Variation in the Net Benefit of Aggressive Cardiovascular Risk Factor Control Across the US Population of Patients With Diabetes Mellitus

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Background: Lowering low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) in patients with diabetes mellitus (DM) can significantly reduce the risk of cardiovascular disease (CVD). However, to our knowledge, previous studies have not assessed variability in both the benefit and harm from pursuing LDL-C and BP target levels.

Methods: Our sample comprised individuals 30 to 75 years old with DM participating in the National Health and Nutrition Examination Survey III. We used Monte Carlo methods to simulate a treat-to-target strategy, in which patients underwent treatment intensification with the goal of achieving LDL-C and BP target levels of 100 mg/dL and 130/80 mm Hg, respectively. Patients received up to 5 titrations of statin therapy and 8 titrations of antihypertensive therapy. Treatment adverse effects and polypharmacy risks and burdens were incorporated using disutilities. Health outcomes were simulated using a Markov model.

Results: Treating to targets resulted in gains of 1.50 (for LDL-C) and 1.35 (for BP) quality-adjusted life-years (QALYs) of lifetime treatment-related benefit, which declined to 1.42 and 1.16 QALYs after accounting for treatment-related harms. Most of the total benefit was limited to the first few steps of medication intensification or to tight control for a limited group of very high-risk patients. However, because of treatment-related disutility, intensifying beyond the first step (LDL-C) or third step (BP) resulted in either limited benefit or net harm for patients with below-average risk.

Conclusion: The benefits and harms from aggressive risk factor modification vary widely across the US population of individuals with DM, depending on a patient’s underlying CVD risk, suggesting that a personalized approach could maximize a patient’s net benefit from treatment.

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Early all diabetes mellitus (DM) practice guidelines recommend aggressive treatment of low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) to lower a patient’s risk of developing cardiovascular disease (CVD) or preventing its sequela.1,2 These recommendations, which are based on the average results of trials evaluating the relative benefits of intensive risk factor control,3-6 are not tailored to an individual’s underlying CVD risk. While this approach is often advocated in patients without DM,2 there is an implicit assumption that all patients with DM are at equally high risk, requiring all patients to be treated aggressively. However, the benefit of intensifying treatment to attain low risk factor targets, or “treating to targets,” could vary greatly across the population of individuals with DM depending on the distribution of CVD risk in the population.

While clinical trials have demonstrated that intensive risk factor control can provide significant benefits on average for persons with DM, most of these trials included many patients with very high CVD risk and limited treatment to statins and up to 3 to 4 blood pressure medications.7,8 Two recent substudies of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial have confirmed that intensive BP control9 and intensive treatment with combination lipid-lowering therapies10 offered no survival advantage overall, and perhaps caused harm, but may still be beneficial to very high risk groups. But for at least 3 reasons, results from these most recent trials provide limited guidance for a typical clinical decision-making context. First, because many of the studies of tight risk factor control enrolled patients with a range...
of CVD risk but did not stratify the results accordingly, the relative benefit of tight control for patients with specific risk levels cannot be determined. Second, clinical trials on primary prevention in patients with DM have rarely examined whether the benefits derive from the first few steps of medication intensification (moderate doses of statins and low to moderate doses of 2-3 antihypertensive medications) or from later intensifications (high doses of statins or high doses of 3-4 antihypertensive medications). This is important because later intensifications tend to reduce the risk factor less effectively than the initial intensifications. Adding a second antihypertensive therapy, for example, produces a 16% lower systolic BP reduction and a 35% lower diastolic BP reduction than would be expected if the treatment effects were additive,12 implying that combination therapy provides a smaller marginal health benefit.

