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Optimizing Statin Treatment for Primary Prevention of Coronary Artery Disease

Rodney A. Hayward, MD; Harlan M. Krumholz, MD; Donna M. Zulman, MD; Justin W. Timbie, PhD; and Sandeep Vijan, MD, MSc

Background: Although treating to lipid targets ("treat to target") is widely recommended for coronary artery disease (CAD) prevention, some have advocated administering fixed doses of statins based on a person's estimated net benefit ("tailored treatment").

Objective: To examine how a tailored treatment approach to statin therapy compares with a treat-to-target approach.

Design: Simulated model of population-level effects of treat-to-target and tailored treatment approaches to statin therapy.

Data Sources: Statin trials from 1994 to 2009 and nationally representative CAD risk factor data.

Target Population: U.S. persons aged 30 to 75 years with no history of myocardial infarction.

Time Horizon: Lifetime effects of 5 years of treatment.

Perspective: Societal and patient.

Intervention: Tailored treatment based on a person's 5-year CAD risk (simvastatin, 40 mg, for 5% to 15% CAD risk and atorvastatin, 40 mg, for CAD risk >15%) versus treat-to-target approaches that escalate statin dose per National Cholesterol Education Program [NCEP] III guidelines (including an intensive approach that advances treatment whenever intensification is optional by NCEP III criteria).

Outcome Measures: Quality-adjusted life-years (QALYs).

Results of Base-Case Analysis: Compared with the standard NCEP III approach, the intensive NCEP III approach treated 15 million more persons and saved 570 000 more QALYs over 5 years. The tailored strategy treated a similar number of persons, as did the intensive NCEP III approach, but saved 500 000 more QALYs and treated fewer persons with high-dose statins.

Results of Sensitivity Analysis: No circumstances were found in which a treat-to-target approach was preferable to tailored treatment.

Limitation: Model assumptions were based on available clinical data, which included few persons 75 years or older.

Conclusion: A tailored treatment strategy prevents more CAD events while treating fewer persons with high-dose statins than low-density lipoprotein cholesterol–based target approaches. Results were robust, even with assumptions favoring a treat-to-target approach.

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For author affiliations, see end of text.

Statins are one of the most effective treatments in medicine. However, several controversies remain about their use, including whether low-density lipoprotein (LDL) cholesterol reduction is their sole mechanism of action and which patients should be treated and at what doses (1–11). The most widely recommended approach to statin therapy is an LDL cholesterol–based, "treat-to-target" strategy, in which lipid-modifying medications are titrated to achieve specific LDL cholesterol levels. This strategy is the basis of the NCEP (National Cholesterol Education Program) III guidelines (6).

Many have questioned the merits of treat-to-target approaches. Shepherd (12) cited concerns with diminishing returns and greater complexity, costs, and potential adverse effects and proposed a "fire-and-forget" approach, which suggested that prescribing a low- to moderate-dose statin for most persons at risk for coronary artery disease (CAD) may be a better public health strategy than treatment based on LDL cholesterol target levels. Tailored treatment advocates have gone further, proposing that treat-to-target strategies are inherently flawed (13–16) and that even highly influential and modifiable risk factors (such as LDL cholesterol levels and blood pressure) should not be considered in isolation but rather in conjunction with all known predictors of a patient's expected net absolute benefit from treatment. Fundamentally, this approach is an attempt to practice personalized medicine by estimating 3 factors: risk for adverse outcomes without treatment (using a prediction tool), expected relative risk reduction with treatment (based on data from randomized, controlled trials), and potential treatment disutility (based on treatment risks, side effects, and inconvenience) (15–17).

Rind and Hayward (17) proposed a simple "tailored treatment" approach for statin therapy, in which a patient's overall CAD risk is calculated (by using the best available multivariable tool for risk prediction) and then either a moderate dose–potency statin therapy (for patients with moderate to high CAD risk) or a high dose–potency statin therapy (for patients with very high CAD risk) is recom-

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Context

Experts debate different approaches for using statins to lower coronary artery disease (CAD) risk.

Contribution

This population-level simulation compared giving fixed doses of statins based on a person's 5-year CAD risk ("tailored treatment") with approaches that use increasing statin doses to achieve particular lipid level targets. Compared with an intensive "treat-to-target" approach, the tailored fixed-dose strategy saved more quality-adjusted life-years and treated fewer persons with high-dose statin therapy.

Implication

Tying statin treatment to a person's CAD risk and potential absolute net benefit may be better than approaches that focus primarily on achieving certain lipid level targets.

—The Editors

mended (17). Unlike Shepherd's (12) fire-and-forget approach, which uses the same fixed dose for all patients, this approach tailors treatment to a patient's overall risk–benefit profile (17).

In this study, we examined how a simple tailored treatment strategy compares with a treat-to-target strategy based on NCEP III treatment recommendations. We used circumstances highly favorable to a treat-to-target strategy. We assumed that LDL cholesterol reduction is a statin's sole mechanism of action and that change in total LDL cholesterol is a perfect indicator of the amount of risk reduction that a patient receives from a statin, thereby conceding the 2 most important assumptions underlying the treat-to-target approach (5, 6). We realize that the first assumption is controversial (5, 18–20) and that the second assumption is untrue (LDL cholesterol determinations have substantial measurement error) (21), but these assumptions allow us to test the hypothesis that tailored treatment is an inherently superior strategy, even under circumstances most favorable for a treat-to-target strategy.

