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The importance of cholesterol follow-up testing under current statin treatment guidelines☆

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ABSTRACT

Under "treat to risk" goals, low-density (LDL)-cholesterol follow-up measurements monitor statin compliance rather than titration to target levels, however, there is little evidence showing that more-frequent monitoring reduces LDL-cholesterol. We therefore tested whether frequency of blood tests significantly predicted lipoprotein improvements in a large anonymized clinical laboratory database. Differences (Δ ± SE) in total cholesterol, triglycerides, and LDL-cholesterol between baseline and follow-up visits were calculated for 97,548 men and 110,424 women whose physicians sent blood to Boston Heart Diagnostics for analysis between 2010 and 2017. When adjusted for age and follow-up duration, plasma concentration changes per each follow-up measurement in men and women respectively were −2.84 ± 0.10 mg/dL and −3.03 ± 0.10 mg/dL for total cholesterol, −3.78 ± 0.30 mg/dL and −2.26 ± 0.19 mg/dL for triglycerides, and −2.54 ± 0.09 mg/dL and −3.06 ± 0.09 mg/dL for LDL-cholesterol (all $P < 10^{-16}$). Relative to baseline, significant decreases ($P < 10^{-16}$) were observed for the 1st, 2nd, and 3rd follow-up measurements for total cholesterol (mean ± SE, men: −9.4 ± 0.1, −11.9 ± 0.2, −13.7 ± 0.3; women: −8.0 ± 0.1, −10.5 ± 0.2, −12.6 ± 0.3 mg/dL, respectively), triglycerides (men: −10.3 ± 0.4, −12.8 ± 0.5, −13.4 ± 0.7; women: −6.4 ± 0.2, −8.8 ± 0.4, −10.1 ± 0.5 mg/dL, respectively) and LDL-cholesterol (men: −7.8 ± 0.1, −9.9 ± 0.2, −11.1 ± 0.2; women: −6.9 ± 0.1, −9.0 ± 0.2, −10.7 ± 0.2 mg/dL, respectively). When adjusted for regression to the mean, 6.9%, 9.9% and 11.8% of men, and 5.7%, 9.7% and 11.5% of women, went from having an LDL-cholesterol ≥160 to < 160 mg/dL for their 1st, 2nd, and 3rd follow-up measurements, respectively. We conclude that under usual physician care, total cholesterol, triglyceride, and LDL-cholesterol concentrations decreased progressively with increased physician monitoring within a large patient population.

1. Introduction

The Third National Cholesterol Education Program (NCEP-III) was defined in term of specific lipid and lipoprotein target values (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). To that end, it proposed that "Lipoprotein profiles should be assessed at least annually, and preferably at each clinic visit to promote compliance." In 2013, new American College of Cardiology and the American Heart Association (ACC/AHA) guidelines for primary prevention moved away from a "treat to target" to a "treat to risk" approach for statin use (Stone et al., 2014). Specifically, moderate- or high-intensity statin therapy was prescribed for adults with clinical atherosclerotic cardiovascular disease (ASCVD), diabetes, low-density lipoprotein (LDL)-cholesterol ≥70 mg/dL or an estimated 10-year ASCVD risk ≥7.5% depending upon other factors (Stone et al., 2014).

The question arises as to the value of follow-up cholesterol testing under the revised recommendations if the prescription is to administer the highest tolerated statin dose regardless of response. The 2013 ACC/AHA Guidelines and their 2018 update both state that testing remains an important indicator of treatment success (Stone et al., 2014; Grundy et al., 2018). They provide considerable latitude in the frequency of

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; LDL, low density lipoproteins; NCEP-III, Third National Cholesterol Education Program; PRODIGY, Prescribing Rationally with Decision Support in General Practice Study; USPSTF, United States Preventive Services Task Force

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follow-up lipoprotein testing, i.e. four to twelve weeks after initiation of statin therapy to determine patient's adherence, and every 3 to 12 months thereafter as clinically indicated. Similarly, the task force for the management of dyslipidaemias of the European Society of Cardiology and European Atherosclerosis Society recommends testing every 8 (± 4) weeks after adjustment of treatment until within target lipid range, and annually thereafter (Catapano et al., 2016). Others have argued that repeated testing to "treat to target" is clinically inefficient and that routine annual testing raises health care costs, laboratory burden and false positive results (Takahashi et al., 2010; Glasziou et al., 2008). Cholesterol testing once every three to five years has been advocated for compliant patients who have reached their targeted goals (Glasziou et al., 2008). Morgen et al. estimated that 10.5% of repeated cholesterol tests near Calgary were inappropriate (Morgen and Naugler, 2015). Doll et al. proposed that 42% to 79% of cholesterol tests performed in the Oxfordshire region of the UK between 2005 and 2007 were potentially unnecessary (Doll et al., 2011). Virani et al. estimated that one-third of coronary heart disease patients with LDL-cholesterol levels at goal received unnecessary retests (Virani et al., 2013). Maddox et al. suggested that 20.8% of cardiology patients in the NCDR Pinnacle registry who received repeat LDL-cholesterol screening may no longer be needed given the shift away from the "treat to target LDL strategy" (Maddox et al., 2014). Moreover, they suggest that cost saving from reduced testing might partially offset the cost of greater statin use under the new guidelines (Maddox et al., 2014). "Annual lipid screening for patients not receiving lipid lowering drugs or diet therapy in the absence of reasons of changing lipid profiles" were deemed by an American College of Physicians' workshop as not providing high value care (Qaseem et al., 2012).

