Determining When to Add Nonstatin Therapy
A Quantitative Approach

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ABSTRACT

BACKGROUND Costs and uncertainty about the benefits of nonstatin therapies limit their use.

OBJECTIVES The authors sought to identify patients who might benefit from the addition of a nonstatin to background statin therapy.

METHODS We performed systematic reviews of subgroup analyses from randomized trials and observational studies with statin-treated participants to determine estimated 10-year absolute risk of atherosclerotic cardiovascular disease (ASCVD) and to define high-risk and very high-risk patients. We used the relative risk reductions for the addition of a nonstatin to lower low-density lipoprotein (LDL-C) used to determine the number needed to treat (NNT) to prevent 1 ASCVD event over 5 years for each patient group and to allow comparisons with 5-year cost analyses.

RESULTS The 10-year ASCVD risk is at least 30% (very high risk) for statin-treated participants with clinical ASCVD and comorbidities, and 20% to 29% (high risk) for those with ASCVD without comorbidities or who have heterozygous familial hypercholesterolemia. Adding ezetimibe to reduce low-density LDL-C by 20% would provide a 5-year NNT ≤50 for very high-risk patients with LDL-C ≥130 mg/dl or for high-risk patients with LDL-C ≥190 mg/dl, and an NNT ≤30 for very high-risk patients with LDL-C ≥160 mg/dl. Adding a PCSK9 monoclonal antibody to lower LDL-C by at least 50% would provide an NNT ≤50 for very high-risk and high-risk patients with LDL-C ≥70 mg/dl, and an NNT ≤30 for very high-risk and high-risk patients with an LDL-C ≥130 mg/dl.

CONCLUSIONS Adding ezetimibe or PCSK9 monoclonal antibodies to maximally tolerated statin therapy may be cost effective in very high-risk and high-risk patients, depending on baseline LDL-C levels.

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Patients may remain at increased risk of an atherosclerotic cardiovascular disease (ASCVD) event despite maximally tolerated statin therapy. The American College of Cardiology (ACC) recently released a clinical pathway for nonstatin therapy for additional low-density lipoprotein cholesterol (LDL-C) lowering in statin-treated patients (1). This pathway is intended to provide a bridge between...
the 2013 ACC/American Heart Association (AHA) cholesterol guideline (2) and future cholesterol guidelines.

The ACC pathway emphasizes consideration of a potential net benefit from adding nonstatin therapy and the role of shared decision-making in the clinician-patient discussion first introduced in the 2013 ACC/AHA cholesterol guideline (Online Appendix A). The ACC pathway supports the recently introduced concept of LDL-C thresholds to trigger consideration of additional nonstatin therapy (3), but provided only general guidance for determining the potential net benefit of such therapy (Online Appendix A).

New evidence has emerged since the ACC pathway was completed that suggests how to determine quantitation of net benefit. We and others have recently shown that quantitation of the absolute benefit from an added therapy can inform clinical decision-making (4–6). Absolute risk reduction (ARR) from added therapy can be quantified as the number needed to treat (NNT) to prevent the first event in a given time horizon, which then allows comparison to the number that would need to be treated to cause 1 adverse event (number needed to harm [NNH]). Consideration of NNT and NNH can be used to inform the clinician-patient discussion and is an important step toward supporting personalized medicine. NNT and NNH can also be used to define patient groups using a combination of absolute risk and LDL-C thresholds likely to benefit from the addition of a nonstatin therapy.

METHODS

ABSORVE KEY POINTS

Absolute risk and ARR. The potential ARR from an added therapy is a function of the absolute risk of the patient and the relative reduction in risk from the added therapy. On the basis of a systematic review of randomized clinical trials (RCTs), the 2013 ACC/AHA cholesterol guideline identified cut points for primary prevention from the placebo groups of primary prevention statin trials (2). We used a similar approach by performing a systematic review of RCTs to identify the lower limit of absolute risk for various patient groups identified in the ACC pathway (Online Appendix B) (1). RCTs identified in the systematic review for the 2013 ACC/AHA guideline (publications between January 1975 and May 2011) were reviewed for ASCVD outcomes (defined as incident nonfatal myocardial infarction [MI], nonfatal stroke, fatal MI or stroke, coronary heart disease, or cardiovascular death) in the statin monotherapy arm as well as adverse effects and percent reduction in LDL-C. We searched MEDLINE for relevant subgroup analyses from trials with ASCVD outcomes published between January 1994 and April 6, 2016, and manually searched our personal files and references of key papers, reviews, and meta-analyses. ASCVD risk was extrapolated to 10 years to facilitate comparisons with risk assessed in primary prevention patients using 10-year risk estimation, as recommended in the 2013 ACC/AHA cholesterol guideline (7).