Treatment harm is a third, and often overlooked, factor that determines the relative benefit of tight risk factor control. All treatments used to lower CVD risk factors are associated with adverse events and burdens, and their combined effects could be substantial when polypharmacy is used to reach tight control targets. When the benefits of treatment are small or accrue mainly to a subset of patients, incorporating a small treatment-related disutility can significantly lessen or negate the benefit of treatment.13 Most trials report adverse event rates that far exceed discontinuation rates,13 indicating that patients will persist with burdensome regimens despite experiencing adverse events. To our knowledge, no studies have assessed the impact of treatment-related disutility on the benefit of treating to aggressive LDL-C and BP target levels in patients with DM.

We therefore examined heterogeneity in the benefits, harms, and net benefit of aggressively treating CVD risk factors in the US population of patients with DM. Using risk factor reductions obtained in clinical trials of specific treatments and estimates of the associated CVD risk reduction, we developed a simulation model of a treat-to-target strategy. We used the model to assess (1) the expected health benefit of treating to aggressive risk factor targets, (2) the expected net health benefit after accounting for treatment-related disutility, and (3) the net benefit of individual treatment steps. To assess variation in the net benefit across the population we stratified all analyses according to a measure of CVD risk—a patient’s expected loss in quality-adjusted life expectancy if risk factors were to remain uncontrolled.

**TREATMENTS**

We specified intensification regimens for patients having risk factors above targets at baseline (an LDL-C level >100 mg/dL [to convert LDL-C to millimoles per liter, multiply by 0.0259] and BP >130/80 mm Hg) that differed according to each patient’s baseline medications (Table 1). Patients who were not receiving lipid-lowering medications at baseline were started on simvastatin, 20 mg, and medications were titrated up to 5 times as needed, ending with simvastatin/ezetimibe combination therapy. Patients receiving no antihypertensives at baseline were started on standard doses of a thiazide, and then given an angiotensin-converting enzyme (ACE) inhibitor, β-blocker, and calcium channel blocker (CCB) as necessary. The treatment of those taking medications at baseline was intensified beyond their initial medications as needed in the same sequence. Treatment for patients who failed to reach the target level while prescribed standard antihypertensive doses was intensified by doubling each dose. We chose this approach because the treatment literature shows greater BP reductions from initial medication doses than from dose titration.14

**TREATMENT EFFICACY MODEL**

Our simulation comprised 2 sets of models, a “treatment efficacy” model that simulated the efficacy of medication intensification in reducing risk factor levels, and an “outcomes” model that translated changes in risk factor levels into risks of DM complications and quality-adjusted life expectancy. The treatment efficacy model used Monte Carlo simulation to (1) estimate the LDL-C and BP reductions produced by each treatment for each patient, and (2) to simulate adverse events and discontinuation from each treatment. Treatment for patients not reaching their target levels after the first set of treatments was intensified with step 2 treatments, and the simulation continued until all patients were below target levels or until all treatments had been exhausted. We ran the Monte Carlo simulation 500 times to estimate each patient’s average risk factor reduction and overall treatment disutility.

**MODEL PARAMETERS**

**Treatment Efficacy**

Our treatment efficacy parameters (ie, risk factor reductions from each treatment) came from 2 meta-analyses of randomized placebo-controlled trials, both by Law et al.1415 and a head-to-head trial comparing ezetimibe combination therapy with statin monotherapy.14 For each treatment we abstracted difference-in-difference estimates (reduction in the treatment arm minus reduction in the placebo arm) and their standard errors. We incorporated a diminishing marginal efficacy in BP reduction for combination antihypertensive therapy, a 16%/39% lower systolic/diastolic BP reduction for any second therapy added to monotherapy, as demonstrated by Wu et al.15 Because no studies, to our knowledge, have assessed the relative efficacy of combinations of 3 or more classes, we assumed that each subsequent class had an additional 16%/35% lower systolic/diastolic BP efficacy (eg, 29%/58% lower efficacy for a third class, and 41%/73% lower efficacy for a fourth class). We modeled treatment effects on risk factors as a percentage change from baseline to allow larger reductions for patients having higher base-
We assumed that all patients incurred a disutility from the use of each medication as well as safety risks. Polypharmacy is associated with a greater incidence of drug-drug interactions that reduce the efficacy of beneficial DM treatments22,23 and increase the incidence of adverse events24 and depression.25 In our base case, we assumed a very small incremental disutility of 0.001 for each drug class added (ie, 0.001, 0.002, 0.003, and 0.004 for the first 4 drug classes). For comparison, a disutility of 0.001 is a commonly cited value for the inconvenience of taking aspirin daily. We equated the disutility of a fifth medication (0.005) with that of a typical drug adverse effect. In sensitivity analyses we assumed a constant 0.001 disutility per class. Given their small magnitude, we assumed all disutilities were additive.