METHODS

Population Data

To estimate the distribution of CAD risk factors in the U.S. population, we used data from NHANES (National Health and Nutrition Examination Survey), which is based on interviews, physical examinations, and diagnostic testing in a nationally representative probability sample of the U.S. population. We chose NHANES III (conducted from 1988 to 1994) because this sample represents a relatively untreated distribution of lipid values (22). Although lipid therapies were used during this era, they are unlikely to have substantially affected the lipid levels of the overall population because of their less widespread use, low adherence rates, and low potency compared with statins (23).

Study Population

We restricted our analyses to persons aged 30 to 75 years with no history of a heart attack because clinical trial data are limited for persons 75 years or older. We augmented data from the 4503 eligible participants in NHANES by using the imputation method of chained equations (24) to create a simulated population of 1 million. The simulated and NHANES populations had similar means and distributions of key variables, and we used sampling weights to make the results representative of the U.S. population.

Risk for CAD Events and Death

We estimated each person's untreated risk for fatal and nonfatal CAD events by using sex-specific Weibull regression models based on the Framingham Cohort Study (25).

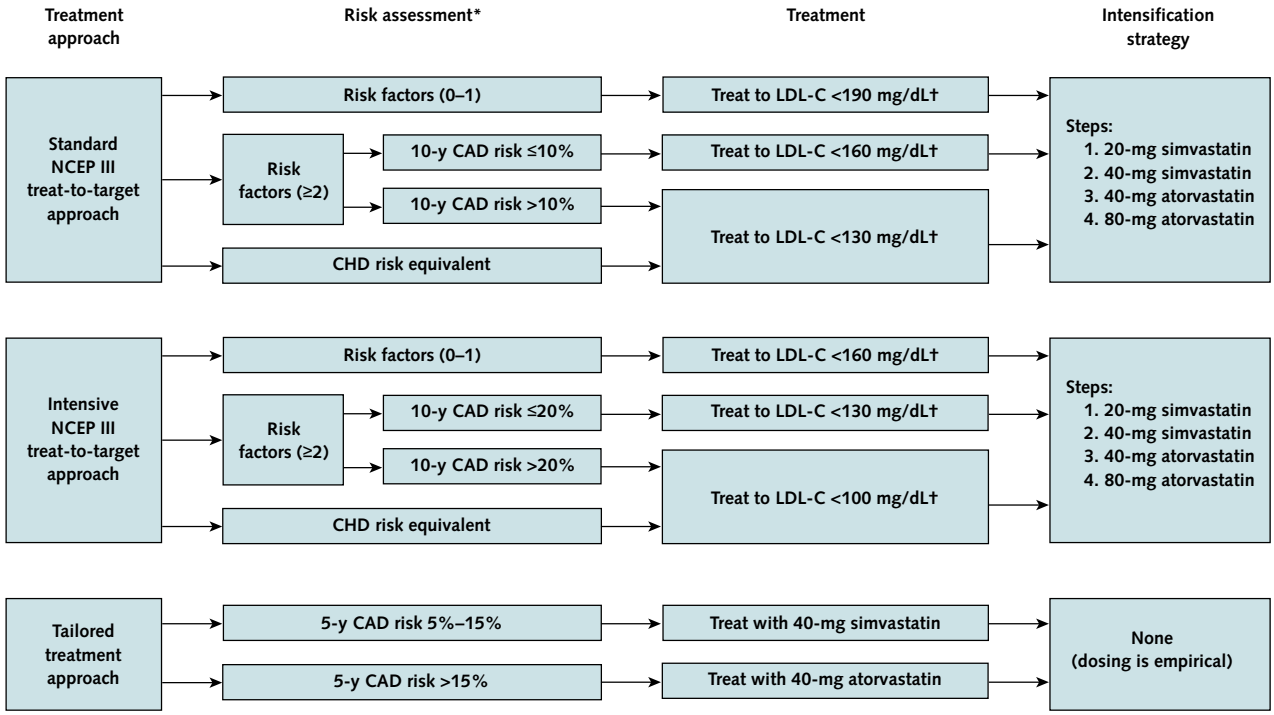
The Treat-to-Target and Tailored Treatment Strategies

We examined benefits achieved by using a 5-year treatment period and assumed that most patients would be reevaluated for CAD risk and changes in medical intervention at least every 3 to 5 years. A 10-year treatment period was evaluated in sensitivity analysis 8 (**Appendix Table 1**, available at www.annals.org). Because adding other lipid treatments to statin therapy has not been demonstrated to reduce CAD events, we limited our analysis to the use of statins.

The treat-to-target strategy was based on NCEP III guidelines (11). These guidelines include instances in which medication intensification is "optional" (such as when a person with 0 to 1 CAD risk factor has an LDL cholesterol level between 4.14 and 4.92 mmol/L [160 and 190 mg/dL]), so we examined 2 treat-to-target strategies: an intensive approach, in which statin therapy was always intensified when NCEP III listed intensification as optional, and a standard approach, in which statin therapy was not intensified when optional (**Figure 1**). We also evaluated a LDL cholesterol target of less than 1.81 mmol/L (<70 mg/dL) on the basis of more recent proposals that persons with very high CAD risk should be treated to this goal (sensitivity analysis 2 [**Appendix Table 1**]) (6, 26).

