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Clinical- and cost-effectiveness of LDL particle-guided statin therapy: A simulation study

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ABSTRACT

We used the Archimedes Model, a mathematical simulation model (Model) to estimate the clinical- and cost-effectiveness of using LDL particle concentration (LDL-P) as an adjunct or alternative to LDL cholesterol (LDL-C) to guide statin therapy. LDL-P by NMR has been shown to be a better measure of cardiovascular disease (CVD) risk than LDL-C, and may therefore be a better gauge of the need for and response to statin treatment. Using the Model, we conducted a virtual clinical trial comparing the use of LDL-C alone, LDL-P alone, and LDL-C and LDL-P together to guide treatment in the general adult population, and in high-risk, dyslipidemic subpopulations. In the general population, the 5-year major adverse cardiovascular event (MACE) relative risk reduction (RRR) of LDL-P alone compared to the control arm (LDL-C alone) was 5.0% (95% CI, 4.7–5.3; $p < .0001$); using both LDL-C and LDL-P (dual markers) led to 3.0% RRR compared to the control arm (95% CI, 2.8–3.3; $p < .0001$). For individuals with diabetes, the RRR was 7.3% (95% CI, 6.4–8.2; $p < .0001$) for LDL-P alone and 6.9% for dual markers (95% CI, 6.1–7.8; both, $p < .0001$).

In the general population, the costs per quality-adjusted life year (QALY) associated with the use of LDL-P alone were \$76,052 at 5 years and \$8913 at 20 years and \$142,825 at 5 years and \$25,505 at 20 years with the use of both markers. In high-risk subpopulations, the use of LDL-P alone was cost-saving at 5 years; whereas the cost per QALY for the use of both markers was \$14,250 at 5 years and \$859 at 20 years for high-risk dyslipidemics, \$19,192 at 5 years and \$649 at 20 years for diabetics, and \$9030 at 5 years and \$7268 at 20 years for patients with prior CHD. In conclusion, the model estimates that using LDL-P to guide statin therapy may reduce the risk of CVD events to a greater extent than does the use of LDL-C alone and maybe cost-effective or cost-saving for high-risk patients.

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1. Introduction

Reducing low-density lipoprotein (LDL) levels with pharmacologic agents has been associated with a marked reduction in cardiovascular disease (CVD) events [1]. LDL cholesterol (LDL-C) has been the historical measure of LDL quantity used to guide LDL-lowering treatment decisions. An alternative measure of LDL

quantity is LDL particle number (LDL-P), determined directly by nuclear magnetic resonance (NMR) spectroscopy [2,3]. Due to variability in the amount of cholesterol per LDL particle, LDL-C and LDL-P levels do not always agree (i.e., are discordant) [4–6]. For example, if an individual patient had a low amount of cholesterol per LDL particle, their LDL-C might appear normal even though their LDL-P was elevated. When LDL-C and LDL-P levels agree (i.e., are concordant), either measure provides a good estimate of LDL-related CVD risk [7,8]. However, when LDL-C and LDL-P are discordant, as is common in patients with type 2 diabetes or metabolic syndrome, risk tracks with LDL-P, not LDL-C [7–10].

These results suggest that LDL-P may provide a more reliable target of therapy for the management of LDL-related risk in some

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patients. A substantial body of evidence supports the efficacy of statin therapy for lowering LDL-P [11–14]. However, statins were found to lower LDL-C more than LDL-P and, despite attainment of LDL-C goals, many statin-treated patients have persistently elevated LDL-P levels [12–14]. Thus, many patients who achieve LDL-C goals have residual CVD risk that may require more aggressive therapy [15–18]. In this context, the aim of this study was to estimate the clinical- and cost-effectiveness of using LDL-P in conjunction with or in place of LDL-C to guide statin therapy.

2. Methods

We used the Archimedes Model (Model) to perform this analysis. The Model is able to conduct studies that would not be feasible in the real world and to forecast long-term outcomes with a high level of precision and accuracy [19–21].

3. The Archimedes model

The Model is a trial-validated, clinically detailed simulation model of human physiology, disease progression, and healthcare delivery [19–21]. The core of the Model is a set of equations representing the physiological pathways pertinent to diseases and their complications [19]. Use of the Model enables a comparison of a wide range of treatments for multiple comorbidities within a single integrated view.

The Model creates a simulated population of virtual individuals with distributions and correlations of risk factors, behaviors, medication usage, and medical histories reflective of a real population. When simulating a clinical trial, a study cohort of patients meeting the trial inclusion/exclusion criteria is recruited from this simulated population. Each patient's life is then simulated for the trial period. The Model allows interventions and protocol changes to be compared using an identical population for each trial arm. This design allows for the simulation of complex treatment protocols and the addition of novel diagnostics. The Model has been validated by simulating more than 50 major clinical trials, including 9 trials related to cardiovascular disease. [21–25]

4. Simulated study population

In this study, we simulated 1,000,000 patients reflective of the general US population aged 20–84. Virtual patients were created based on the profiles of patients in the National Health and Nutrition Examination Survey (NHANES), 1999–2008 [26]. We also examined the following embedded subpopulations: patients at moderate and high risk of coronary heart disease (CHD) (as defined below) and patients with diabetes (fasting plasma glucose [FPG] > 125 mg/dL) or CHD (at least 1 episode of coronary heart failure [CHF], atrial fibrillation, left ventricular hypertrophy [LVH], or coronary artery disease [CAD], which includes MI and angina). Only patients eligible for lipid-lowering therapy (see below) were included in these subpopulations.

