg/dL or higher (HR, 0.79; 95% CI, 0.68-0.92). We tested ezetimibe use as an independent covariate, but it was not associated with an additional reduction in risk (HR, 1.06; 95% CI, 0.53-1.59).

We estimated that there would have been 2069 events across all patients over the same follow-up period if patients were treated optimally (50% combined measure) compared with the

Figure 1. Proportion of Adherent Patients Over Time by Cohort and Treatment Intensity
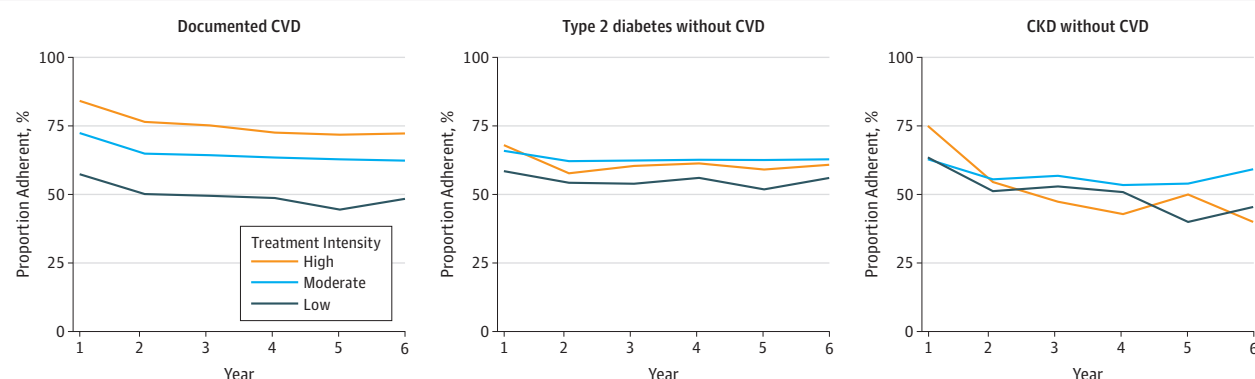
Adherent patients are defined as those with a proportion of days covered of 80% or higher for the year. The mean duration of follow-up was approximately 3 years; therefore, sample sizes in years 4 through 6 are smaller. CKD indicates chronic kidney disease; CVD, cardiovascular disease.

3086 actual observed events (21% combined measure) (eFigure 3 in the Supplement). This estimate represents a theoretical decline from the observed rate of 72.1 events per 1000 person-years to 48.3 events per 1000 person-years, reflecting an absolute difference of 23.7 (95% CI, 15.7-31.4) per 1000 person-years. Results were similar for the diabetes cohort and the CKD cohort.

Sensitivity analyses excluding heart failure from the composite end point yielded results similar to those using the primary end point. These findings are summarized in Table 2.

In analyses of percentage of LDL-C change (Figure 2), a 10% increase in the combined adherence and treatment intensity measure was associated with a mean 9.1% (95% CI, 8.8%-9.4%) LDL-C reduction in the CVD cohort, a mean 10.3% (95% CI, 10.0%-10.5%) reduction in the diabetes cohort, and a mean 10.2% reduction (95% CI, 8.7%-11.7%) in the CKD cohort.

Discussion

Our study assesses, for the first time to date to our knowledge, the association of the combination of adherence and treatment intensity with LDL-C reduction and with cardiovascular outcomes in patients newly treated with lipid-lowering therapy who are at high risk of cardiovascular events by virtue of having documented CVD, diabetes, or CKD. Adherent patients receiving high-intensity therapy had a 40% lower risk of a cardiovascular event compared with 5% among nonadherent patients receiving low-intensity therapy. These findings were consistent across the 3 cohorts and suggest that high-intensity regimens are feasible and effective in routine clinical practice. Optimal therapy with complete use of and adherence to high-intensity regimens could result in a one-third reduction in the number of cardiovascular events in patients with CVD within approximately 3 years. However, it may not be possible for nonadherent patients to receive the full benefits of therapy because adherence is a proxy for a wide array of patient-related factors.