Adherence to medications has been shown to improve with follow-up visits (Sewitch et al., 2003; DiMatteo et al., 1993). Although several studies show that more frequent monitoring improves statin compliance (Sewitch et al., 2003; DiMatteo et al., 1993; Benner et al., 2004; Brookhart et al., 2007), to our knowledge none show lipoprotein improvements per se. We therefore examine whether, under usual physician care, lipoproteins improve with greater monitoring as measured by the number of follow-up tests in 97,548 men and 110,424 women whose physicians sent blood to a national clinical laboratory for analysis.

2. Methods

Epidemiological analyses of large clinical laboratory datasets have been previously used to study the effects of health policy (Kaufman et al., 2015), environmental impact (McClure et al., 2016), temporal trends (Kaufman et al., 2013; Kroll et al., 2015), and the associations of other blood components (Quispe et al., 2015; Ponda et al., 2012; Elshazly et al., 2015) on health biomarkers. The current paper uses this approach to examine the anonymized total cholesterol, triglyceride, and LDL-cholesterol measurements of 207,972 patients whose physicians sent blood to a clinical laboratory (Boston Heart Diagnostics, Framingham, MA) for analysis between 2010 and 2017. Total cholesterol, triglycerides, and direct LDL-cholesterol assays were run at the time of collection in the College of American Pathologist (CAP) and Clinical Laboratory Improvement Amendments (CLIA) accredited laboratory using Cobas C-501 autoanalyzers and standardized enzymatic methods (Roche Diagnostics, Mannheim/Germany) (Schaefer et al., 2000). Results are presented in conventional units (mg/dL), which may be convert to SI units (mmol/L) by multiplying total cholesterol and LDL-cholesterol by 0.0259 and triglycerides by 0.0113.

2.1. Statistics

Mean changes are presented with their standard error (± SE) or standard deviations (SD) with significance determined by paired *t*-test (JMP version 13.2. SAS Institute, Cary, NC). Regression analysis was used to estimate the reduction in cholesterol and triglycerides by the number of follow-up visits when adjusted for baseline age and the duration of follow-up. Analysis of covariance was used to estimate the effects of the number of follow-up visits by categories (1, 2, 3, 4, 5, ≥6) when adjusted. We excluded the possibility of our results being explained by a greater cholesterol and triglyceride response in patients with lower baseline values (observed) by showing that a lower average of the baseline and the follow-up measurement was associated with a smaller cholesterol reduction (i.e., contrary to lower baseline value predicting a greater cholesterol reduction as observed, Oldham's method (Oldham, 1962)).

We also tested whether patients initially diagnosed as having high total cholesterol (≥240 mg/dL), high to very high triglycerides (≥200 mg/dL), and high to very high LDL-cholesterol (≥160 mg/dL) improved with more frequent monitoring when adjusted for regression to the mean. Regression to the mean was estimated by randomly permuting the measurements over all visits within each individual and then calculating the percent of the sample moving out of the high risk category by chance. This process was repeated ten times to estimate the expected mean reduction due to regression to the mean and the standard error associated with the estimate. The percent reduction in the original data minus the percent reduction in the average of the permuted samples was used to estimate the percent reduction corrected for regression to the mean.

All analyses were performed on anonymized data collected in a large clinical laboratory and are exempt from human subjects. Prior reports from this dataset have examined national trends in LDL-cholesterol between 2012 and 2017 (Superko et al., in press), and HDL-subclass concentrations in response to body weight change (Dansinger et al., 2018).

3. Results

Tables 1 and 2 show that men had lower baseline total and LDL cholesterol than women, but higher triglycerides. There were 207,972 patients followed-up for total cholesterol, 207,849 for triglycerides, and 195,852 for LDL-cholesterol. Those with follow-up measurements were older at baseline than those without (men: 60.2 ± 0.02 vs. 54.4 ± 0.03 years old, women: 60.8 ± 0.02 vs. 53.9 ± 0.03 years old), and there was a trend for the number of follow-up measurements to increase with baseline age. In addition, baseline total cholesterol and LDL-cholesterol were lower in those with follow-up. Men's baseline total cholesterol, triglycerides and LDL-cholesterol decreased with the number of follow-up measurements, as did women's baseline total and LDL-cholesterol.

3.1. Total cholesterol

Tables 1 and 2 show statistically significant decreases in total cholesterol from baseline to each follow-up visit, with the cumulative decrease becoming progressively greater through at least the seventh follow-up. The greatest cholesterol decrease occurred between baseline and the first follow-up visit, penultimate decrease between the first and second follow-up, and significant but still smaller decrease between 2nd and 3rd follow-up visit. Both men and women achieved approximately a 17-mg/dL cumulative cholesterol reduction by the 6th follow-up.