### Treatment Discontinuation

We simulated discontinuation separately for patients who did and did not experience adverse events on each treatment to accurately reflect the frequency with which patients continued treatment despite having adverse effects. We estimated average, all-cause discontinuation rates across several large statin trials3,26-29; Bruckert et al17 documented a 20% discontinuation rate for patients experiencing myalgia. A meta-analysis by Ross et al15 provided both all-cause and adverse event–related discontinuation rates for all 4 categories of antihypertensives.

### OUTCOMES MODEL

We used a previously published Markov model30,31 to estimate the health benefits associated with the simulated LDL-C and BP reductions. The model simulates the progression of DM as a function of an individual’s age, time since diagnosis, prior complications, and baseline measures of LDL-C, hemoglobin A1c, and BP. Patients proceed through the model, incurring complications (blindness, amputation, nephropathy, renal failure, stroke, and coronary artery disease), in accordance with probabilities derived from randomized controlled trials32,34 and prospective cohort studies.3,33 The fundamental underlying relationship between risk factor levels and outcomes is a log-linear relationship that has been firmly established in cohort studies and analy-
Table 2. Base Case Simulation Results

<table>
<thead>
<tr>
<th>Baseline Treatment</th>
<th>Prevalence, %</th>
<th>Baseline Level</th>
<th>Absolute Reduction</th>
<th>Target Attainment, %</th>
<th>Gain, QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>89.9</td>
<td>150.4</td>
<td>56.0</td>
<td>78.6</td>
<td>1.49</td>
</tr>
<tr>
<td>Nonstatin</td>
<td>5.9</td>
<td>153.3</td>
<td>57.9</td>
<td>76.5</td>
<td>1.75</td>
</tr>
<tr>
<td>Low-dose statin</td>
<td>4.2</td>
<td>157.7</td>
<td>44.2</td>
<td>48.4</td>
<td>1.57</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>150.8</td>
<td>55.7</td>
<td>77.2</td>
<td>1.50</td>
</tr>
<tr>
<td>BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>42.5</td>
<td>141.5, 78.6</td>
<td>-16.4, -6.6</td>
<td>80.0</td>
<td>1.59</td>
</tr>
<tr>
<td>1 Class</td>
<td>31.6</td>
<td>145.4, 77.8</td>
<td>-15.2, -4.9</td>
<td>58.0</td>
<td>1.28</td>
</tr>
<tr>
<td>2 Classes</td>
<td>21.7</td>
<td>145.9, 80.9</td>
<td>-12.4, -3.6</td>
<td>27.5</td>
<td>1.14</td>
</tr>
<tr>
<td>3 Classes</td>
<td>3.5</td>
<td>154.8, 80.1</td>
<td>-8.2, -2.0</td>
<td>18.5</td>
<td>0.58</td>
</tr>
<tr>
<td>4 Classes</td>
<td>0.6</td>
<td>141.6, 87.9</td>
<td>-3.7, -1.0</td>
<td>0.1</td>
<td>0.62</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>144.1, 79.0</td>
<td>-14.8, -5.2</td>
<td>59.0</td>
<td>1.35</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life-year.

*SI conversion factor: To convert LDL-C to millimoles per liter, multiply by 0.0259.