In the tailored treatment approach, all patients with a 5% to 15% CAD risk over 5 years received a moderate-potency statin (simvastatin, 40 mg), and those with risk greater than 15% received a high-potency statin (atorvastatin, 40 mg). The tailored treatment strategy did not include any LDL cholesterol measures or statin dose adjustments. Because tailored treatment is based on a precise, and therefore continuous, estimate of net benefit (or harm), the exact placement of treatment cut-points is obviously more arbitrary than it is in most current guideline developments (which tend to rely on mean benefits of patient populations) (13–16). For this reason, tailored treatment guidelines better delineate legitimate "gray zones" when a person's expected benefit is modest, and in these

Figure 1. **The LDL-C–based treat-to-target and tailored treatment strategies.**



CAD = coronary artery disease; CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program.
* Based on risk factors and CAD.
† To convert mg/dL to mmol/L, multiply values by 0.0259.

instances, patient preferences should be the dominant factor influencing whether treatment is intensified (16). However, to facilitate comparisons with the NCEP III guidelines, we predefined cut-points in which the proposed treatment intensification would be expected to prevent 1 CAD event for every 50 persons treated for 5 years (**Appendix Table 1**). Section D of the **Appendix** (available at www.annals.org) shows the effect of considering different number-needed-to-treat thresholds for the tailored treatment strategy.

Baseline Assumptions and Sensitivity Analyses

Appendix Tables 2 and **3** (available at www.annals.org) show our baseline assumptions. We estimated the relative effect of a statin dose on LDL cholesterol levels on the basis of an extensive review of the literature by Law and colleagues (27). We based the relationship between LDL cholesterol reduction and clinical benefit of the moderate dose–potency statin on the largest study to evaluate this treatment, the HPS (Heart Protection Study) (28)—a clinical trial of placebo versus simvastatin, 40 mg, with more than 20 000 randomly assigned patients. Although many trials have examined the benefits of low- to moderate-dose statins, studies vary dramatically in their degree of protocol contamination (amount of crossover and nonadherence or intolerance of statin therapy), which make it difficult to interpret the aggregate estimate of existing meta-analyses. However, in additional analyses, we varied the estimated effectiveness of statin therapy across the spectrum found in the literature (sensitivity analysis 1 [**Appendix Table 1**]) and also used estimates based on a meta-analysis of primary prevention trials (section F of the **Appendix**)—all of which produced similar results. Our estimate of the benefits of a high dose–potency statin (atorvastatin, 40 to 80 mg) versus low to moderate dose–potency statin (simvastatin, 20 to 40 mg) are based on the pooled analysis (29) of the only 2 clinical trials that have assessed this question in clinically stable patients (IDEAL [Incremental Decrease in End Points Through Aggressive Lipid Lowering] [30] and TNT [Treating to New Targets] [31]). Although no mortality benefit was observed in IDEAL or TNT, we included a mortality benefit proportional to that found in placebo versus statin therapy in sensitivity analysis 7 (**Appendix Table 1**).

Unfortunately, these trials did not report estimates of patient-level variation in LDL cholesterol response to statins so we used estimates from 2 other large trials (AFCAPS/TexCAPS [Air Force/Texas Coronary Atherosclerosis Prevention Study] [32] and CARE [Cholesterol and Recurrent Events] [33]) that included these estimates.

Table 1. **Complications Prevented With the NCEP III Treat-to-Target Strategies Versus the Tailored Treatment Strategy**

Treatment Scenario	Adults Aged 30–75 y Who Received Treatment, % (million n)			Adults Aged 65–75 y Who Received Treatment, % (million n)		
	Any Statin	Standard Statin	High-Dose–Potency Statin	Any Statin	Standard Statin	High-Dose–Potency Statin
Standard NCEP III treat-to-target strategy	26.2 (37.9)	20.8 (30.0)	5.4 (7.9)	27.2 (5.7)	23.4 (4.9)	3.8 (0.8)
Intensive NCEP III treat-to-target strategy	36.8 (53.4)	24.5 (35.6)	12.3 (17.8)	66.4 (13.9)	38.0 (7.9)	28.4 (5.9)
Tailored treatment strategy	36.6 (53.0)	27.4 (39.7)	9.2 (13.3)	91.7 (19.1)	50.6 (10.6)	41.1 (8.6)

CAD = coronary artery disease; LDL = low-density lipoprotein; NCEP = National Cholesterol Education Program; QALY = quality-adjusted life-year.

After we adjusted for treatment discontinuation, we obtained a pooled coefficient of variation of 42.1% (**Appendix Table 2** and section B of the **Appendix**) (21, 34, 35).