Regression analysis showed that the cholesterol reduction between the first and last measurement was strongly related to the number of follow-ups, decreasing an average of 2.84 ± 0.10 mg/dL per follow-up in men, and 3.03 ± 0.10 mg/dL in women ($P < 10^{-16}$), when adjusted for baseline age and the time interval between the first and last measurement (analyses not displayed). Nearly identical results were obtained with or without adjustment for age, suggesting that the higher baseline age of the more-frequently followed patients does not explain the association. In addition, the average of the baseline and follow-up total cholesterol measurements predicted slightly greater total

Table 1
Analysis of lipid and lipoprotein concentrations by follow-up measurement in men.

Visit	Sample, N	Baseline age, years.	Δ years since baseline	Baseline	Follow-up	Change from baseline
Total cholesterol (mg/dL)						
Baseline	313,065	55.7 (14.6)		184.9 ± 0.1		
1st followup	97,548	59.2 (13.6)	0.8 (0.6)	182.0 ± 0.1	172.7 ± 0.1	−9.4 ± 0.1§
2nd "	44,719	61.2 (13.0)	1.3 (0.8)	179.1 ± 0.2	167.2 ± 0.2	−11.9 ± 0.2§
3rd "	23,205	62.5 (12.6)	1.8 (0.8)	176.8 ± 0.3	163.2 ± 0.3	−13.7 ± 0.3§
4th "	12,794	63.8 (12.3)	2.1 (0.9)	174.9 ± 0.4	160.0 ± 0.4	−14.9 ± 0.4§
5th "	7227	65.0 (11.9)	2.5 (0.9)	173.4 ± 0.5	157.2 ± 0.5	−16.2 ± 0.5§
6th "	4416	66.1 (11.5)	2.9 (0.9)	171.7 ± 0.7	154.5 ± 0.6	−17.3 ± 0.7§
7th "	2814	67.0 (11.4)	3.2 (1.0)	170.2 ± 0.8	153.0 ± 0.7	−17.2 ± 0.8§
8th "	1693	68.2 (11.0)	3.5 (0.9)	168.6 ± 1.1	151.6 ± 0.9	−17.0 ± 1.0§
9th "	1050	69.9 (10.4)	3.8 (1.0)	168.1 ± 1.4	150.6 ± 1.2	−17.5 ± 1.4§
Triglycerides (mg/dL)						
Baseline	311,609	55.7 (14.6)		149.0 ± 0.2		
1st followup	97,415	59.2 (13.5)	0.8 (0.6)	149.5 ± 0.4	139.2 ± 0.4	−10.3 ± 0.4§
2nd "	44,797	61.3 (12.9)	1.3 (0.8)	148.9 ± 0.6	136.1 ± 0.5	−12.8 ± 0.5§
3rd "	23,307	62.7 (12.6)	1.7 (0.8)	147.2 ± 0.8	133.9 ± 0.7	−13.4 ± 0.7§
4th "	12,820	64.0 (12.2)	2.2 (0.9)	146.9 ± 1.2	131.2 ± 0.9	−15.8 ± 1.0§
5th "	7199	65.2 (11.9)	2.5 (0.9)	145.3 ± 1.6	129.4 ± 1.2	−15.9 ± 1.4§
6th "	4338	66.1 (11.5)	2.9 (0.9)	145.6 ± 2.0	129.1 ± 1.7	−16.5 ± 2.0§
7th "	2765	67.1 (11.3)	3.2 (1.0)	143.0 ± 2.5	124.0 ± 1.7	−19 ± 2.4.0§
8th "	1664	68.1 (11.0)	3.5 (0.9)	138.8 ± 2.4	125.6 ± 2.2	−13.2 ± 2. §2
9th "	1024	69.8 (10.3)	3.8 (1.0)	136.5 ± 3.1	122.1 ± 2.5	−14.4 ± 2.9§
LDL-cholesterol (mg/dL)						
Baseline	299,302	55.6 (14.6)		115.6 ± 0.1		
1st followup	91,963	59.2 (13.5)	0.8 (0.6)	112.4 ± 0.1	104.6 ± 0.1	−7.8 ± 0.1§
2nd "	41,594	61.2 (13.0)	1.3 (0.7)	109.4 ± 0.2	99.5 ± 0.2	−9.9 ± 0.2§
3rd "	21,537	62.7 (12.6)	1.7 (0.8)	107.0 ± 0.3	95.9 ± 0.2	−11.1 ± 0.2§
4th "	11,838	64.0 (12.3)	2.1 (0.9)	105.0 ± 0.4	93.2 ± 0.3	−11.7 ± 0.3§
5th "	6595	65.2 (11.8)	2.5 (0.9)	103.4 ± 0.5	91.1 ± 0.4	−12.4 ± 0.5§
6th "	3955	66.1 (11.5)	2.9 (0.9)	101.6 ± 0.6	88.7 ± 0.6	−12.9 ± 0.6§
7th "	2457	66.9 (11.4)	3.2 (1.0)	100.5 ± 0.8	87.9 ± 0.7	−12.6 ± 0.8§
8th "	1445	67.9 (11.0)	3.6 (0.9)	99.2 ± 1.0	86.7 ± 0.9	−12.5 ± 1.0§
9th "	861	69.4 (10.4)	3.9 (1.0)	97.7 ± 1.3	85.7 ± 1.2	−12.0 ± 1.3§

Results are presented as means (standard deviation) and mean ± SE. Significance levels are coded: *P < 0.0001; †P < 10^{-5}; ‡P < 10^{-10}; and §P < 10^{-16}.

cholesterol reductions at each visit (analysis not displayed), showing that declining baseline cholesterol levels with increasing follow-ups would not explain the highly significant (P < 10^{-16}) association between the cholesterol decrease and the number of cholesterol tests ordered.