Reducing the likelihood of preventable cardiovascular events is the objective of United Kingdom and European clinical guideline updates for patients either with established CVD or those at high risk of developing CVD. The National Institute for Health and Care Excellence guidelines recommend high-intensity statin therapy, with the goal of ensuring at least a 40% reduction in non–high-density

Table 2. Separate and Combined Associations of Adherence and Treatment Intensity With Cardiovascular Risk by Cohort[a]

Variable	HR (95% CI)		
	Documented CVD	Type 2 Diabetes Without CVD	CKD Without CVD
Model 1: Adherence Alone			
Per 10% increase	0.95 (0.94-0.97)	0.97 (0.95-0.99)	0.93 (0.88-0.98)
Adherent	0.65 (0.60-0.70)	0.74 (0.68-0.81)	0.52 (0.41-0.66)
Nonadherent	0.78 (0.78-0.78)	0.85 (0.84-0.85)	0.69 (0.68-0.70)
Model 2: Treatment Intensity Alone			
Per 10% increase	0.90 (0.86-0.95)	0.93 (0.89-0.98)	0.87 (0.76-0.99)
High intensity	0.60 (0.52-0.68)	0.71 (0.62-0.81)	0.47 (0.32-0.71)
Moderate intensity	0.69 (0.65-0.73)	0.78 (0.73-0.83)	0.59 (0.49-0.72)
Low intensity	0.78 (0.78-0.78)	0.85 (0.85-0.85)	0.70 (0.68-0.73)
Model 3: Combined Adherence and Treatment Intensity			
Per 10% increase	0.90 (0.86-0.94)	0.92 (0.87-0.97)	0.81 (0.70-0.95)
Per 10% increase, no heart failure[b]	0.90 (0.86-0.94)	0.90 (0.85-0.96)	0.86 (0.73-1.02)
High intensity, adherent	0.60 (0.54-0.68)	0.67 (0.57-0.79)	0.39 (0.25-0.61)
High intensity, nonadherent	0.90 (0.86-0.95)	0.92 (0.87-0.98)	0.82 (0.73-0.92)
Moderate intensity, adherent	0.70 (0.66-0.74)	0.75 (0.69-0.82)	0.50 (0.38-0.65)
Moderate intensity, nonadherent	0.93 (0.87-0.99)	0.94 (0.88-1.02)	0.87 (0.74-1.02)
Low intensity, adherent	0.78 (0.78-0.79)	0.82 (0.81-0.84)	0.62 (0.57-0.68)
Low intensity, nonadherent	0.95 (0.89-1.02)	0.96 (0.88-1.05)	0.91 (0.75-1.11)

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio.

[a] Adherent patients are defined as those with a proportion of days covered of 80% or higher for the year. Models are adjusted for sex, smoking status, hypertension status, antithrombotic medication use, CKD status (except for the CKD cohort), history of chronic CVD (CVD cohort only), diabetes status (except for the diabetes cohort), duration of diabetes (diabetes cohort only), atrial fibrillation status, year of follow-up, and Charlson Comorbidity Index.

[b] Sensitivity analysis excluding heart failure from the composite end point.