Disutilities (that is, the negative effect of illness and treatment on patient quality of life) are difficult to determine precisely and can vary considerably from person to person. We therefore varied the CAD event and treatment-related disutilities across a broad range in our sensitivity analyses (**Appendix Table 1** and section F of the **Appendix**). In the base-case model, the disutility of having a nonfatal CAD event was set at 0.25 in year 1 and then 0.05 per year of life expectancy (which can be thought of as lower quality of life after a nonfatal CAD event or lower life expectancy) (29, 36). The risk for adverse effects from statins increases with greater treatment intensity (17), so we also examined the effect of a small treatment disutility (0.001 per treatment intensification), such as that found in medications with very low (but not zero) risk for side effects, medical complications, and drug–drug interactions. Treatment-related disutilities were limited to the 5-year treatment period, but the calculation of quality-adjusted life-years (QALYs) lost because of CAD mortality and morbidity accounted for the patient's overall life expectancy, discounted at 3% per year into the future (37).

Our study did not specifically consider costs for several reasons: The costs of medications vary dramatically across different segments of the U.S. health care system; several of the medications involved will soon become generic (so cost-effectiveness analyses results will shortly become outdated); and of most importance, this article is designed to focus on the merits of a tailored treatment approach under circumstances ideal for a treat-to-target approach, and we did not want cost considerations to confound that comparison.

To ensure that we obtained adequate input from supporters of treat-to-target approaches, we asked 10 prominent lipid experts who have been involved in NCEP III or other lipid guidelines to assess our assumptions and recommend testing additional clinically reasonable scenarios that would favor a treat-to-target approach (**Appendix**). We included all of the recommendations from these 10 experts in our sensitivity analyses.

Benefits of Statin Treatment Strategies

For each strategy, we conducted simulations by using the base-case assumptions. We first estimated the number of CAD events and deaths prevented. We then estimated the QALYs gained by using each strategy and compared the overall population benefit (total QALYs gained) and the benefit per person treated (QALYs gained per 1000 adults treated) (**Appendix**).

Finally, we conducted extensive sensitivity analyses (**Appendix Table 1** and section F of the **Appendix**). Initially, we varied assumptions one at a time, but then we varied influential assumptions (that is, those that affected the relative difference between the treat-to-target and tailored treatment strategies) in combinations of 2 and 3 at a time. We conducted additional sensitivity analyses relating to the discount rate, differential timing and degree of a statin's effectiveness, and alternative treatment strategies, but we found no appreciable effect on the tailored treatment versus the treat-to-target comparison (**Appendix**). We conducted all analyses by using Stata, version 10 (StataCorp, College Station, Texas).

Role of the Funding Source

The study was funded by the Veteran Affairs Health Services Research & Development Service's Quality Enhancement Research Initiative. The funding source had no role in the design and conduct of the study; collection, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

RESULTS

NCEP III Treat-to-Target Strategies

The standard NCEP III treat-to-target approach would recommend that 37.9 million U.S. persons should receive statins, of which 7.9 million should receive high dose–potency therapy (atorvastatin, 40 to 80 mg) (**Table 1**). Compared with no treatment, the standard NCEP III approach was estimated to save 48 QALYs per 1000 persons treated for 5 years, resulting in about 1.83 million total QALYs saved in the United States. In comparison, the intensive NCEP III treat-to-target approach would recom-

Table 1—Continued

Change in LDL Cholesterol Levels and CAD Risk With Treatment (Before/After)		Outcomes Prevented per 5 y of Treatment in Adults Aged 30–75 y With No History of Heart Attack					
		Total in U.S. Population, *million n*			Rate per 1000 Persons Treated		
Mean LDL Cholesterol Level, *mmol/L (mg/dL)*	Mean 5-y CAD Risk, %	Events	Deaths	QALYs Saved	Events	Deaths	QALYs Saved
4.61 (178)/3.13 (121)	8.8/5.6	1.67	0.07	1.83	44.0	1.9	48
4.27 (165)/2.79 (108)	10.9/6.4	2.39	0.10	2.40	44.9	1.9	45
3.83 (148)/2.51 (97)	12.7/7.0	2.82	0.13	2.92	53.2	2.4	55

mend that 53.4 million U.S. persons receive statins—15.5 million more than in the standard NCEP III approach (**Table 1**) but preventing about 720 000 more nonfatal CAD events and 30 000 more deaths—resulting in about 570 000 more QALYs saved. The intensive NCEP III approach was only slightly less efficient than the standard NCEP III approach, accruing 45 QALYs saved per 1000 persons treated compared with 48 for the standard NCEP III approach (**Table 1**).

Tailored Treatment Strategy

The tailored treatment strategy would recommend that about 53 million U.S. persons (about the same number as that in the intensive NCEP III approach) should receive a statin, and 13.3 million persons should receive a high dose–potency statin, which is 4.5 million fewer than in the intensive NCEP III strategy. The tailored treatment approach was superior to both NCEP III approaches, resulting in both more CAD morbidity and mortality prevented in the overall population and higher treatment efficiency (greater benefit per person treated). For example, the tailored treatment approach was predicted to save 520 000 more QALYs than the intensive NCEP III treat-to-target approach per 5 years of treatment while also saving 10 more QALYs per 1000 persons treated (**Table 1**).