Fig. 1 displays the improvement between the first and last cholesterol measurement per incremental increase in follow-up measurements when adjusted for baseline age and total follow-up duration by an analysis of covariance. In men, total cholesterol decreased 4.6 ± 0.3 mg/dL by going from 1 to 2 follow-up measurements (P = 10^{-42}), an additional 4.0 ± 0.5 mg/dL decrease going from 2 to 3 follow-ups (P = 5×10^{-17}), 2.1 ± 0.7 mg/dL additional decrease going from 3 to 4 (P = 0.001), 2.5 ± 0.9 mg/dL additional decrease going from 4 to 5 (P = 0.006), and an additional 4.8 mg/dL decrease in going 5 to ≥6 follow-up measurements (P = 8.0×10^{-7}). In women, the corresponding incremental improvements were 4.4 ± 0.3 (P = 5×10^{-45}), 3.3 ± 0.5 (P = 10^{-13}), 3.2 ± 0.6 (P = 6×10^{-7}), 2.8 ± 0.9 mg/dL (P = 0.001), and 5.0 mg/dL (P = 4.6×10^{-8}).

Table 3 shows that for the 10,110 men that had high cholesterol at baseline, 6.3% were no longer high at the first follow-up, 9.6% at the second follow-up, and 11.7% at the third follow-up. Similar improvements were seen in 20,006 high-cholesterol women.

3.2. Triglycerides

Significant reductions in triglyceride concentrations from baseline were observed at all follow-up visits (Tables 1 and 2). For the sample as a whole, the average triglyceride reductions in men were greater than those achieved in women. Regression analyses showed the average triglyceride concentrations declined 3.78 ± 0.30 mg/dL per follow-up in men and 2.26 ± 0.19 mg/dL per follow-up in women when adjusted for baseline age and total follow-up duration (P < 10^{-16}, analyses not displayed). As in the case of total cholesterol, the average of the baseline and follow-up total triglyceride measurements predicted slightly greater triglyceride reductions at each visit (analysis not displayed), showing that the lower baseline triglycerides in those with more follow-up measurements would not explain their greater triglyceride reduction. The analysis of covariance of Fig. 1 shows the triglyceride difference between the first and last measurement increased incrementally with number of follow-up visits.

The follow-up included 18,422 men and 14,677 women with high or very high triglycerides (≥200 mg/dL). Among those initially classified as high to very high triglycerides, 11.1 ± 1.5% of men and 10.7 ± 1.6% of women were reduced to borderline or optimal triglycerides by the 5th visit.

3.3. LDL-cholesterol

LDL–cholesterol significantly decreased relative to baseline at all follow-up visits in both men and women (Tables 1 and 2). The declines were similar between the sexes through the 6th follow-up visit. As with total cholesterol, the decreases were greatest initially and continued to increase by smaller increments thereafter. Regression analyses showed the average total cumulative LDL-cholesterol reduction was 2.54 ± 0.09 mg/dL greater per follow-up in men, and 3.06 ± 0.09 mg/dL per follow-up in women, when adjusted for baseline age and follow-up duration. The decrease in LDL-cholesterol with increased monitoring would not be attributable to baseline age or baseline LDL-cholesterol for the reasons previously described.

Fig. 1 shows that each incremental increase in the number of follow-up measurements was associated with a significant mg/dL addition to the total cumulative reduction in LDL-cholesterol cholesterol: in men

Table 2
Analysis of lipid and lipoprotein concentrations by follow-up measurement in women.