5. Risk categories and LDL goals

CHD risk categories and LDL-C goals were defined according to Adult Treatment Panel III (ATP III) guidelines [1]. Low-risk patients were identified as those with 0–1 risk factors. ATP III guidelines recommend managing these patients to an LDL-C goal of 160 mg/dL. Since statin therapy is applied infrequently to such patients, we focused this study on higher risk patients. Moderate-risk (including moderately high-risk) patients were those with 2 or more risk factors and a 10-year CHD risk <20%. They had an LDL-C goal of <130 mg/dL. High-risk (including very high-risk) patients were

those with 2 or more risk factors and a 10-year CHD risk >20%. They had an LDL-C goal of <100 mg/dL.

LDL-P goals were defined as the percentile equivalents to the corresponding LDL-C goals, using observed percentile values in the Multi-Ethnic Study of Atherosclerosis (MESA) [27]. The LDL-P goals were 1383 (68th percentile) and 1053 (30th percentile) nmol/L for moderate- and high-risk patients, respectively.

6. LDL management protocol

The protocol for the management of LDL-C was based on ATP III guidelines and consisted of 3 steps: (1) risk stratification, based on the levels of total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) and other risk factors, by which patients were assigned to low-, moderate-, or high-risk categories; (2) LDL evaluation, in which patients whose LDL-C level was above goal were referred to treatment; and (3) treatment, in which patients received lipid-lowering therapy until their LDL-C was below goal. Risk stratification and evaluation occurred at each visit for all patients, allowing their risk category to be upgraded (but not downgraded) if their risk increased between visits. The treatment protocol for all patients consisted initially of lifestyle modification, and also simvastatin 10 mg/day if they were high-risk or had LDL-C >220 mg/dL.

The lifestyle modification intervention was based on diet, and was modeled as a 3% reduction in weight and 1.9% reduction in both systolic and diastolic blood pressure [28]. The rate of adherence to lifestyle modification was assumed to be 9.5% for primary prevention and 14% for patients with CAD, based on calibration to prevalence as observed in NHANES, 2007–2008 [29,30]. Individuals who received only lifestyle modification at trial start were followed-up at 3 months and assigned simvastatin 10 mg/day if their LDL-C was above goal. After starting simvastatin, patients were followed-up after 6 weeks and then every 4–6 months, as recommended by guidelines [1]. If their LDL-C was still above goal, they were given intensification of simvastatin to 20 mg, then 40 mg, and ultimately atorvastatin 80 mg. Patients who still did not reach goal were not given additional drugs/therapy. Patients with LDL-C values below goal or who were receiving a statin at the maximum dose returned only for annual visits. This protocol, in which all patients start low and titrate upwards, is an idealization of actual practice, in which many patients start on simvastatin 20 or 40 mg, but do not increase their dose even if their LDL-C remains above goal [23].

7. Simulated trial design

Patients received care according to all standard care protocols, including measurements of body mass index (BMI) annually, FPG every 3 years, and LDL-C every 1–3 years, in order to diagnose cases of obesity, diabetes, or dyslipidemia, respectively. BMI, FPG, and LDL-C/LDL-P were also measured for diagnostic purposes at the start of the trial. Patients could also be diagnosed with and treated for CHD based on symptoms both before and during the trial.

Patients were placed into 3 trial arms titled: Control, LDL-P Alone, and LDL-C and LDL-P (henceforth called the Dual arm). In all three arms, the titration sequence was the same as described above (i.e. simvastatin 10, 20, 40 mg and atorvastatin 80 mg), but the arms differed as to whether treatment was to targets of LDL-C, LDL-P, or both. In the Control arm, treatment was given in accordance with LDL-C goals only. In the LDL-P Alone arm, the only measure of LDL used was LDL-P. Therefore, patients received an LDL-P by NMR test to determine LDL-P levels, and were referred to statin treatment or received increases in dosage *only* if their LDL-P was above goal. In this arm, the final statin dose could be higher or lower than in Control for the same patient profile. A patient with discordantly high

LDL-P might be titrated to a higher dose in the LDL-P arm than in Control, while a patient with discordantly low LDL-P might be titrated to a lower dose, depending on the particular patient's evolution. In the Dual arm, evaluation was based solely on LDL-C levels. If treatment was indicated, an LDL-P test was done and both LDL-C and LDL-P goals were used for management, with patients increasing their statin dose if *either* their LDL-C or their LDL-P was above goal. In the Dual arm, the statin dose was always at least as high as would be given to patients in the Control arm with the same LDL-C value, but a patient with discordantly high LDL-P might be titrated to a higher statin dose than in Control. Of note, in the LDL-P Alone arm, LDL-P information is used for both LDL evaluation and treatment, whereas in the Dual Arm, LDL-P information is used only when a patient has been referred to treatment based on having LDL-C above goal. This resulted in more patients being referred to treatment or having their risk category upgraded than in the Control and Dual arms. All 1,000,000 patients were run through each of 3 arms, in order to reduce random noise between arms.