Incremental Benefits of Tailored Treatment Versus Treat-to-Target Approach

For the purposes of comparing alternative approaches, it is more informative to consider the incremental gains or losses that occur for persons who receive different treatment (37). Overall, about 70% of persons received similar treatment under the tailored and intensive NCEP III approaches, receiving either no statin; simvastatin, 20 to 40 mg; or atorvastatin, 40 to 80 mg when either strategy was applied (**Table 2**). Overall, 13.6% of the population would have had more aggressive statin therapy recommended under the tailored treatment approach, whereas 16.8% of the population would receive more aggressive treatment with the intensive NCEP III approach. Those who received

Table 2. **Comparison of the Incremental Gains of the Intensive NCEP III Treat-to-Target Approach Versus the Tailored Treatment Approach***

Variable	Treated Similarly by Tailored Treatment and NCEP III			Treated More Intensively by NCEP III		Treated More Intensively by Tailored Treatment	
	No Statin	Simvastatin, 20–40 mg	Atorvastatin, 40–80 mg	Simvastatin, 20–40 mg	Atorvastatin, 40–80 mg	Simvastatin, 20–40 mg	Atorvastatin, 40–80 mg
Proportion treated, % *(n million)*	53.3 (77.3)	11.7 (17.0)	4.6 (6.7)	9.1 (13.1)	7.7 (11.2)†	9.0 (13.0)	4.6 (6.7)†
Mean age (SD), *y*	41 (8.5)	57 (10.0)	65 (7.2)	42 (8.7)	55 (10.2)	59 (9.1)	67 (6.4)
Women, %	60	48	38	45	49	44	25
Mean LDL cholesterol level (SD)							
mmol/L	2.95 (0.67)	3.93 (0.67)	4.63 (0.90)	4.48 (0.54)	4.76 (0.95)	2.92 (0.69)	3.26 (0.72)
mg/dL	114 (26)	152 (26)	179 (35)	173 (21)	184 (37)	113 (27)	126 (28)
Mean 5-y CAD risk (SD), %	1.6 (1.3)	9.0 (3.0)	24.1 (7.6)	2.5 (1.4)	9.9 (3.9)	7.8 (2.4)	22.8 (6.5)
Effectiveness: CAD events prevented per 1000 persons treated	NA	29	44	9	6	30	32
Benefit of treatment: QALYs saved per 1000 treated (NNT)‡	NA	33 (31)	66 (8)	6 (172)	−8 (−129)	25 (39)	19 (53)

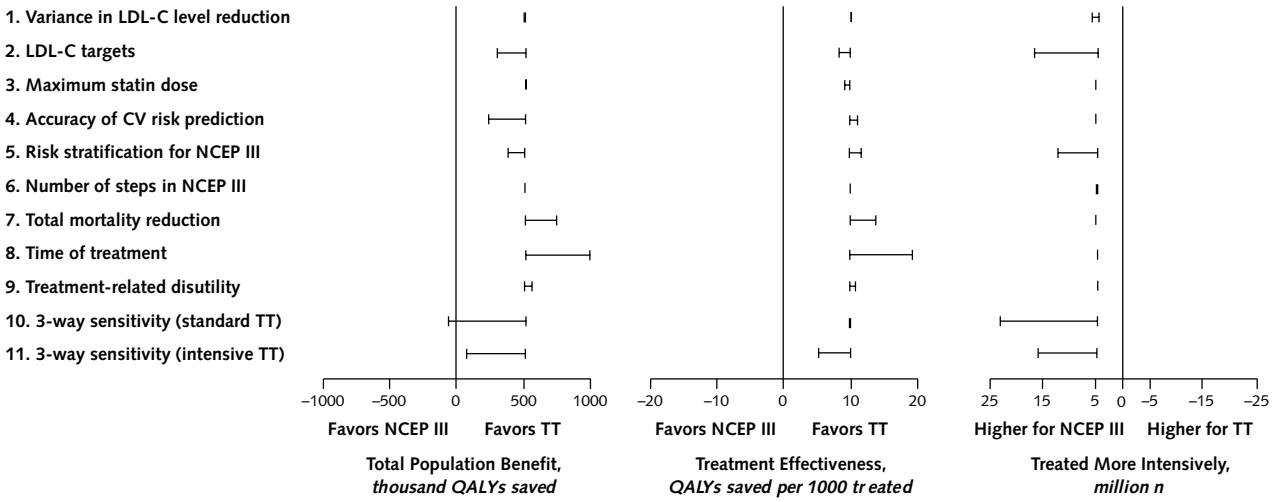
CAD = coronary artery disease; LDL = low-density lipoprotein; NA = not applicable; NCEP = National Cholesterol Education Program; NNT = number needed to treat; QALY = quality-adjusted life-year.

* A patient was considered to be treated more intensively by a strategy when the strategy recommended 20 to 40 mg of simvastatin and the other strategy recommended no statin therapy or when the strategy recommended 40 to 80 mg of atorvastatin and the other strategy recommended either 20 to 40 mg of simvastatin or no statin therapy.

† Of the 11.2 million persons treated with 40 to 80 mg of atorvastatin under the NCEP III strategy but treated less aggressively under the tailored treatment approach, 79.2% were treated with 20 to 40 mg of simvastatin under the tailored treatment approach. Of the 6.7 million persons treated with 40 to 80 mg of atorvastatin under the tailored treatment approach but treated less aggressively under the NCEP III approach, 85.9% were treated with 20 to 40 mg of simvastatin under the NCEP III approach.