Visit	Sample, N	Baseline age, years	Δ years since baseline	Baseline	Follow-up	Change from baseline
Total cholesterol (mg/dL)						
Baseline	383,074	55.4 (15.0)		200.8 ± 0.1		
1st followup	110,424	59.8 (13.9)	0.8 (0.6)	201.0 ± 0.1	192.9 ± 0.1	−8.0 ± 0.1§
2nd "	49,379	62.1 (13.1)	1.3 (0.8)	199.8 ± 0.2	189.4 ± 0.2	−10.5 ± 0.2§
3rd "	24,990	63.6 (12.5)	1.8 (0.8)	198.0 ± 0.3	185.4 ± 0.3	−12.6 ± 0.3§
4th "	13,581	64.9 (12.0)	2.1 (0.8)	196.9 ± 0.4	182.7 ± 0.4	−14.2 ± 0.4§
5th "	7736	66.0 (11.6)	2.5 (0.9)	195.7 ± 0.5	180.2 ± 0.5	−15.5 ± 0.5§
6th "	4722	67.0 (11.4)	2.8 (0.9)	194.6 ± 0.7	178.0 ± 0.6	−16.6 ± 0.6§
7th "	2957	67.8 (11.3)	3.2 (0.9)	192.8 ± 0.8	175.3 ± 0.8	−17.5 ± 0.8§
8th "	1878	69.1 (11.1)	3.5 (0.9)	192.9 ± 1.0	173.6 ± 1.0	−19.3 ± 1.0§
9th "	1061	70.5 (10.7)	3.7 (0.9)	192.4 ± 1.4	174.3 ± 1.3	−18.2 ± 1.4§
Triglycerides (mg/dL)						
Baseline	382,182	55.4 (15.1)		125.3 ± 0.1		
1st followup	110,434	59.7 (13.9)	0.8 (0.6)	130.1 ± 0.3	123.7 ± 0.3	−6.4 ± 0.2§
2nd "	49,384	62.2 (13.1)	1.3 (0.8)	132.4 ± 0.4	123.7 ± 0.4	−8.8 ± 0.4§
3rd "	25,062	63.7 (12.6)	1.7 (0.8)	133.3 ± 0.6	123.2 ± 0.5	−10.1 ± 0.5§
4th "	13,540	65.0 (12.1)	2.1 (0.8)	133.1 ± 0.8	122.4 ± 0.7	−10.7 ± 0.7§
5th "	7638	66.2 (11.6)	2.5 (0.9)	132.8 ± 1.0	120.5 ± 0.9	−12.4 ± 0.8§
6th "	4625	67.1 (11.4)	2.8 (0.9)	131.7 ± 1.2	119.7 ± 1.4	−12.0 ± 1.1§
7th "	2904	67.9 (11.3)	3.2 (0.9)	132.1 ± 1.5	119.3 ± 1.5	−12.8 ± 1.3§
8th "	1810	69.1 (11.1)	3.5 (0.9)	132.0 ± 1.8	119.7 ± 1.8	−12.4 ± 1.6§
9th "	1040	70.5 (10.7)	3.7 (0.9)	134.3 ± 2.4	121.8 ± 2.6	−12.5 ± 2.2§
LDL-cholesterol (mg/dL)						
Baseline	366,578	55.3 (15.0)		121.2 ± 0.1		
1st followup	103,889	59.7 (13.9)	0.8 (0.6)	120.7 ± 0.1	113.8 ± 0.1	−6.9 ± 0.1§
2nd "	45,853	62.1 (13.1)	1.3 (0.7)	119.3 ± 0.2	110.3 ± 0.2	−9.0 ± 0.2§
3rd "	23,121	63.6 (12.6)	1.7 (0.8)	117.2 ± 0.3	106.5 ± 0.3	−10.7 ± 0.2§
4th "	12,553	65.0 (12.1)	2.1 (0.8)	115.7 ± 0.4	104.0 ± 0.3	−11.8 ± 0.3§
5th "	7094	66.1 (11.7)	2.5 (0.9)	114.4 ± 0.5	101.5 ± 0.5	−12.9 ± 0.5§
6th "	4267	66.9 (11.5)	2.8 (0.9)	113.3 ± 0.6	99.8 ± 0.6	−13.5 ± 0.6§
7th "	2620	67.6 (11.5)	3.2 (0.9)	111.7 ± 0.8	97.4 ± 0.8	−14.3 ± 0.7§
8th "	1605	68.8 (11.2)	3.5 (0.9)	111.8 ± 1.0	96.1 ± 1.0	−15.7 ± 1.0§
9th "	869	70.0 (11.0)	3.8 (0.9)	112.4 ± 1.4	97.0 ± 1.3	−15.4 ± 1.4§

Results are presented as means (standard deviation) and mean ± SE. Significance levels are coded: *P < 0.0001; †P < 10^{-5}; ‡P < 10^{-10}; §P < 10^{-16}.

4.2 ± 0.3 in going from 1 to 2 (P = 8×10^{-45}), 3.8 ± 0.4 in going from 2 to 3 (P = 5×10^{-19}), 1.5 ± 0.6 in going from 3 to 4 (P = 0.009), 2.2 ± 0.8 in going from 4 to 5 (P = 0.006), and 3.7 ± 0.9 mg/dL in going 5 to ≥6 follow-up measurements (P = 1.6×10^{-5}). In women, the corresponding declines were 4.5 ± 0.3 (P = 9×10^{-54}), 3.5 ± 0.4 (P = 7.0×10^{-17}), 2.7 ± 0.6 (P = 6.1×10^{-6}), 2.9 ± 0.8 (P = 0.0005), and 5.0 ± 0.9 mg/dL (P = 7.1×10^{-9}).

At baseline, 11,292 men and 16,504 women had high to very high LDL-cholesterol. Under usual physician care, by the 6th follow-up visit the proportion of men and women with high or very high LDL declined by 15.1% and 16.4%, respectively (Table 3).

4. Discussion

We found that under usual physician care, total cholesterol, triglyceride, and LDL-cholesterol concentrations decreased progressively with increased physician monitoring within a large patient population. Progressive improvements were modest (i.e. around −12 mg/dL for LDL-cholesterol), potentially corresponding to relative risk reductions in ASCVD events of approximately 10% (Silverman et al., 2016), however the principle of persistent clinician monitoring to identify patients with suboptimal control may be important on a population or practice level (Stone et al., 2014; Baigent et al., 2005; Lancet, 1994; Phatak et al., 2008; Primatesta and Poulter, 2000; Slejko et al., 2014). Statins substantially reduce LDL-cholesterol, with moderate-intensity statin therapy producing 30% to 50% LDL-cholesterol lowering and intense therapy producing ≥50% lowering (Stone et al., 2014). Statins reduce myocardial risk by about 30% and significantly reduce ASCVD mortality (Baigent et al., 2005; Lancet, 1994). The challenge is getting patients to adopt lifelong strategies for controlling LDL-cholesterol.