8. Clinical outcomes

The primary outcomes were Major Adverse Cardiovascular Events (MACE) and CVD death. MACE included fatal and nonfatal MI, fatal and nonfatal stroke, and CVD death. CVD death included death due to CHD and stroke. All clinical outcomes are expressed as relative risk reductions (RRR), absolute number of events averted per 100,000 patients, and number needed to treat (NNT) [31] compared to events in the Control arm.

9. Economic outcomes and assumptions

Economic outcomes reported were cost per quality-adjusted life-year (QALY) saved. Costs for statins were obtained from healthwarehouse.com as of July, 2013 [32]. The costs for the lipid panel and LDL-P NMR test were \$18.05 and \$42.29, respectively, based on Medicare pricing [33]. Other costs were also based on Medicare [33,34] or, when Medicare costs were not applicable, on the most recent available data in the literature [35–37] and were updated to 2012 dollars. Costs for stroke and CHF include both an initial cost as well as a continuing cost accrued over time (for up to two years for stroke and indefinitely until death for CHF). QALYs were calculated based on the time individuals spent with different disorders using published disutilities based on a meta-analysis [38]. The base value is 1, which represents perfect health, and the disutility of each condition that a patient has at a given time is subtracted from this value. There was an additional correction for patients with multiple chronic conditions [38]. The cost and disutility assumptions are summarized in Table 1. All costs and QALYs were discounted at a rate of 3% per year.

10. LDL-P model

Because the source dataset for constructing the virtual population did not include measurements of LDL-P, it was necessary to impute LDL-P values for each patient from otherwise available biomarkers, including LDL-C, HDL-C, TG, FPG, and BMI. We used the MESA dataset to build the LDL-P model [27]. In this dataset, LDL-P was measured using the *NMR LipoProfile*[®] test.

11. Results

The baseline characteristics for the full simulated population and subpopulations are shown in Table 2. At baseline, average age was 46 years, mean LDL-C was 111 mg/dL, and mean LDL-P was 1193 nmol/L. The prevalence of various diagnosed conditions was

10% with moderate-risk dyslipidemia, 12% with high-risk dyslipidemia, 10% with diabetes and 7% with CHD.

12. Clinical outcomes

In the general population, statin therapy guided by LDL-P alone was associated with a 5-year MACE RRR of 5.0% (95% CI: 4.7%, 5.3%) and a 5-year CVD death RRR of 6.5% (95% CI: 5.8%, 7.3%), whereas statin therapy guided by both LDL-C and LDL-P was associated with a 5-year MACE RRR of 3.0% (95% CI: 2.8%, 3.3%) and a 5-year CVD death RRR of 4.0% (95% CI: 3.5%, 4.6%) (Table 3). In absolute terms, the numbers of events averted per 100,000 patients associated with LDL-P alone at 5-years were 136 (95% CI: 91, 180) (NNT of 738 [95% CI: 555, 1101]) for MACE and 41 (95% CI: 19, 62) (NNT of 2468 [95% CI: 1,610, 5286]) for CVD death, and the numbers associated with Dual goals at 5-years were 82 (95% CI: 37, 127) (NNT of 1221 [95% CI: 788, 2705]) for MACE and 25 (95% CI: 3, 47) (NNT of 4033 [95% CI: 2,149, 32,702]) for CVD death (Tables 4 and 5). When interpreting these values, one must be aware that the Control arm used for comparison is an active treatment arm in accordance with ATP III guidelines.

Among the subpopulations, patients with diabetes experienced the greatest RRR in MACE (7.3% [95% CI: 6.4%, 8.2%] for LDL-P alone and 6.9% [95% CI: 6.1%, 7.8%] for dual goals) (Table 3). Patients with CHD experienced the greatest RRR in CVD death (9.1% [7.4%, 10.8%] for LDL-P alone and 8.6% [7.0%, 10.2%] for dual goals) (Table 3). There was a linear relationship between RRR and the degree of discordance, defined as the difference between LDL-C and LDL-P percentiles ($R^2 = 0.973$ – 0.998 for MACE, Fig. 1, and $R^2 = 0.798$ – 0.816 for CVD death, Fig. 2). This indicates that subpopulations with a greater degree of discordance experienced a greater benefit from using LDL-P to guide treatment. In absolute terms, the degree of

Table 1
Cost and health disutility assumptions.

Event or treatment	Cost	Source
Full lipid panel	\$18.05	Medicare physicians fee schedule (33)
LDL-P NMR	\$42.29	Medicare physicians fee schedule (33)
Statins	\$4.00/mo	Healthwarehouse.com (32)
MI	\$23,653.34	Medicare LDS (34)
Stable angina	\$9944.49	Medicare LDS (34)
Unstable angina	\$18,435.37	Medicare LDS (34)
Stroke	\$11,402.49 - \$105,735.60	Samsa (35)
CHF initial cost	\$9809.58	Esposito (36)
CHF continuing cost	\$8800.14/yr	Esposito (36)
Atrial Fibrillation	\$23,528.43/yr	Wu (37)
Condition	Disutility	
Hypertension	−0.025	Sullivan (38)
Diabetes	−0.0351	Sullivan (38)
MI	−0.0409	Sullivan (38)
Angina	−0.0412	Sullivan (38)
Stroke	−0.046	Sullivan (38)
CHF	−0.063	Sullivan (38)
Num. Chron. Cond.	Disutility	
1	−0.0942	Sullivan (38)
2	−0.0876	Sullivan (38)
3	−0.0711	Sullivan (38)
4	−0.0547	Sullivan (38)
5	−0.0419	Sullivan (38)
6	−0.0035	Sullivan (38)
7	−0.0344	Sullivan (38)
8	0.0026	Sullivan (38)
9	0.0097	Sullivan (38)
10	−0.0942	Sullivan (38)

LDL-P NMR = low-density lipoprotein particle concentration by nuclear magnetic resonance; MI = myocardial infarction; CHF = congestive heart failure; Num. Chron. Cond. = number of chronic conditions.