Because no trial specifically enrolled patients with familial hypercholesterolemia (FH), we performed a systematic review of observational studies. We were unable to identify any publications reporting 10-year ASCVD rates in statin-treated FH patients, although 2 were identified subsequent to the completion of the search (8,9). We therefore undertook an analysis of the national cascade screening program conducted in the Netherlands from 1994 to 2010, which has been described in detail previously (Online Appendix C) (10,11).

Relative risk reduction with nonstatin therapy. The ACC pathway identified ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and bile acid sequestrants as nonstatin options for additional LDL-C lowering. The magnitude of LDL-C lowering with these nonstatins varies, and only ezetimibe has been shown to clearly reduce ASCVD events when added to background statin therapy (2,12). Cholestyramine has been shown to reduce cardiovascular events in men with hypercholesterolemia, but no cardiovascular outcomes trials have been performed for bile acid sequestrants in the setting of background statin therapy (13). The ACC pathway did not recommend niacin or fibrates for additional LDL-C lowering. These treatments modestly reduce LDL-C <10%, and do not appear to reduce ASCVD risk when added to background statin therapy; niacin substantially increases adverse events (2,14).

The relative reduction in cardiovascular events for statins, ezetimibe, and possibly PCSK9 monoclonal antibodies (mAbs), has been found to be consistent with the relationship described in the CTT (Cholesterol Treatment Trialists) meta-analysis, wherein each 39 mg/dl (1 mmol/l) reduction in LDL-C was associated with a 21% reduction in major cardiovascular events (Figure 1) (3,12,15–17). Thus, the average relative risk reduction from adding 1 of these LDL-C-lowering therapies was considered a linear function of the reduction in LDL-C level on statin therapy and approximated by $0.21 \times$ the mmol/l reduction in LDL-C for this analysis.

ABBREVIATIONS AND ACRONYMS

ARR = absolute risk reduction
ASCVD = atherosclerotic cardiovascular disease
FH = familial hypercholesterolemia
ICER = Institute for Clinical and Economic Review
LDL-C = low-density lipoprotein cholesterol
mAb = monoclonal antibody
MI = myocardial infarction
NNH = number needed to harm
NNT = number needed to treat
PCSK9 = proprotein convertase subtilisin-like/kexin type 9
QALY = quality-adjusted life year
ARR = absolute risk reduction
ASCVD = atherosclerotic cardiovascular disease
FH = familial hypercholesterolemia
ICER = Institute for Clinical and Economic Review
LDL-C = low-density lipoprotein cholesterol
mAb = monoclonal antibody
MI = myocardial infarction
NNH = number needed to harm
NNT = number needed to treat
PCSK9 = proprotein convertase subtilisin-like/kexin type 9
QALY = quality-adjusted life year
Abbreviations and Acronyms
To identify the average LDL-C-lowering efficacy and rate of adverse events in statin-treated patients, we used a previously published individual level meta-analysis of ezetimibe trials and IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efﬁcacy International Trial) to determine ezetimibe efﬁcacy, a systematic review of PCSK9 mAb trials, and previous systematic reviews of bile acid sequestrants (Online Appendix D) (2,12,18,19).

**RESULTS**

**ABSOLUTE RISKS.** We identified 6 RCTs from the 2013 ACC/AHA guideline systematic review and MEDLINE search that reported ASCVD events as a primary or secondary outcome (Online Appendix B). These trials had been graded as fair to good quality by the National Heart, Lung, and Blood Institute criteria developed for their systematic review (7). From these 6 trials, 16 papers reported ASCVD event rates for subgroups that were used to identify absolute risk levels for the patient risk categories used in the ACC pathway or other patient subgroups on the basis of sex, age, or multivessel ASCVD (Online Appendix B, Online Table B1). The large majority of these were post hoc subgroup analyses.