Many patients prescribed statins fail to achieve their treatment goals (Phatak et al., 2008; Primatesta and Poulter, 2000). Despite being well tolerated, adherence to statin medications tends to decline over time (Slejko et al., 2014). Approximately 15% of patients fail to fill new statin prescriptions (Gadkari and McHorney, 2010), and only about one-half of statin-prescribed patients remain on statins after one year (Jackevicius et al., 2002; Ho et al., 2006; Hudson et al., 2007). Pittman et al. reported that about one-third of non-elderly adults took < 80% of their prescribed statin dosage during one-year follow-up (Pittman et al., 2011). In patients 65 years and older, Benner et al. estimated non-adherence was 29% after six months, 38% after one year, 42% after two years, and 56% after five years (Benner et al., 2005). Non-adherent patients blamed inconvenience, lifestyle preferences, and uncertainty regarding statin risks vs. benefits (Vicki et al., 2010). Noncompliance is probably substantially greater than indicated by the clinical trial data (Lemstra et al., 2012).

Prior studies have largely focused on the effects of testing or physician visits on cholesterol lowering behavior rather than improved cholesterol concentrations per se. Benner et al. reported that patients were more likely to adhere to statin therapy when tested for cholesterol or meeting their physician within the first 3 months (Benner et al., 2004). Brookhart et al. reported on 129,167 out of 239,911 new Canadian statin users who were non-adherent over 90 days, of whom 48% restarted their medications within 1 year and 60% within two years (Brookhart et al., 2007). They reported that the odds for restarting medication were 6.1-fold greater for those who revisited the prescribing physician, 2.9-fold greater for visiting another physician, and 1.5-fold greater after receiving a cholesterol test. Moreover, they reported a synergistic effect between cholesterol testing and physician visit. Although, Doganer et al. did show that lipid goal attainment was associated with testing frequency in 271 family practice patients, they did

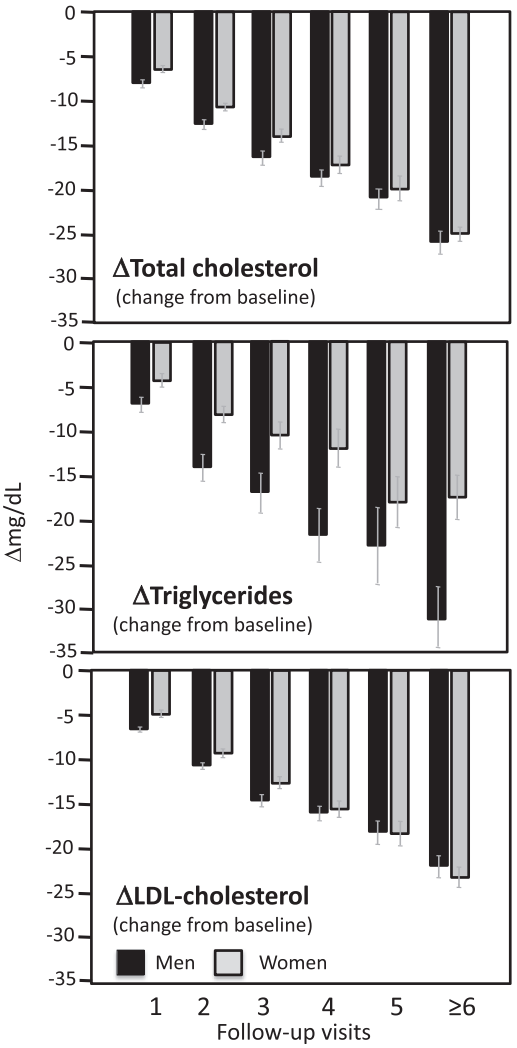

Fig. 1. Analysis of covariance of the mean total cholesterol, triglyceride, and LDL-cholesterol difference between baseline and the last laboratory measurement by the number of follow-up visits, adjusted for baseline age and the years of follow-up. Brackets represent 95% confidence intervals. Sample sizes are provided in Tables 1 and 2.

not report the lipoprotein changes (Doganer et al., 2015). Compared to patients with fewer tests, total cholesterol < 200 mg/dL was significantly higher at the last monitoring in patients tested greater than twice annually (90.9 vs. 65.7%) and greater than annually (75.2 vs. 62.2%), and LDL-cholesterol < 100 mg/dL was significantly higher at the last monitoring in patients tested greater than twice annually (72.7 vs. 50.2%), greater than annually (67.3 vs. 40.5%), and greater than biennially (57.3 vs. 37.7%). To the best of our knowledge, the current study is the only report on change in lipoprotein concentrations vs. follow-up testing in a large sample.