Table 2
Baseline population characteristics.

Characteristic	All	MR Dyslipidemia ^a	HR Dyslipidemia ^a	Diabetes ^b	CHD ^b
N	1,000,000	98,635	122,148	72,372	51,668
Age (years)	46 (15.9)	55 (13.6)	62 (12.5)	61 (11.9)	64 (12.6)
Men (%)	48	66	55	49	56
BMI (kg/m ²)	28 (6.4)	29 (5.2)	32 (7.2)	35 (7.2)	30 (6.1)
Blood Pressure (mmHg)					
Systolic	122 (15.8)	130 (16.3)	127 (17)	125 (14.2)	126 (16.8)
Diastolic	72 (11.4)	74 (12.4)	70 (12.1)	70 (11.8)	68 (11.9)
Cholesterol (mg/dL)					
TC	192 (35.9)	198 (25.6)	171 (23.4)	175 (25.6)	174 (27.3)
LDL-C	111 (30.1)	121 (20.1)	89 (15.4)	90 (18.1)	93 (20.6)
HDL-C	54 (16.7)	45 (10.8)	51 (15)	52 (13.8)	51 (15)
Triglycerides	136 (100.9)	161 (90.1)	156 (91.3)	166 (89.8)	148 (86.9)
Fasting plasma glucose	101 (32.1)	100 (23.6)	141 (53.6)	166 (36.6)	121 (48.3)
HbA1c (%)	5.4 (0.9)	5.4 (0.7)	6.5 (1.3)	7.1 (1)	5.9 (1.2)
LDL-P	1193 (334.5)	1354 (294.9)	1062 (257.3)	1091 (269.9)	1081 (270.7)
Medical History (%)					
No Dyslipidemia	70	0	0	0	0
Low-Risk Dyslipidemia ^a	8	0	0	2	2
Moderate-Risk Dyslipidemia ^a	10	100	0	5	11
High-Risk Dyslipidemia ^a	12	0	100	93	86
Discordantly High LDL-P ^c	25	31	45	47	41
Concordant LDL-P ^c	49	48	45	44	46
Discordantly Low LDL-P ^c	26	21	10	9	13
Obesity	31	36	54	74	41
Diagnosed diabetes	10	4	58	100	28
CHD	7	6	37	20	100
CKD	4	4	20	31	15
Current smoker	24	39	19	14	19
Hypertension	24	49	56	65	46
MI	2	1	15	8	37
Stroke	2	1	12	5	6

Subpopulations (excluding All) include only patients eligible for LDL-lowering therapy. Values are means, except where indicated as percents of the population. BMI = body mass index; TC = total cholesterol; LDL = low density lipoprotein; HDL = high-density lipoprotein; LDL-C = LDL cholesterol; LDL-P = LDL particles; CHD = coronary heart disease; CKD = chronic kidney disease; MI = myocardial infarction; MR = moderate-risk; HR = high-risk.

^a Dyslipidemia categories defined according to Adult Treatment Panel (ATP III) guidelines [1].

^b The diabetic and CHD subpopulations include only patients who also have dyslipidemia.

^c Discordance defined as high if $\geq 12\%$, low if $\leq -12\%$, and concordant otherwise.

benefit observed tracked with the level of baseline risk more than with discordance. Patients with CHD, who have the highest baseline risk, received the greatest absolute benefit; the numbers of MACE averted per 100,000 patients at 5-years were 463 (95% CI: 209, 716) (NNT of 144 [95% CI: 93, 320]) for LDL-P alone and 441 (95% CI: 187, 695) (NNT of 154 [95% CI: 97, 374]) for dual goals (Tables 4 and 5). The reduction in number of events was also greater at longer time horizons, indicating that the benefit of treating to LDL-P targets accrues gradually over time, as is to be expected for a preventative measure.

13. LDL reductions

For patient subpopulations with elevated LDL-C at baseline, statin therapy guided by both LDL-P alone and Dual goals resulted in reductions in LDL-C that significantly exceeded those guided by LDL-C alone (Table 6), mainly because of the use of higher doses of statins to achieve LDL-P goals in high-risk patients. Like the MACE RRR's, the percent change in both LDL-C and LDL-P tracked with the degree of discordance, and the largest reduction relative to Control was seen in those with diabetes.

Table 3
Mean (95% confidence interval) relative risk reduction of MACE and CVD death at 5, 10, and 20 years, for the Dual and LDL-P arms, relative to control.