‡ Number needed to treat for 5 y to gain 1 QALY (a minus sign signifies that the treatment caused net harm; therefore, this is a number needed to harm).

Figure 2. **Factors influencing the relative benefits of the intensive NCEP III versus the TT approaches to statin therapy.**



Results are shown when key assumptions are varied in sensitivity analyses (see **Appendix Table 1**, available at www.annals.org, for more details), demonstrating how the TT approach results in more total population benefit, greater treatment effectiveness, and fewer persons treated intensively across the range of assumptions. CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; NCEP = National Cholesterol Education Program; QALY = quality-adjusted life-year; TT = tailored treatment.

more intensive tailored treatment generally had substantially better outcomes. For example, about 13.0 million persons would receive simvastatin, 40 mg, recommended by tailored treatment but no statin recommended by intensive NCEP III (**Table 2**). The main attribute of this group is that they had relatively low LDL cholesterol levels but moderately high CAD risk. For every 39 of these persons who would receive treatment for 5 years, 1 QALY would be saved. In contrast, the 13.1 million persons who would have been recommended simvastatin, 40 mg, under intensive NCEP III but no statin under tailored treatment generally had high LDL cholesterol levels but low CAD risk, and 172 persons would need to receive treatment for 5 years to gain 1 QALY (**Table 2**). Even more striking, the 11.2 million persons who received treatment with high dose–potency statins under NCEP III but not under tailored treatment would be expected to incur a net loss in QALYs because the small amount of treatment harms would outweigh the very small amount of expected treatment benefits (number needed to harm, 129).

Sensitivity Analyses

No single assumption that varied in the sensitivity analyses had a large effect on the results; however, 3 factors resulted in a moderate improvement in overall population benefit for the intensive NCEP III approach compared with the tailored treatment approach: 1) implementation of the recently recommended lower LDL cholesterol target (<1.81 mmol/L [<70 mg/dL]), 2) use of full risk stratification for the NCEP III approach, and 3) reduction of 20% in the predictive accuracy of the Framingham score (sensitivity analyses 2, 4, and 5) (**Figure 2**). When we combined all 3 of these changes in a 3-way sensitivity analysis, the NCEP III approach was estimated to save slightly more QALYs in the overall population but at a price of treating about 24 million persons more intensively than they would be treated with the tailored treatment approach. However, even in this extreme situation, the tailored treatment approach would once again become fully dominant if we slightly lowered its treatment thresholds to account for the reduced reliability of the risk prediction tool. We tested additional assumptions, but none substantially improved how a treat-to-target approach performed relative to a tailored treatment approach (section F of the **Appendix**).

Discussion

Our study suggests that treat-to-target strategies based on NCEP III guidelines are inferior to a simple, tailored approach to statin therapy. Even when we used a hypothetical best-case scenario for an NCEP III–style approach, tailored treatment was more efficient (greater benefit per person treated) and produced more benefit across the U.S. population than any of the variations of the NCEP III approaches, including more recent recommendations to treat very high-risk patients to an LDL cholesterol level less than 1.81 mmol/L (<70 mg/dL).

The purpose of our study was to evaluate the comparative effectiveness of treat-to-target strategies with tailored treatment rather than to try to determine the best tailored treatment approach or the precise number of QALYs that would be saved by a tailored treatment approach. Tailored treatment is a personalized approach to treatment; it is antithetical to develop a single dichotomous cut-point above which a treatment should be given (section D of the

Appendix). Although tailored treatment estimates can improve our ability to identify patients for whom a treatment should or should not be recommended, many patients will still reside in a gray zone, in which the expected benefits are modest or uncertain. Calls for acknowledgment of such gray zones date back decades (38) but have rarely been effectively incorporated into modern guidelines.

Our study has several limitations. Data are limited for statin therapy in persons 75 years or older, which makes recommendations in this group more uncertain. Consequently, we did not study this group and recommend great caution in giving high doses of statin for primary CAD prevention in elderly persons without substantial risk factors other than age. Tailored treatment requires that clinicians calculate a patient's CAD risk, which could be a barrier to its adoption. However, NCEP III guidelines also require such calculation and require much more clinician time overall (checking, reviewing, and rechecking LDL cholesterol levels and stepped escalations of statin doses). Although the relative benefit of tailored treatment over the treat-to-target approach was robust across all sensitivity analyses, the absolute population-level benefit of the tailored treatment and treat-to-target approaches are much less certain and can vary substantially on the basis of several factors, such as a statin's effect on total mortality (estimates of which are less precise in the literature than estimates for nonfatal CAD events) and the level of treatment adherence that is achievable in real-world clinical practice (9, 27, 29, 39). Finally, the precise treatment-related disutility of statin therapy is unknown.

Tailored treatment is not a new concept. Its structure uses modern predictive modeling to return to the basic medical precept of carefully weighing a patient's risks and benefits when making treatment decisions (14–16, 40, 41). Many examples of a tailored treatment approach are either proposed or in use, such as recommendations for aortic aneurysm repair, chemotherapeutic regimens, carotid endarterectomy, and use of fibrinolytic therapy (42–45). Tailored treatment simply uses prediction tools and all available information to estimate a patient's expected absolute net benefit (treatment benefits minus treatment harms) rather than just their relative treatment benefit or whether a modifiable risk factor is at a predetermined goal.