Multiple factors affect statin compliance (maintaining prescribed dosage) and persistence (continuous uninterrupted use). In those 65 years and older, meta-analyses show the odds for non-compliance are 66% higher in nonwhite minorities, 8% higher in women, 12% higher in smokers, 38% higher with a higher copayment, and 58% higher in new users. Moreover, the odds for discontinuing statin therapy is 20% higher for lower income, 14% higher for smoking, 61% higher with a higher copay, and 66% higher for primary prevention (Ofori-Asenso et al., 2018). Others report that the risk for a significant gap in statin use was 10% greater in women than men, 52% greater than older than younger patients, 10% greater for primary prevention, 44% greater for low-dose and 56% higher for standard dose vs. high dose statins, and 19% higher when there is no concurrent cardiovascular medications (Alfian et al., 2018). These are unfortunate statistics given that the most-statin-adherent patients have 32% less mortality, ischemic heart disease, stroke, or cardiovascular events than the least-adherent patients, and 22% fewer CVD events when compared with all other patients (Martin-Ruiz et al., 2018). Medical care costs, hospitalizations, and mortality all increase with poor statin adherence (Jackevicius et al., 2002; Ho et al., 2006; Rasmussen et al., 2007; Blackburn et al., 2005; Wei et al., 2002).

Under the 2013 ACC/AHA guidelines, the purpose of lipoprotein testing shifted from a treatment to target approach to one of monitoring compliance (Stone et al., 2014). The National Cholesterol Education Program NCEP-III guidelines recommend that patients be monitored every 4 to 6 months, or more frequently to assess response to treatment (Grundy et al., 2004). The United States Preventive Services Task Force (USPSTF) recommends regular screening every 5 years for men ≥ 35 and women ≥ 45, with more frequent screening for those close to levels requiring treatment (http://www.uspreventiveservicestaskforce.org/uspstf/uspschol.htm, n.d.). In the United Kingdom, the PRODIGY (Prescribing Rationally with Decision Support in General Practice Study) guideline recommends annual retesting (National Library for Health Clinical knowledge summaries, n.d.), whereas the Cardiac Society of Australia and New Zealand guidelines recommends testing every 6–12 months (Tonkin et al., 2005). The 2013 and 2018 ACC/AHA guidelines recommended repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed in order to assess adherence and response to medication and lifestyle changes (Stone et al., 2014; Grundy et al., 2018). Catapano et al. recommended every 8 weeks after adjustment of treatment until within target lipid range, and annually thereafter (Catapano et al., 2016). Takahashi et al. (2010) proposed three years as an optimal re-screening interval in stable Japanese patients not taking cholesterol-lowering drugs, but cautioned that changes in cardiovascular risk factors, lifestyle, and drug treatment should be considered. Glasziou et al. (2008) estimated that re-testing every three to five years was needed in patients who achieved their target goals for the number of true positives to exceed the number of false positives.

We could not attribute the association to the two factors that were most strongly associated with the number of follow-up visits: baseline age and the baseline lipid and lipoprotein concentrations. The analysis of covariance and the regression analysis were both significant when adjusted for baseline age. Moreover, the adjustment had only a very minor influence on the estimated effects of the number of visits. The lower baseline levels in those with more follow-up visits are contrary to the notion of more frequent testing in those initiating statin treatment (expected to have higher baseline) vs. those not initiating statin therapy, and the association between higher cholesterol and more frequent testing reported by others (Phatak et al., 2008).

4.1. Caveats and limitations

Our analyses do not explain how more-frequent testing lowers LDL-cholesterol. We had no direct measurement of the providers' health care priorities, their aggressiveness in treating high cholesterol, or their willingness to prescribe intensive statin therapy on the basis of risk. Physicians ordering more tests may have placed a higher priority on treating patients' cholesterol levels and more aggressively treated the condition, and may have been more likely to adopt the more-aggressive 2013 ACC/AHA guidelines. Clinical trials and wellness programs both provide greater patient oversight than the general patient population. This may explain the greater adherence to statin therapy after one year in clinical trials (90.3%) vis-à-vis in observational studies (49%) (Lemstra et al., 2012), and in diabetics who participate in comprehensive wellness assessment programs vis-à-vis those who did not (Guerard et al., 2018).

External circumstances may have contributed an association

Table 3
Net percent reduction in high total cholesterol, triglycerides and LDL-cholesterol concentrations by follow-up measurement after eliminating the regression-to-the-mean.