MACE	LDL-P arm			Dual arm		
	5 Year	10 Year	20 Year	5 Year	10 Year	20 Year
All	-5.03 (-5.34;-4.72)	-4.75 (-4.97;-4.53)	-3.93 (-4.08;-3.79)	-3.04 (-3.26;-2.82)	-3.30 (-3.46;-3.14)	-2.98 (-3.08;-2.87)
Moderate-risk	-5.38 (-6.27;-4.49)	-5.66 (-6.30;-5.02)	-5.35 (-5.79;-4.91)	-3.86 (-4.52;-3.20)	-4.52 (-5.01;-4.03)	-4.21 (-4.54;-3.88)
High-risk	-6.69 (-7.30;-6.07)	-7.05 (-7.52;-6.58)	-6.13 (-6.46;-5.80)	-6.68 (-7.29;-6.08)	-7.17 (-7.63;-6.71)	-6.35 (-6.68;-6.03)
Diabetes	-7.27 (-8.19;-6.35)	-7.88 (-8.56;-7.20)	-6.86 (-7.33;-6.39)	-6.93 (-7.80;-6.05)	-7.51 (-8.15;-6.87)	-6.82 (-7.27;-6.38)
CHD	-6.60 (-7.40;-5.79)	-6.46 (-7.07;-5.85)	-5.25 (-5.70;-4.80)	-6.18 (-6.93;-5.42)	-6.18 (-6.76;-5.60)	-5.17 (-5.60;-4.75)
CVD death						
	LDL-P arm			Dual arm		
All	-6.54 (-7.32;-5.77)	-6.26 (-6.79;-5.74)	-5.37 (-5.71;-5.03)	-4.00 (-4.56;-3.45)	-4.35 (-4.74;-3.97)	-4.04 (-4.28;-3.80)
Moderate-risk	-7.10 (-9.48;-4.71)	-7.13 (-8.76;-5.50)	-7.25 (-8.34;-6.16)	-2.93 (-4.33;-1.54)	-4.06 (-5.14;-2.98)	-5.24 (-5.99;-4.49)
High-risk	-8.06 (-9.41;-6.72)	-8.51 (-9.45;-7.56)	-7.44 (-8.08;-6.80)	-8.19 (-9.50;-6.87)	-8.56 (-9.49;-7.63)	-7.73 (-8.36;-7.10)
Diabetes	-8.78 (-10.82;-6.74)	-9.06 (-10.45;-7.67)	-8.66 (-9.62;-7.71)	-7.79 (-9.66;-5.93)	-8.29 (-9.58;-7.00)	-8.31 (-9.21;-7.41)
CHD	-9.08 (-10.79;-7.38)	-8.21 (-9.39;-7.04)	-6.76 (-7.59;-5.93)	-8.58 (-10.16;-7.00)	-7.86 (-8.96;-6.76)	-6.60 (-7.37;-5.83)

Table 4
Mean (95% confidence interval) absolute reduction in number of events per 100,000 patients of MACE and CVD death at 5, 10, and 20 years, for the Dual and LDL-P arms, relative to control.

MACE	LDL-P arm			Dual arm		
	5 Year	10 Year	20 Year	5 Year	10 Year	20 Year
All	136 (91; 180)	275 (210; 341)	525 (427; 624)	82 (37; 127)	191 (126; 257)	397 (298; 496)
Moderate-risk	497 (287; 707)	1049 (754; 1344)	1876 (1450; 2301)	496 (286; 706)	1066 (772; 1361)	1944 (1519; 2370)
High-risk	215 (42; 389)	502 (245; 758)	1123 (729; 1517)	155 (-20; 329)	400 (143; 658)	884 (489; 1278)
Diabetes	693 (312; 1075)	1235 (724; 1745)	1865 (1158; 2572)	649 (267; 1030)	1182 (671; 1692)	1838 (1131; 2545)
CHD	463 (209; 716)	1072 (703; 1440)	2039 (1491; 2587)	441 (187; 695)	1022 (653; 1390)	2029 (1481; 2577)
CVD death	LDL-P arm			Dual arm		
All	41 (19; 62)	91 (58; 125)	209 (153; 266)	25 (3; 47)	63 (30; 97)	157 (101; 214)
Moderate-risk	174 (58; 290)	412 (234; 589)	884 (584; 1185)	177 (61; 293)	415 (237; 592)	918 (618; 1219)
High-risk	56 (-22; 134)	138 (14; 262)	420 (193; 647)	23 (-56; 102)	78 (-47; 203)	303 (76; 531)
Diabetes	338 (104; 572)	630 (285; 975)	1127 (573; 1680)	319 (85; 553)	603 (258; 948)	1100 (546; 1654)
CHD	159 (21; 298)	386 (170; 603)	959 (582; 1337)	142 (3; 280)	353 (136; 571)	921 (543; 1298)

14. Economic outcomes

In the full study population, statin therapy guided by LDL-P alone had a cost per QALY of \$76,052 at 5 years and \$8913 at 20 years (Table 7). Statin therapy guided by dual goals had a cost per QALY of \$142,825 at 5 years and \$25,505 at 20 years (Table 7). Costs per QALY were much lower in the high-risk subpopulations. Statin therapy guided by LDL-P alone was cost-saving at 5 years in patients with high-risk dyslipidemia, diabetes and CHD. The 5-year cost per QALY of statin therapy guided by dual goals was \$14,250 for high-risk dyslipidemic patients, \$19,192 for patients with diabetes and \$9030 for patients with CHD.

15. Discussion

This simulation study examined the relative effectiveness of statin therapy guided by LDL-P levels compared to statin therapy guided by LDL-C levels in reducing the incidence of CVD events. The Model estimated that treating patients to LDL-P goals, either in conjunction with or in place of LDL-C goals, would be substantially more effective in reducing MACE and CVD death risk than treatment to LDL-C goals alone; especially in patients with high risk as defined by ATP III guidelines, diabetes, or prior CHD.