Patients included in the ACC pathway category of “clinical ASCVD with comorbidities” were at very high risk, and largely had a projected 10-year ASCVD risk ≥30% despite moderate- or high-intensity statin therapy: 26% to 43% for those with ASCVD and diabetes, 34% to 35% for those with recent acute coronary syndromes (<10 days), and 28% to 41% for those with ASCVD and poorly controlled risk factors of current smoking or resistant hypertension (deﬁned as a glomerular filtration rate <60 ml/min/1.73 m²), 32% for those with recent acute coronary syndromes (<10 days), and 28% to 41% for those with ASCVD and poorly controlled risk factors of current smoking or resistant hypertension (deﬁned as a glomerular filtration rate <60 ml/min/1.73 m²). Other patient subgroups also had ≥30%
Patients included in the ACC pathway category of "clinical ASCVD without comorbidities" were high risk, with 10-year ASCVD risks of 20% to 29% on moderate- or high-intensity statin therapy. However, lower 10-year risks were consistently observed among some groups of ASCVD patients without comorbidities who were receiving high-intensity statin therapy (e.g., no diabetes: 16% to 20%; nonsmokers or former smokers: 10% to 26%; and controlled hypertension: 16% to 20%) (Online Appendix B, Online Table B1). Other high-risk patient groups with coronary heart disease included those who had undergone coronary artery bypass grafting, those without peripheral arterial disease, patients age <65 years, and women with a history of stroke or transient ischemic attack. The presence or absence of metabolic syndrome and its components did not increase 10-year ASCVD risk above the 30% threshold (15% to 26% 10-year ASCVD risks).

The ACC pathway patient category of primary prevention with baseline primary LDL-C ≥190 mg/dl was addressed with our analysis of untreated Dutch FH patients with severe low-density lipoprotein receptor mutations, which found a rate of nonfatal cardiovascular events (including coronary revascularizations) of 20% to 40% in those who were age 40 to 80 years. This is likely equivalent to a similar or higher rate of nonfatal and fatal ASCVD events (Online Appendix C). Another analysis of 6 large epidemiological studies used an LDL-C ≥190 mg/dl to define an FH phenotype in individuals free of ASCVD, but did not correct for statin use after baseline (9). They found increasing ASCVD event rates with advancing age, ranging from 14 per 1,000 patient-years at age 40 to 49 years to 26 per 1,000 patient-years at age 70 to 79 years. Due to lifetime exposure to high LDL-C levels, the lower risk in statin-treated FH patients would likely be higher than expected from the on-treatment LDL-C levels.

**TABLE 1** The 5-Year NNT to Prevent 1 Cardiovascular Event for Very High-, High-, Moderate-, and Lower-Risk Individuals on Maximal Statin Therapy

<table>
<thead>
<tr>
<th>Initial LDL-C, mg/dl</th>
<th>Add Ezetimibe</th>
<th>Combination Therapy</th>
<th>PCSK9 mAb</th>
<th>PCSK9 mAb Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>190</td>
<td>32</td>
<td>18</td>
<td>13</td>
<td>10</td>
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<tr>
<td>160</td>
<td>38</td>
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<tr>
<td>70</td>
<td>263</td>
<td>150</td>
<td>105</td>
<td>81</td>
</tr>
</tbody>
</table>