Figure 2. Cardiovascular Risk Reduction and LDL-C Reduction Using the Combined Measure of Adherence and Treatment Intensity
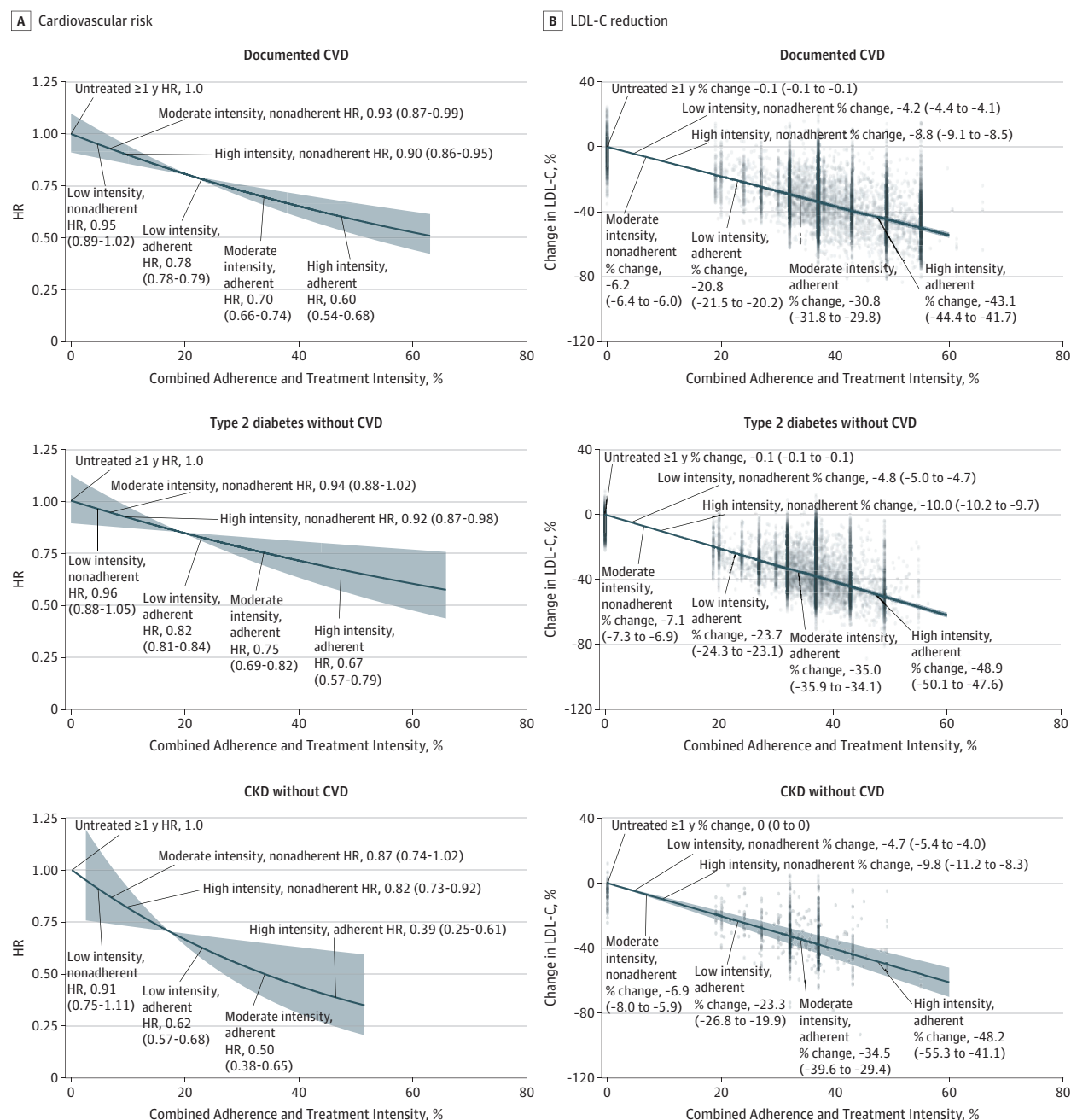
Adherent patients are defined as those with a proportion of days covered of 80% or higher for the year. Analyses are based on the combined measure of adherence and treatment intensity as a continuous variable. For patient subgroups by adherence and treatment intensity, labels indicate the result at the mean value of the combined measure for the subgroup. Shaded areas (and parentheses) indicate 95% CIs. Cardiovascular risk models are adjusted for initial use of high-intensity therapy, sex, smoking status, hypertension status, antithrombotic medication use, chronic kidney disease (CKD) status (except for the CKD cohort), history of chronic cardiovascular disease (CVD) (CVD cohort only), diabetes status (except for the diabetes cohort), duration of diabetes (diabetes cohort only), atrial fibrillation status, year of follow-up, and Charlson Comorbidity Index. The low-density lipoprotein cholesterol (LDL-C) change models include random effects for patient and baseline LDL-C above 135 mg/dL (to convert to millimoles per liter, multiply by 0.0259) and fixed effects for age, sex, hypertension, smoking, CKD (except for the CKD cohort), diabetes (except for the diabetes cohort), Charlson Comorbidity Index, and year of follow-up. The LDL-C change values show the adjusted percentage of LDL-C change for individuals. HR indicates hazard ratio.

lipoprotein cholesterol after 3 months.[3] The European Society of Cardiology has recently recommended a reduction of 50% if baseline LDL-C is between 70 and 135 mg/dL or a target of less than 70 mg/dL if LDL-C is higher than 135 mg/dL in an attempt to ensure that physicians maximize the absolute LDL-C reduction.[5] This recommendation is based in part on the observations from the Cholesterol Treatment Trialists meta-analysis[15] showing that the absolute LDL-C reduction is proportional to the benefit in risk reduction.