In addition, the Model was used to estimate the relative cost-effectiveness of using the two measures to guide statin therapy. If one assumes a cost-effectiveness threshold of \$50,000 per QALY gained, then in the general population the use of Dual LDL-P and LDL-C goals was cost-effective only at 20 years whereas the use of LDL-P goals alone was cost-effective at 10 and 20 years. However, in patients with diabetes or at high risk for CHD, management to Dual goals was cost-effective while management to LDL-P goals alone

was cost-saving at 5, 10, and 20 years. In high risk patients with prior CHD, the use of LDL-P goals alone was cost-saving only at 5 years but not at 10 and 20 years since most of the savings are due to the prevention of recurrent MI events shortly after the previous MI, and the risk of recurrent MI wanes with time.

The relative risk reductions in MACE and CVD death observed in the LDL-P Alone arm were at least as great as in the Dual arm in all subpopulations, and were significantly higher in the general population and in patients with moderate-risk dyslipidemia. This advantage is due to the use of LDL-P information at an earlier step in the treatment protocol. Moreover, the LDL-P alone arm was considerably more cost-effective, due to the facts that a standard lipid panel test measuring LDL-C is not performed and that statin treatments are targeted more selectively to those patients most likely to benefit (i.e. those with discordantly high LDL-P).

Using LDL-P information in addition to LDL-C to manage LDL-related CVD risk represents a minimal departure from standard care, and is conservative in the sense that since the recommended LDL-C goals are maintained, at a minimum, patients receive the same treatment as they would in the Control arm. The use of LDL-P alone for both evaluation and treatment represents a greater departure from standard care, in that no LDL-C information is used to guide treatment decisions, only LDL-P. Patients with high LDL-P levels receive more aggressive therapy, regardless of their LDL-C level, whereas patients with low LDL-P levels receive lower doses of statin, even if their LDL-C level is discordantly high. For these patients, using LDL-P alone reduces unnecessary treatment. Since, in the setting of discordance, CVD risk tracks with LDL-P and not with LDL-C [7,9], these patients have a lower risk than would be determined based on LDL-C levels and thus do not require aggressive statin therapy.

Table 5
Mean (95% confidence interval) number needed to test (NNT) to prevent one occurrence of MACE and CVD death at 5, 10, and 20 years, for the Dual and LDL-P arms, relative to control.

MACE	LDL-P arm			Dual arm		
	5 Year	10 Year	20 Year	5 Year	10 Year	20 Year
All	738 (555; 1101)	363 (293; 476)	190 (160; 234)	1221 (788; 2705)	522 (389; 795)	252 (201; 335)
Moderate-risk	464 (257; 2387)	199 (132; 409)	89 (66; 137)	647 (304; 5117)	250 (152; 700)	113 (78; 205)
High-risk	201 (142; 349)	95 (74; 133)	53 (43; 69)	202 (142; 349)	94 (73; 130)	51 (42; 66)
Diabetes	216 (140; 478)	93 (69; 142)	49 (39; 67)	227 (144; 534)	98 (72; 153)	49 (39; 68)
CHD	144 (93; 320)	81 (57; 138)	54 (39; 86)	154 (97; 374)	85 (59; 149)	54 (39; 88)
CVD death	LDL-P arm			Dual arm		
All	2468 (1610; 5286)	1095 (801; 1729)	477 (376; 653)	4033 (2149; 32702)	1576 (1030; 3352)	635 (467; 991)
Moderate-risk	1794 (749; 4535)	727 (382; 7367)	238 (155; 517)	4343 (984; 1799)	1277 (492; 2142)	330 (188; 1320)
High-risk	574 (345; 1718)	243 (170; 427)	113 (84; 171)	566 (342; 1642)	241 (169; 422)	109 (82; 162)
Diabetes	627 (336; 4678)	259 (166; 590)	104 (75; 172)	706 (357; 32211)	283 (175; 734)	109 (77; 184)
CHD	296 (175; 960)	159 (103; 351)	89 (60; 174)	313 (181; 1175)	166 (105; 388)	91 (60; 183)

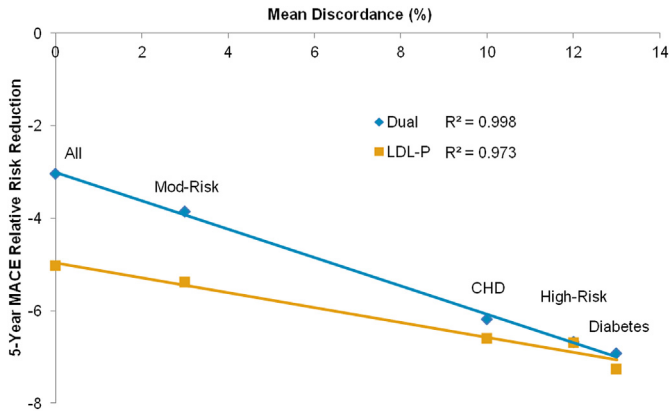


Fig. 1. Mean discordance versus 5-year MACE RRR – Subpopulations with higher discordance have greater risk reduction.