Visits	Males			Females		
	Sample (N)	% improved*	Significance	Sample (N)	% improved*	Significance
High total cholesterol (≥240 mg/dL)						
1st followup	10,110	−6.3 ± 0.5	$< 10^{-16}$	20,006	−5.6 ± 0.4	$< 10^{-16}$
2nd "	4269	−9.6 ± 0.8	$< 10^{-16}$	8878	−9.5 ± 0.6	$< 10^{-16}$
3rd "	2065	−11.7 ± 1.1	$< 10^{-16}$	4331	−12.0 ± 0.8	$< 10^{-16}$
4th "	1041	−14.1 ± 1.4	$< 10^{-16}$	2287	−14.7 ± 1.1	$< 10^{-16}$
5th "	551	−14.6 ± 1.7	$< 10^{-16}$	1270	−13.1 ± 1.4	$< 10^{-16}$
6th "	301	−13.8 ± 2.4	9.6×10^{-9}	762	−15.3 ± 1.8	$< 10^{-16}$
7th "	176	−19.8 ± 2.7	9.2×10^{-14}	454	−15.5 ± 2.3	2.1×10^{-1}
8th "	99	−17.6 ± 4.1	1.8×10^{-5}	301	−14.8 ± 2.8	$8..6 \times 10^{-8}$
9th "	51	−23.2 ± 4.7	8.3×10^{-7}	168	−15.1 ± 3.9	0.0001
High to very high triglycerides (≥200 mg/dL)						
1st followup	18,422	−4 ± 0.4	$< 10^{-16}$	14,677	−3.4 ± 0.4	4.4×10^{-16}
2nd "	8313	−6.6 ± 0.6	$< 10^{-16}$	6762	−6.2 ± 0.6	$< 10^{-16}$
3rd "	4230	−7.6 ± 0.8	$< 10^{-16}$	3475	−7.6 ± 0.9	$< 10^{-16}$
4th "	2255	−9.1 ± 1.1	$< 10^{-16}$	1853	−7.9 ± 1.2	7.6×10^{-11}
5th "	1237	−11.1 ± 1.5	3.3×10^{-14}	1051	−10.7 ± 1.6	1.8×10^{-11}
6th "	735	−9.8 ± 1.9	3.0×10^{-7}	629	−11.4 ± 2.1	5.5×10^{-8}
7th "	441	−16.6 ± 2.4	4.4×10^{-12}	405	−9.9 ± 2.6	0.0002
8th "	262	−10.5 ± 3.1	0.0009	244	−15.8 ± 3.2	6.1×10^{-7}
9th "	140	−11.6 ± 4.2	0.006	145	−11.9 ± 4.2	0.005
High to very high LDL-cholesterol (≥160 mg/dL)						
1st followup	11,292	−6.9 ± 0.5	$< 10^{-16}$	16,504	−5.7 ± 0.4	$< 10^{-16}$
2nd "	4590	−9.9 ± 0.7	$< 10^{-16}$	7206	−9.7 ± 0.6	$< 10^{-16}$
3rd "	2188	−11.8 ± 1.1	$< 10^{-16}$	3488	−11.5 ± 0.8	$< 10^{-16}$
4th "	1096	−12.1 ± 1.3	$< 10^{-16}$	1802	−14.3 ± 1.2	$< 10^{-16}$
5th "	579	−14.7 ± 1.9	2.9×10^{-15}	979	−12.0 ± 1.5	4.9×10^{-15}
6th "	320	−15.1 ± 2.3	1.0×10^{-10}	585	−16.4 ± 2.0	2.2×10^{-16}
7th "	187	−14.9 ± 3.3	7.0×10^{-16}	350	−12.1 ± 2.6	3.4×10^{-6}
8th "	100	−13.8 ± 4.3	0.001	225	−10.8 ± 3.4	0.001
9th "	52	−23.0 ± 4.9	2.5×10^{-6}	124	−8.9 ± 4.6	0.05
Very high LDL-cholesterol (≥190 mg/dL)						
1st followup	3305	−4.5 ± 0.8	3.0×10^{-9}	5573	−5.0 ± 0.6	6.2×10^{-15}
2nd "	1351	−8.1 ± 1.2	1.3×10^{-11}	2452	−7.6 ± 0.9	8.9×10^{-16}
3rd "	643	−9.1 ± 1.7	1.1×10^{-7}	1189	−10.4 ± 1.3	2.7×10^{-15}
4th "	329	−11.5 ± 2.3	6.4×10^{-7}	627	−10.6 ± 1.8	2.5×10^{-9}
5th "	166	−14.1 ± 2.8	4.7×10^{-7}	343	−8.4 ± 2.4	0.0005
6th "	91	−8.3 ± 3.9	0.03	207	−17.0 ± 3.0	2.4×10^{-8}
7th "	51	−13.5 ± 4.9	0.006	118	−15.8 ± 4.1	0.0001
8th "	31	−17.8 ± 7.8	0.02	73	−9.0 ± 5.4	0.10

The percent reduction in the percent in the high lipid category adjusted for regression to the mean (see Supplementary Tables 1–3).

between testing and improved adherence to treatment. For example, hospitalization for acute myocardial infarction is reported to change over one-third of patients non-adherent to statin therapy to adherent statin users (Kronish et al., 2016). An increase in testing following an acute myocardial infarction could arise from cholesterol lowering due to greater adherence in myocardial infarction survivors.

Most importantly, we had no data on which lipid-lowering drugs the patients received, the doses prescribed, changes in the doses during the study, and if or when the patients discontinued medications.

4.2. Conclusions

Numerous studies have shown that nonadherence substantially attenuates the population-level benefits of statin therapy (Gadkari and McHorney, 2010; Jackevicius et al., 2002; Ho et al., 2006; Hudson et al., 2007; Pittman et al., 2011). Although we cannot exclude the possibility that patients who are more successful at controlling LDL-cholesterol self-select for more frequent follow-up, our results are consistent with the more tenable hypothesis that under usual physician care, improvements in lipids and lipoproteins are in accordance with the level of physician monitoring. The lipid improvements associated with greater follow-up testing needs to be considered before characterizing repeat cholesterol testing as overuse.

Competing interest statement

Michael Dansinger, Paul Williams, H Robert Superko, and Ernst J. Schaefer all receive financial support as employees or consultants for Boston Heart Diagnostics, Inc., which could benefit financially from cholesterol testing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2019.02.003.

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