*Target levels were 100 mg/dL [2.59 mmol/L] (LDL-C) and 130/80 mm Hg (BP). The measurement scale for absolute reductions is the same as that used for baseline levels.

b Unadjusted for treatment-related harms.

c Unless indicated otherwise, data for LDL-C are given as milligrams per deciliter.

d Results for BP are shown as systolic, diastolic. Unless indicated otherwise, data for BP are given as millimeters of mercury.

The weighted NHANES III data provide representative estimates for the nearly 8 million individuals with DM aged 30 to 75 years in the early 1990s, a period when aggressive LDL-C and BP treatment was uncommon. After excluding the 15% of patients with DM who had an LDL-C level lower than 100 mg/dL at baseline, the mean LDL-C level in the remainder of the population was approximately 151 mg/dL. Most patients were not receiving lipid-lowering treatment at baseline, and only 4% were taking statins (Table 2). Nearly 38% of patients had a baseline BP lower than 130/80 mm Hg. The average BP among those lacking tight BP control at baseline was 144/79 mm Hg; 53% of these patients were taking 1 or 2 medications to control their BP, while 43% were prescribed no BP medications.

Among patients above goal at baseline, our treat-to-target simulation resulted in 77.2% reaching the LDL-C target level (100 mg/dL) and 59.0% reaching the BP target level (130/80 mm Hg) (Table 2). Those already taking medication at baseline were much less likely to attain tight control. For example, patients taking low-dose statins at baseline were only 30 percentage points less likely to reach an LDL-C level lower than 100 mg/dL, reflecting the diminishing return of dose titration for statins. Results for BP were even more extreme. Patients prescribed 3 or more treatments at baseline achieved target levels less than 20% of the time, whereas 80% of those untreated at baseline reached the BP target level. The population undergoing LDL-C treatment intensification had a mean quality-adjusted life expectancy at baseline of 11.5 years, whereas those undergoing BP treatment intensification had a mean quality-adjusted life expectancy of 10.1 years. Aggressively treating LDL-C and BP led to an average gain of 1.50 and 1.35 quality-adjusted life-years (QALYs), respectively, but after accounting for treatment-related harms, the net benefit was reduced to 1.42 and 1.16 QALYs, respectively.

The magnitude of the benefit depended highly on a patient’s baseline risk of developing DM complications, a measure of risk that incorporates expected losses in both the quality and quantity of life. To identify the baseline risk, we used our outcomes model to estimate the QALYs at risk owing to a patient’s baseline risk factor level relative to the target level. We then stratified our analyses of treatment intensification by this measure of risk. Figure 1 indicates that patients who were below the median (“below-average”) risk had an average net gain of less than 1 QALY from treating to LDL-C target levels, whereas patients in the highest risk decile had a net gain of 4.1 QALYs. A similar pattern was found for BP: the net health gains from treating to target levels ranged from 0.4 to 3.0 QALYs across risk groups. Disutilities from treatment had a much larger impact on the net benefit of treating to BP target levels compared with LDL-C target levels. Because of the skewed distribution of baseline risk in the population, average-risk patients had benefits similar to those with below-average risk, whereas the top 2 risk deciles accounted for nearly 50% of the population benefit attained by treating to LDL-C target levels and 40% for BP target levels.

In Figure 2 we display the health gains attributable to individual treatment steps for the population of patients that was untreated at baseline. First-line treatments were associated with the largest gains in health outcomes. There was no incremental benefit of intensifying beyond simvastatin, 20 mg, for patients with below-average risk, and treatment intensification produced net harm at step 5 owing to the incremental disutility of combination lipid-lowering therapy. For the BP simulation, patients with below-average risk began experiencing significantly diminished
benefits with the fourth treatment step (the addition of CCB) and net harm at all subsequent steps. The dramatic diminishing of health benefits from later treatment intensifications depicted in Figure 2 has 2 sources. First, each additional treatment used provided diminishing efficacy in decreasing the risk factor (eTable 1 and eTable 2). Second, a patient's pretreatment risk of CHD decreased at each successive step because of the risk factor reductions (and health benefits) achieved from prior steps.