Multiple expert panels and guidelines advocate the use of LDL particle number in the management of at-risk patients [39–43]. The American Association of Clinical Endocrinologists (AACE) [39], the National Lipid Association (NLA) [40], the American Diabetes Association (ADA) in conjunction with the American College of Cardiology (ACC) [41], and the American Association for Clinical Chemistry (AACC) [42,43] have all developed consensus position statements on lipoprotein particle management in individuals at risk for CVD. The 2013 AACE consensus statement cites expert opinion that LDL-P “must be recognized and included in treatment recommendations” for patients with type 2 diabetes, insulin resistance, metabolic syndrome, and/or hypertriglyceridemia who often have persistently elevated LDL-P, even when LDL-C and non-HDL-C are at goal levels (p. 23) [39].

The results of this analysis show a strong link between CVD risk and the degree of LDL discordance. The greater the discordance, the more effective it was to treat to LDL-P goals (Figs. 1 and 2). Further, the economic analyses showed much lower costs per QALY gained for subpopulations with high discordance. Our model of LDL-P estimates that patients with high BMI, TG, and FPG, and low HDL are more likely to have higher discordance (see supplemental material). This set of characteristics is commonly observed in patients with diabetes. Thus, of the subpopulations considered, the model estimated the highest level of discordance, the greatest relative risk reduction, and the greatest cost-effectiveness for the diabetic subpopulation.

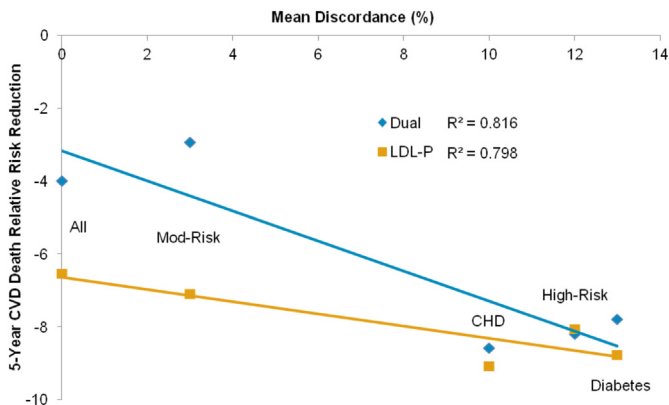


Fig. 2. Mean discordance versus 5-year CVD death RRR – Subpopulations with higher discordance have greater risk reduction.

16. Limitations

There are several limitations of this study. First, it is based on a mathematical simulation model and is subject to the assumptions used to create the Model. However, the Model has been found to be very accurate in numerous validation studies [21–23]. Some of the data sources used to parameterize the Model consist primarily of Caucasian persons, so the results may not be as generalizable to non-white populations. Costs for events are based on Medicare costs and may underestimate the actual costs for a non-Medicare population. However, Medicare costs represent a relatively objective standard and are routinely used in cost effectiveness studies. Also, event-related costs were represented in 2012 dollars, whereas costs for tests and medications are in 2013 dollars. However, updating the cost assumptions by one or two years would be very unlikely to change materially our results, particularly the relative benefit of LDL-P testing and its use in lipid management. Furthermore, if the costs associated with events have been underestimated, then the simulation results represent a conservative assumption because higher costs for events would make the intervention (i.e. LDL-P testing) appear more cost-effective.

The analysis assumed 100% adherence to statin therapy, with no statin intolerance (which would necessitate changing dose or coming off therapy) in order to approximate a per-protocol or on-treatment analysis. While this is not typically observed in clinical practice, the aim of this analysis was to estimate the impact of using LDL-P information to guide patients who adhere to statin treatment. For many patients, the use of LDL-P information led to more aggressive statin therapy in order to reach goal. The inclusion of adverse effects in the model would be expected to reduce the observed benefit. Furthermore, the model assumes that the effect of treatment is constant for the duration of the model, even though in reality treatment effects are likely not constant over long durations, possibly due to either waning adherence or waning efficacy. We have greater confidence in the results for the 0–5 year time horizon because the majority of trial data used to parameterize the treatment model was generated on this time scale. Although longer time scales may introduce greater uncertainty, it is often useful to model the cost-effectiveness of an intervention over longer time horizons.

Another important limitation is the absence of data on measured LDL-P in the dataset used to model this virtual population, which necessitated the imputation of LDL-P from other biomarkers. We demonstrated that LDL-P could be imputed using, in order of significance, LDL-C, HDL-C, TG, FPG, and BMI. While at the population level the distribution of imputed LDL-P was a very close fit to the data, at the individual level, our model of LDL-P was slightly biased in that it overestimated LDL-P for individuals with low LDL-P and underestimated LDL-P for patients with high LDL-P (see Appendix). Hence, our imputed LDL-P was less discriminating than actual LDL-P. This is indicative of the fact that LDL-P is truly an independent risk factor. If measured LDL-P levels better predict CVD events than imputed LDL-P levels, then the actual benefit of treating to LDL-P targets will be greater than that estimated by the Model.

This study compared LDL-C and LDL-P but did not estimate the effectiveness of other alternate measures of LDL-related risk, such as apolipoprotein B (apo B) or non-HDL-C. Apo B is associated with a number of lipoprotein particles, including LDL, and thus can be used to estimate the number of LDL particles, but it is less specific than LDL-P by NMR [43]. Although non-HDL-C provides a more accurate measure of the risk of CVD events than LDL-C, both LDL-P by NMR and apo B have been shown to be superior to non-HDL-C, particularly in the setting of discordance caused by variations in the amount of cholesterol per lipoprotein particle [10,44]. Considering that all three measures of LDL-related risk outperform LDL-C as a

Table 6
Mean (95% CI) percent change in LDL-C and LDL-P for subpopulations with elevated LDL-C at baseline.