In contrast to the guidelines, patients in our 3 cohorts were primarily treated with moderate-intensity regimens, a finding consistent with other research.[27] While it might be hypothesized that clinicians avoided using higher-intensity regimens out of concern about patients' ability to adhere to therapy, patients receiving high-intensity therapy were at least as likely to be adherent as other patients. In particular, patients with documented CVD receiving high-intensity therapy were the most adherent throughout follow-up; those receiving low-intensity therapy were the least adherent. The reasons for this outcome are unclear; however, one explanation might be that the patients treated with high-intensity regimens had a greater understanding of their disease severity, making them more diligent. Conversely, adverse effects or statin intolerance may have led to discontinuation or reductions in the intensity of therapy, but we did not have data to evaluate this hypothesis.

The use of a combined measure of adherence and treatment intensity is intended to reflect the magnitude of LDL-C reduction after accounting for adherence (ie, it is the product of adherence times treatment intensity). Results using the combined measure are consistent with the Cholesterol Treatment Trialists meta-analysis[15] findings for more vs less LDL-C intensive therapy. In the Cholesterol Treatment Trialists results, a mean LDL-C reduction of 20 mg/dL (20% lower than the baseline of 100 mg/dL) was associated with a 15% reduction in the risk of major vascular events. In our CVD cohort, this same difference might be accomplished by increasing treatment intensity by 20% (eg, from 30% to 50%). In someone with an adherence of 75%, this regimen would result in a 15% change in the adherence times treatment intensity product (0.75 × 0.50 − 0.75 × 0.30 = 0.15). According to our model, this change would be associated with a 15% lower risk of events (HR, 0.85; 95% CI, 0.80-0.91). In patients with better adherence, the difference in risk for the same intensity of statin therapy would be even greater. Because the combined measure assessed in our study demonstrates concordance with the risk reductions observed in clinical trials, we believe that other assumptions are reliable.

Figure 3. Cardiovascular Risk Reduction per 10% Increase in the Combined Measure of Adherence and Treatment Intensity for Documented CVD and Subgroups
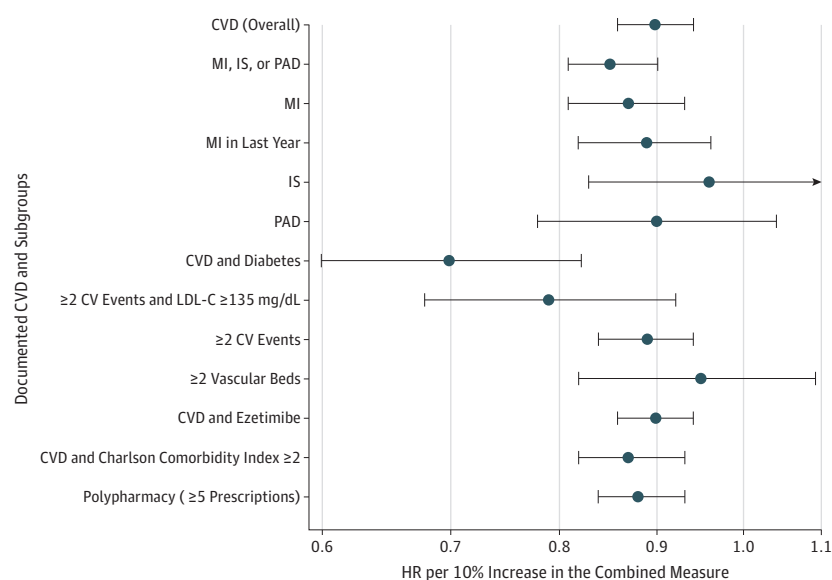
Subgroups are not mutually exclusive. The number of vascular beds ranges from 1 to 3 (coronary, cerebrovascular, and peripheral). The model was adjusted for initial use of high-intensity therapy, sex, smoking status, hypertension status, antithrombotic medication use, chronic kidney disease status, history of chronic cardiovascular disease (CVD), diabetes status, atrial fibrillation status, year of follow-up, and Charlson Comorbidity Index. Error bars indicate 95% CIs. CV indicates cardiovascular; HR, hazard ratio; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and PAD, peripheral artery disease. To convert cholesterol level to millimoles per liter, multiply by 0.0259.