The magnitude of the treatment benefit also depended on whether patients underwent treatment intensification for 1 or both risk factors. Each treatment was associated with a smaller marginal health gain for patients treated for both risk factors, again owing to the fact that treating each risk factor lowered a patient's overall cardiovascular risk. Figure 3 illustrates the benefits for those who had both elevated LDL-C levels and BP values and who were untreated at baseline, and is a more accurate representation of the expected health benefits than that depicted in Figure 2, which assumed that the other risk factor was not treated at all. If we alternated intensifying LDL-C and BP treatments, the marginal gain in QALYs at each treatment step was much smaller than that displayed in Figure 2 (although the overall risk reduction was greater). For example, thiazide therapy produced an incremental gain of 1.6 QALYs for high-risk patients when considered independently, but only 1.3 QALYs after a patient began treatment with simvastatin, 20 mg. Among patients with below-average risk undergoing treatment intensification, nearly half the benefit of BP treatments was lost to medication harms after step 2 (adding standard-dose ACE inhibitors), whereas in the isolated analysis it occurred at step 4 (adding standard-dose CCBs).

The results of our sensitivity analyses are provided in eTable 4. Lower adherence, higher discontinuation rates, and the use of discounting had the greatest impact on the benefit of treating to targets, but the relative QALY benefit for the highest-risk group was not notably diminished in any sensitivity analysis. We did not explore the implications of alternative parameter values on the risks and benefits of individual treatment steps, but we would expect much higher rates of net harm for patients with below-average risk when any individual parameter was changed to be less favorable to a treat-to-target strategy.
Previous trials have provided limited information on the variability of benefits and harms of treating to targets across the spectrum of the US population of patients with DM, making it difficult for clinicians to tailor their care to individual patients. We developed a simulation model using the best available evidence from clinical trials and found that patients with DM with the highest CVD risk accounted for nearly all of the benefits of treating to targets, whereas average-risk patients—nearly three-quarters of the population—received very little benefit. By accounting for treatment-related harms, we identified numerous examples in which intensifying treatment would be contraindicated on the basis of risk-benefit considerations, and many more instances in which the expected benefits would be so small that shared patient-clinician decision making would seem to be the appropriate medical intervention.

Of note, even for very high-risk patients with DM, intensifying treatment to high levels to moderate levels, or in other words, from low- to medium-levels, will receive little or no benefit when intensification is based solely on their current LDL-C and BP levels, while at the same time, some high-risk patients might be undertreated. Disutility from adverse effects and high levels of polypharmacy have the potential to cause net harm in populations for the lack of benefit of intensive control, one likely explanation is that most of the benefit experienced by patients in both arms came from lowering patients’ BP from high levels to moderate levels, or in other words, from lowering BP among the highest-risk patients. While there was no overall benefit of combination therapy in the ACCORD-Lipid trial, a subgroup analysis suggested that there might be a benefit for patients with the lowest levels of HDL-C and highest levels of triglycerides. Taken together, these results provide additional support for a more nuanced view of selecting risk factor target levels for patients with DM.

Our results highlight the implication of heterogeneity of treatment effects for current DM treatment guidelines and that simply because the average CVD risk across all patients with DM is high, this does not mean that most people with DM have high risk. Most primary prevention guidelines are moving even more strongly to base recommendations on an individual patient’s calculated CVD risk, and our results suggest that having DM should perhaps no longer be an exception to this general rule. Furthermore, because LDL-C and BP values are individually poor predictors of a person’s overall CVD risk, many patients will receive little or no benefit when intensification is based solely on their current LDL-C and BP levels, while at the same time, some high-risk patients might be undertreated. Disutility from adverse effects and high levels of polypharmacy have the potential to cause net harm in patients receiving little or no benefit from intensification, especially those who are already taking several medications, which means most patients with DM today.