The main reason why treat-to-target strategies fall short arises from a single risk factor (in this case, LDL cholesterol) receiving dramatically more weight than all other predictors of treatment benefit, resulting in other highly relevant information being either ignored or underweighted (14–16). To further elucidate how a treat-to-target approach based on LDL cholesterol both over- and undertreats patients, section A of the **Appendix** provides some examples of individual cases.

Although some have advocated the use of treatment targets other than LDL cholesterol (such as C-reactive protein) (19, 20), our results demonstrate that a tailored treatment approach is superior to a treat-to-target approach even if LDL cholesterol is a perfect marker of a statin's benefits. Developing better biomarkers is still important, but they are best used to inform tailored treatment approaches rather than to determine treatment targets. Our results suggest that biomarkers are clinically useful when they help us better estimate the 2 critically important components for predicting expected treatment benefit: a patient's baseline risk and the relative risk reduction of therapy (sections A and D of the **Appendix**). For example, although LDL cholesterol has generally not been found to be an independent CAD risk factor when other lipid measures are considered (20, 25, 46), increasing evidence shows that C-reactive protein is an independent marker, and it may help identify intermediate-risk persons who should or should not receive a tailored treatment (20, 47). Furthermore, if the baseline level of a risk factor is demonstrated to be an independent predictor of a treatment's relative risk reduction, then that risk factor could also help inform a tailored treatment strategy. At this time, however, we know of no evidence that any single CAD risk factor or biomarker helps predict the relative effectiveness of starting statin therapy (5).

Our study also shows the shortcomings of single fixed-dosed strategies (such as the fire-and-forget approach) (12, 48–50) by demonstrating that millions of Americans are likely to benefit substantially from high dose–potency statin for primary CAD prevention (**Table 2**). The goal behind the treat-to-target approach was a good one—to identify high-risk and high-benefit patients and to treat them more aggressively—but the treat-to-target strategy is an inferior approach for identifying these patients compared with tailored treatment.

In conclusion, we found that under a wide range of assumptions and circumstances, a simple, tailored treatment strategy for statin therapy for persons aged 30 to 75 years was more efficient and prevented substantially more CAD morbidity and mortality than any of the currently recommended treat-to-target approaches. The benefits of tailored treatment result from targeting high-risk patients better and basing intensification decisions on a person's estimated treatment benefit rather than concentrating on whether a desired treatment target has been reached. Given its potential to better tailor treatments to individual patients, we suggest that the principles underlying a tailored treatment approach, including the effect of small amounts of treatment disutilities, should be considered during deliberations about guidelines and performance measures. Whether a tailored treatment approach is superior for other conditions in which treat-to-target strategies are currently recommended, such as blood pressure and glycemic control, warrants examination.

From University of Michigan and Veteran Affairs Ann Arbor Healthcare System, Ann Arbor, Michigan, and Yale University and Yale-New Haven Hospital, New Haven, Connecticut.

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Reproducible Research Statement: *Study protocol, statistical code, and data set:* Available from Dr. Hayward (e-mail, rhayward@umich.edu).

Corresponding Author: Rodney A. Hayward, MD, The Robert Wood Johnson Clinical Scholars Program, University of Michigan Medical School, 6312 Medical Science Building I, 1150 West Medical Center Drive, Ann Arbor, MI 48109; e-mail, rhayward@umich.edu.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Hayward and Zulman: The Robert Wood Johnson Clinical Scholars Program, University of Michigan Medical School, 6312 Medical Science Building I, 1150 West Medical Center Drive, Ann Arbor, MI 48109.
Dr. Krumholz: Yale University School of Medicine, 1 Church Street, Suite 200, New Haven, CT 06510.
Dr. Timbie: The RAND Corporation, 1200 South Hayes Street, Arlington, VA 22202-5050.
Dr. Vijan: Veteran Affairs Health Services Research & Development Center of Excellence, VA Ann Arbor Healthcare System, PO Box 130170, Ann Arbor, MI 48113-0170.

Author Contributions: Conception and design: R.A. Hayward, S. Vijan.
Analysis and interpretation of the data: R.A. Hayward, H.M. Krumholz, D.M. Zulman, S. Vijan.
Drafting of the article: R.A. Hayward, D.M. Zulman, J.W. Timbie, S. Vijan.
Critical revision of the article for important intellectual content: R.A. Hayward, H.M. Krumholz, D.M. Zulman, J.W. Timbie, S. Vijan.
Final approval of the article: R.A. Hayward, H.M. Krumholz, D.M. Zulman, J.W. Timbie, S. Vijan.
Statistical expertise: R.A. Hayward, J.W. Timbie, S. Vijan.
Obtaining of funding: R.A. Hayward.
Administrative, technical, or logistic support: R.A. Hayward.
Collection and assembly of data: R.A. Hayward, J.W. Timbie.