To provide biological plausibility for our findings, we also compared the observed LDL-C reduction against the value that would be expected by the adherence times treatment intensity product. This additional result provides a biological framework around which our findings can be interpreted; namely, the combined measure reflects "average achieved treatment intensity." Our findings are consistent with the observations from others that LDL-C is not only causal but also cumulative: that is, a modest difference in LDL-C of approximately 13 mg/dL maintained over 52 years from genetic studies affords the same protection as a difference of 39 mg/dL maintained over a 5-year period with statins.[28] Moreover, those individuals who have the greatest variability in LDL-C reduction over time in statin trials have the worst outcomes independent of the intensity of therapy.[29] Taken together, these prior observations and our own novel findings suggest that public health would be better served by optimizing the cumulative LDL-C reduction over time.

Limitations

There are several limitations to our study. Adherence is a proxy for a variety of patient-related health care behaviors. Patients who adhere to therapy tend to have better adherence to other lifestyle factors, such as diet and physical activity. We could not address such factors in our analyses because these data are not captured in routine health care records. Similarly, we could not account for better adherence to other cardiovascular medications, which could explain part of the benefit of adherence with lipid-lowering therapy. Because of these factors, it may be challenging for nonadherent patients to experience the full benefits of statins.

Because we required 1 year to estimate adherence, patients were considered to be untreated during their first year on therapy. Constructing a control group in an observational study of adherence requires trade-offs; however, our approach may be considered conservative because at least some treatment association is likely to be present during this untreated period. Based on the Cholesterol Treatment Trialists meta-analysis,[15] this benefit is approximately one-half the benefit observed in subsequent years. Some guidelines, such as those from the European Society of Cardiology,[5] consider patients with diabetes with "marked hypercholesterolemia" to be at very high risk and other patients with diabetes to be at high risk. However, because LDL-C levels were not available for all patients and because clinicians may treat these patients to reduce their risk of cardiovascular events regardless of LDL-C, we included all patients with type 2 diabetes who initiated lipid-lowering therapy. While we used age as the timescale to avoid a spurious, temporal association between diagnosis of cardiovascular conditions and initiation of lipid-lowering therapy, we cannot rule out the associations of other interventions. Also, prescription data may not reflect the actual use by the patient.

Conclusions

Results of our study not only provide evidence that patients newly treated with statins and/or ezetimibe are as adherent to high-intensity regimens as to lower-intensity regimens but also demonstrate the joint association of both adherence and treatment intensity with the risk of cardiovascular events, which is likely mediated through the mean LDL-C reduction. The lowest cardiovascular risk was observed among adherent patients receiving high-intensity therapy, and the highest cardiovascular risk was observed among nonadherent patients receiving low-intensity therapy. Strategies that optimize LDL-C reduction through better use of high-intensity statins and improved adherence could potentially reduce the risk of CVD in high-risk populations.

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REFERENCES

1. Catapano AL, Graham I, De Backer G, et al; ESC Scientific Document Group. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J*. 2016;37(39):2999-3058. doi:10.1093/eurheartj/ehw272

2. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart*. 2014;100(suppl 2):ii1-ii67. doi:10.1136/heartjnl-2014-305693

3. National Clinical Guideline Centre. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline CG181. https://www.nice.org.uk/guidance/cg181/evidence/lipid-modification-update-full-guideline-243786637. Published July 2014. Accessed March 18, 2018.

4. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25)(suppl 2):S1-S45. doi:10.1161/01.cir.0000437738.63853.7a

5. Piepoli MF, Hoes AW, Agewall S, et al; ESC Scientific Document Group. 2016 European guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2016;37(29):2315-2381. doi:10.1093/eurheartj/ehw106

6. Jansen J, McKinn S, Bonner C, et al. General practitioners' decision making about primary prevention of cardiovascular disease in older adults: a qualitative study. *PLoS One*. 2017;12(1):e0170228. doi:10.1371/journal.pone.0170228

7. Reiner Z, Sonicki Z, Tedeschi-Reiner E. Physicians' perception, knowledge and awareness of cardiovascular risk factors and adherence to prevention guidelines: the PERCRO-DOC survey. *Atherosclerosis*. 2010;213(2):598-603. doi:10.1016/j.atherosclerosis.2010.09.014

8. Mosca L, Linfante AH, Benjamin EJ, et al. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. *Circulation*. 2005;111(4):499-510. doi:10.1161/01.CIR.0000154568.43333.82