For these patients, the next treatment is likely to have limited efficacy (owing to the diminishing benefit of combination therapy), more adverse effects (because third-, fourth-, and fifth-line agents and high doses tend to be less well tolerated), and a high polypharmacy burden. Although the magnitude of the treatment harm might seem trivial, there

**Figure 3.** Health benefit and net health benefit of treating to target levels, by baseline risk level and treatment, combined analysis. ACEI indicates angiotensin-converting enzyme inhibitor; BBL, β-blocker; BP, blood pressure; CCB, calcium channel blocker; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life-year; THI, thiazide. The white space at the top of each bar represents the magnitude of the benefit that is lost to treatment-related disutility.
are compelling reasons not to discount it. Greater use of polypharmacy is associated with a higher risk of drug interactions; more uncertain long-term safety risks (particularly when newer treatments are used); and significant cost, inconvenience, and adverse effect burdens that might engender higher rates of nonadherence. Given the large number of comorbidities often associated with DM, pursuing small marginal health gains through polypharmacy could have considerable opportunity costs. We accounted for these factors by using a small disutility that increased with the level of polypharmacy, but formally quantifying these effects is a challenge.

By attempting to simulate a complex clinical process, our model required a number of simplifications. There is no 1 standard treatment protocol for controlling LDL-C and BP, and using a different set of treatments, additional treatments, or allowing therapeutic substitutions instead of simply additions or titrations could have an impact on our results. We restricted our focus to treatments likely to be considered standard in most practice settings and considered only therapies with known efficacy in lowering each risk factor. We did not consider fibrate therapy, for example, which is often prescribed to lower triglyceride levels and increase high-density lipoprotein cholesterol levels because it has limited efficacy in lowering LDL-C and has not been shown to reduce CVD mortality.10,45 Although we might have considered substituting therapies for patients having adverse events to lower the contribution of treatment harms, doing so would have resulted in lower rates of successful control and smaller health improvements.

Although we assessed all assumptions in sensitivity analyses, we were unable to find values for several model parameters in the clinical literature. We found no estimates for the relative BP reduction observed with combination therapy involving 3 or more antihypertensives, so we extrapolated estimates from 2-drug combinations. The absence of these data are alarming given the high level of combination therapy used today. Lacking an estimate of the disutility for statin-induced myalgia, we assigned a value of 0.10; otherwise, we were unable to find values for several model parameters addressed in our study to help make treatment decisions that are more in line with an individual patient's risks and benefits. Therefore, our model and assumptions may or may not represent how clinicians currently practice but rather what would happen if current guidelines were followed rigidly by clinicians. Furthermore, we are not posing that clinicians should solely consider quantitative estimates of models such as ours when making individual patient decisions. However, having such estimates could greatly assist clinicians in helping their patients make personalized decisions, and given the complexity of the factors involved in estimating risks and benefits of lipid and BP treatments, it seems likely that information systems that can assimilate this information and support evidence-based treatment recommendations will be needed for models like ours to be used in clinical practice. Decision support is even more important owing to the speed with which the clinical literature evolves in this area.

**CONCLUSIONS**

Aggressively treating cardiovascular risk factors to achieve low target levels can produce large health benefits on average, but these benefits accrue disproportionately to a small subset of very high-risk patients; below average to average-risk patients seem to receive virtually no net benefit from titrating beyond standard doses of a statin and 2 to 3 BP medications, even if commonly recommended LDL-C and BP goals have not been met. Given the large set of factors that moderate the benefit of treatment intensification, including patients' underlying CVD risk, the diminishing efficacy of combination therapy, and increasing polypharmacy and adverse effects, we recommend a strategy of tailoring treatments to individual patients on the basis of their expected benefit of intensifying treatment. Current treatment approaches that encourage uniformly lowering risk factors to common target levels can be both inefficient and cause unnecessary harm.

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