Subpopulation	LDLP arm			Dual arm		
	Year 5	Year 10	Year 20	Year 5	Year 10	Year 20
LDL-C reduction (%)						
Moderate-risk	-4.81 (-4.97, -4.65)	-4.34 (-4.5, -4.18)	-4.8 (-4.97, -4.63)	-4.96 (-5.11, -4.81)	-4.6 (-4.75, -4.44)	-4.36 (-4.52, -4.2)
High-risk	-6.96 (-7.12, -6.8)	-7.03 (-7.18, -6.87)	-7.27 (-7.44, -7.11)	-7.29 (-7.44, -7.13)	-7.54 (-7.7, -7.37)	-8.1 (-8.26, -7.93)
Diabetes	-7.63 (-7.79, -7.47)	-7.63 (-7.78, -7.47)	-7.81 (-7.97, -7.65)	-7.64 (-7.8, -7.48)	-7.83 (-7.99, -7.67)	-8.34 (-8.51, -8.18)
CHD	-6.06 (-6.25, -5.88)	-6.16 (-6.34, -5.99)	-6.19 (-6.37, -6)	-6.24 (-6.43, -6.05)	-6.54 (-6.72, -6.37)	-6.95 (-7.13, -6.78)
LDL-P reduction (%)						
Moderate-risk	-4.76 (-4.92, -4.59)	-4.4 (-4.58, -4.23)	-4.65 (-4.83, -4.47)	-4.59 (-4.76, -4.42)	-4.19 (-4.37, -4.02)	-3.83 (-4.01, -3.64)
High-risk	-6.38 (-6.57, -6.2)	-6.39 (-6.57, -6.2)	-6.49 (-6.68, -6.3)	-6.57 (-6.75, -6.39)	-6.69 (-6.88, -6.5)	-6.99 (-7.18, -6.8)
Diabetes	-6.96 (-7.14, -6.79)	-6.91 (-7.09, -6.73)	-6.91 (-7.09, -6.74)	-6.86 (-7.05, -6.68)	-6.95 (-7.13, -6.77)	-7.2 (-7.38, -7.01)
CHD	-5.58 (-5.77, -5.39)	-5.56 (-5.75, -5.37)	-5.52 (-5.71, -5.33)	-5.6 (-5.79, -5.4)	-5.7 (-5.88, -5.52)	-5.94 (-6.13, -5.75)

predictor of CVD events in epidemiological studies, one would expect that, similar to LDL-P, the use of apo B or non-HDL-C to guide statin therapy in the Model would also reduce the risk of CVD events to a greater extent than the use of LDL-C alone.

The treatment protocols of this study were based on ATP III guidelines, which recommended treatment to specific risk-based LDL-C targets [1]. Since this analysis was performed, new guidelines were issued by the American College of Cardiology (ACC) and the American Heart Association (AHA) [45], which emphasize use of statin therapy in groups demonstrating cardiovascular risk reduction in randomized controlled trials. Due to exclusive reliance on RCT data, this guideline made no recommendation for or against use of specific LDL targets in managing patients to prevent cardiovascular events. Importantly, the new guideline does advise LDL testing after instituting therapy to monitor individual response, patient adherence, and to guide clinical judgment regarding adjustment of medications to achieve an improved individual response. By contrast, international guidelines, including the 2013 International Atherosclerosis Society (IAS) position paper on recommendations for the management of dyslipidemia, continue to endorse LDL targets, basing their position on evidence from epidemiological studies and genetic studies as well as RCT's [46].

The primary objective of our study was not to evaluate outcomes related to specific LDL-P targets, but rather to compare the effectiveness of using LDL-P (alone or in conjunction with LDL-C) to using LDL-C alone to monitor patients on statin therapy. Our study suggests the use of LDL-P to evaluate and monitor high risk patients with dyslipidemia has the potential to reduce rates of CVD events and mortality and to be cost-saving to cost-effective at 5 years.

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Conflict of interest

Funding for this research was provided by LipoScience, Inc. This research was conducted by Archimedes, Inc. as consultants for LipoScience. Dr. Folse, Mr. Goswami, and Dr. Rangarajan are employees of Archimedes, Inc. Dr. Budoff and Dr. Kahn served as independent advisors. LipoScience also provided advice in the design of the study, interpretation of the results, and editing of the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.atherosclerosis.2014.06.027>.

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Table 7
Cost per QALY gained, relative to control.

Subpopulation	Size	LDL-P		
		5 Yr	10 Yr	20 Yr
All	1,000,000	\$76,052	\$24,484	\$8913
Mod-risk	98,635	\$58,791	\$12,699	\$1963
High-risk	122,148	-\$2079	-\$7098	-\$3037
Diabetes	72,372	-\$2418	-\$9000	-\$3672
CHD	51,668	-\$398	\$1440	\$4847
Dual				
All	1,000,000	\$142,825	\$54,251	\$25,505
Mod-risk	98,635	\$197,432	\$60,896	\$21,060
High-risk	122,148	\$14,250	\$787	\$859
Diabetes	72,372	\$19,192	\$326	\$649
CHD	51,668	\$9030	\$5841	\$7268

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