9. Ramkumar S, Raghunath A, Raghunath S. Statin therapy: review of safety and potential side effects. *Acta Cardiol Sin*. 2016;32(6):631-639. doi:10.6515/ACS20160611A

10. Setia S, Fung SS, Waters DD. Doctors' knowledge, attitudes, and compliance with 2013 ACC/AHA guidelines for prevention of atherosclerotic cardiovascular disease in Singapore. *Vasc Health Risk Manag*. 2015;11:303-310. doi:10.2147/VHRM.S82710

11. Laufs U, Karmann B, Pittrow D. Atorvastatin treatment and LDL cholesterol target attainment in patients at very high cardiovascular risk. *Clin Res Cardiol*. 2016;105(9):783-790. doi:10.1007/s00392-016-0991-z

12. Boggon R, Eaton S, Timmis A, et al. Current prescribing of statins and persistence to statins following ACS in the UK: a MINAP/GPRD study. *Br J Cardiol*. 2012;19(24). doi:10.5837/bjc.2012

13. Kotseva K, Wood D, De Bacquer D, et al; EUROASPIRE Investigators. EUROASPIRE IV: a European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol*. 2016;23(6):636-648. doi:10.1177/2047487315569401

14. Lindgren P, Eriksson J, Buxton M, et al; ASCOT Trial Investigators. The economic consequences of non-adherence to lipid-lowering therapy: results from the Anglo-Scandinavian-Cardiac Outcomes Trial. *Int J Clin Pract*. 2010;64(9):1228-1234. doi:10.1111/j.1742-1241.2010.02445.x

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

16. Deshpande S, Quek RG, Forbes CA, et al. A systematic review to assess adherence and persistence with statins. *Curr Med Res Opin*. 2017;33(4):769-778. doi:10.1080/03007995.2017.1281109

17. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA*. 2007;297(2):177-186. doi:10.1001/jama.297.2.177

18. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol*. 2014;78(4):684-698. doi:10.1111/bcp.12339

19. Stone MA, Camosso-Stefinovic J, Wilkinson J, de Lusignan S, Hattersley AT, Khunti K. Incorrect and incomplete coding and classification of diabetes: a systematic review. *Diabet Med*. 2010;27(5):491-497. doi:10.1111/j.1464-5491.2009.02920.x

20. Raebel MA, Schmittdiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med Care*. 2013;51(8)(suppl 3):S11-S21. doi:10.1097/MLR.0b013e31829b1d2a

21. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15(8):565-574. doi:10.1002/pds.1230

22. Reiner Ž, De Backer G, Fras Z, et al; EUROASPIRE Investigators. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries—findings from the EUROASPIRE IV survey. *Atherosclerosis*. 2016;246:243-250. doi:10.1016/j.atherosclerosis.2016.01.018

23. Cannon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397. doi:10.1056/NEJMoa1410489

24. Holme I, Szarek M, Cater NB, et al; Incremental Decrease in End Points Through Aggressive Lipid Lowering Study Group. Adherence-adjusted efficacy with intensive versus standard statin therapy in patients with acute myocardial infarction in the IDEAL study. *Eur J Cardiovasc Prev Rehabil*. 2009;16(3):315-320. doi:10.1097/HJR.0b013e32832130f5

25. Griffin BA, Anderson GL, Shih RA, Whitsel EA. Use of alternative time scales in Cox proportional hazard models: implications for time-varying environmental exposures. *Stat Med*. 2012;31(27):3320-3327. doi:10.1002/sim.5347

26. Nordestgaard BG, Chapman MJ, Humphries SE, et al; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J*. 2013;34(45):3478-3490a. doi:10.1093/eurheartj/eht273

27. Lin I, Sung J, Sanchez RJ, et al. Patterns of statin use in a real-world population of patients at high cardiovascular risk. *J Manag Care Spec Pharm*. 2016;22(6):685-698. doi:10.18553/jmcp.2016.22.6.685

28. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease, 1: evidence from genetic, epidemiologic, and clinical studies: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38(32):2459-2472. doi:10.1093/eurheartj/ehx144

29. Bangalore S, Breazna A, DeMicco DA, Wun CC, Messerli FH; TNT Steering Committee and Investigators. Visit-to-visit low-density lipoprotein cholesterol variability and risk of cardiovascular outcomes: insights from the TNT trial. *J Am Coll Cardiol*. 2015;65(15):1539-1548. doi:10.1016/j.jacc.2015.02.017