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Appendix Table 1. **Other Variable Estimates and Sensitivity Analyses**

Variable of Interest	Base-Case Estimate	Range Assessed, by Sensitivity Analysis	Applied Changes to Strategy*	
			NCEP III	Tailored Treatment
1. Variance in LDL cholesterol level reduction	See Appendix Table 2	LDL cholesterol level reduction adjusted by (0.5–1.5) base case*	Yes	Yes
2. LDL cholesterol level targets for NCEP III approach	See Figure 1	LDL cholesterol level targets ranged from standard NCEP III guidelines to LDL cholesterol level <1.81 mmol/L (<70 mg/dL) for those with 10-y CAD risk >20%	Yes	No
3. Maximum statin dose in NCEP III approach	Atorvastatin, 80 mg	Maximum statin dose ranged from 40-mg atorvastatin to 40-mg rosuvastatin	Yes	No
4. Accuracy of Framingham CAD risk prediction	No regression dilution*	Accuracy of prediction tool ranged from base case to 20% reduction due to regression dilution	Yes	Yes
5. Risk stratification for NCEP III approach	Use NCEP III CAD risk index as first step	Risk stratification ranged from NCEP III CAD risk stratification to full Framingham equation	Yes	No
6. Number of steps in statin titration in NCEP III guidelines	4 steps	Number of titration steps range, 2–6	Yes	No
7. CAD mortality reduction resulting from increase in statin dose potency from moderate to high	None	CAD mortality reduction range, 0%–6%	Yes	Yes
8. Time of treatment	5 y	Time of treatment range, 5–10 y	Yes	Yes
9. Treatment-related disutility	See Appendix Table 3	See Appendix Table 3	Yes	Yes
10. 3-way sensitivity analysis (standard tailored treatment)†	NA	Combination of sensitivity analyses 2 (LDL cholesterol level <1.81 mmol/L [<70 mg/dL]), 4 (20% regression dilution), and 5 (full Framingham risk stratification)	Yes	Yes
11. 3-way sensitivity analysis (intensive tailored treatment)†‡	NA	Same as sensitivity analysis 10	Yes	Yes

CAD = coronary artery disease; LDL = low-density lipoprotein; NA = not applicable; NCEP = National Cholesterol Education Program.
* Some associations only affect the treat-to-target approach (such as variations in LDL cholesterol level reduction), whereas other assumptions affect both approaches (for example, the accuracy of the CAD prediction tool).
† A combination of the range of assumptions listed under sensitivity analyses 2, 4, and 5.
‡ The intensive tailored treatment strategy treats patients with a 4% to 12.5% CAD risk over 5 y with simvastatin, 40 mg, and patients with >12.5% CAD risk over 5 y with atorvastatin, 40 mg (see section D of the **Appendix**).

Appendix Table 2. Statin Effectiveness in LDL Cholesterol Reduction and Relative Risk Reduction

Change in Statin Treatment	Mean Reduction in LDL Cholesterol Level (SD)		Relative Risk Reduction, %	
	mmol/L	*mg/dL*	Nonfatal CAD Events	Total Mortality Rate
No treatment → simvastatin, 20 mg	0.69 (0.29)	27 (11.4)	33	11
No treatment → simvastatin, 40 mg*	0.80 (0.33)	31 (13.1)	38	12
Simvastatin, 20 mg → simvastatin, 40 mg	0.15 (0.06)	6 (2.5)	7	2
Simvastatin, 40 mg → atorvastatin, 40 mg	0.44 (0.18)	17 (7.2)	14	0
Simvastatin, 40 mg → atorvastatin, 80 mg†	0.59 (0.25)	23 (9.7)	19	0‡
Atorvastatin, 40 mg → atorvastatin, 80 mg	0.20 (0.08)	8 (3.4)	7	0‡

CAD = coronary artery disease; LDL = low-density lipoprotein.

* Estimates obtained from the Heart Protection Study (28), which compared placebo with simvastatin, 40 mg. Specific treatment crossover and adherence rates are available. Analyses using a meta-analysis of primary prevention studies (49) yielded similar results (section E of the **Appendix**).

† Estimates obtained from pooled analyses of the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) (30) and TNT (Treating to New Targets) (31) trials. The moderate-potency statin in the IDEAL study was 20 to 40 mg of simvastatin, with 76% to 79% receiving 20 mg (the average adherence to study drug was about 85% during the trial). The moderate-potency statin in the TNT study was 10 mg of atorvastatin. The high-potency statin in both studies was 80 mg of atorvastatin (29–31).

‡ Although no mortality benefit was observed in pooled analysis of trials of low- to moderate-dose versus high-dose statins for stable patients (29–31), we included a mortality benefit proportional to that found in placebo versus statin therapy in sensitivity analysis 7.

Appendix Table 3. Disease- and Treatment-Related Adverse Effects

Treatments and Complications	Disutility	Range
Nonfatal CAD event	0.25 in 1 y and 0.05/y thereafter	0.2–0.4 and 0.025–0.1/y
Simvastatin, 20 mg	0.001/y	0.0005–0.003/y
Simvastatin, 40 mg	0.002/y	0.001–0.004/y
Atorvastatin, 40 mg	0.003/y	0.0015–0.005/y
Atorvastatin, 80 mg	0.004/y	0.002–0.006/y
Visit and blood draw	0.0009/y	0.0003–0.0015/y

CAD = coronary artery disease.