*Excluding PCSK9 mAbs. NNT calculated for lower limit of range; Very high risk (≥30% 10-yr ASCVD risk) is defined as: clinical ASCVD = diabetes; clinical ASCVD = chronic kidney disease; clinical ASCVD with poorly controlled risk factors (smoking or hypertension); recent acute coronary syndrome (<3 months); clinical ASCVD = primary LDL-C <190 mg/dl or familial hypercholesterolemia; recent acute coronary syndrome (<3 months); clinical ASCVD with multiple recurrent events (included in an ACC pathway patient category but no subgroup analyses identified in systematic review); or clinical ASCVD with elevated lipoprotein (a) (included in an ACC pathway patient category but no subgroup analyses identified in systematic review). High Risk (20% to <30% 10-yr ASCVD risk) is defined as: clinical ASCVD (no diabetes and primary LDL-C <190 mg/dl); or primary prevention familial hypercholesterolemia (heterozygous; no clinical ASCVD; age >40 yr) or primary LDL-C <190 mg/dl (included in an ACC pathway patient category but no subgroup analyses identified in systematic review). Moderate Risk (10% to <20% 10-yr ASCVD risk) is defined as: primary prevention LDL-C <190 mg/dl (with or without diabetes). To estimate 10-year ASCVD risk on statin and if pretreatment. If pre-treatment cholesterol levels are known: use Pooled Equations Cohort or other validated risk prediction equation calibrated to the clinical population when primary LDL-C <190 mg/dl. Then apply the average relative risk reduction of 30% for moderate intensity and 45% for high intensity statin to estimate 10-year ASCVD risk on statin therapy. Risk prediction equations have not been validated when on-treatment total cholesterol levels are used. Bold = NNT ≥30. italic = NNT 31-50; ACC = American College of Cardiology; ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; mAb = monoclonal antibody; NNT = number needed to treat; PCSK9 = proprotein convertase subtilisin-like/kexin type 9; RRR = relative risk reduction.

Patients included in the ACC pathway category of “primary prevention diabetes with LDL-C <190 mg/dl” had a 10-year ASCVD risk <20% on a moderate-intensity statin (Online Appendix B, Online Table B1). **RELATIVE RISK REDUCTION AND NNTS FOR NONSTATINS.** To compare NNTs, representative LDL-C reductions of 20%, 35%, 50%, and 65% were selected on the basis of average efficacies for ezetimibe, combinations of 2 nonstatins other than a PCSK9 mAb, and PCSK-9 mAbs (Online Appendix D) (12,16–19,22–27).

Preliminary data has shown that evolocumab and alirocumab reduced major cardiovascular events over a period of 11 to 18 months in patients with average baseline LDL-C levels of 120 to 122 mg/dl (16,17).
Representative NNTs for 5 years of treatment for several percent reductions in LDL-C, absolute risk thresholds, and baseline LDL-C levels are provided in Table 1.

### ADVERSE EVENT RATES FOR NONSTATINS

Ezetimibe had no significant adverse effects with long-term use in the IMPROVE-IT trial (12). Bile acid sequestrants may have significant gastrointestinal adverse effects and drug interactions (Online Appendix D) (19).

Neurocognitive events were the most significant adverse effect reported for the 2 PCSK9 mAbs (Online Appendix D) (16,17,27). The NNH for PCSK9 mAbs over this time period was calculated from the average annualized excess rate of the broad category of neurocognitive adverse events reported in the ODYSSEY LONG TERM and OSLER (Open-Label Study of Long-Term Evaluation against LDL Cholesterol) trials (average approximately 0.5%/year), yielding a 1-year NNH of 186. This rate was not extrapolated to 5 years in the absence of longer-term safety data.

### DISCUSSION

These findings largely validate the patient categories used in the ACC nonstatin clinical pathway. They also provide strong support for the use of absolute risk and LDL-C thresholds for informing the decision to add a nonstatin, providing quantitative information that can guide decision making within the context of

| NNT 10–14 | Very high-risk individuals with LDL-C ≥190 mg/dl or LDL-C ≥160 mg/dl if ≥65% LDL-C reduction No discount $= $150,000 QALY |
| NNT 21–28 | Very high-risk patients with LDL-C ≥100 mg/dl High-risk patients with LDL-C ≥130 mg/dl Depending on discount: Discount = 50% ($7,700/yr)/$150,000 QALY Discount = 60% ($5,400/yr)/$100,000 QALY Discount = 77% ($3,200/yr)/$50,000 QALY Discount = 85% ($2,200/yr) to avoid exceeding growth targets U.S. health care costs |
| NNT <30 | Very high-risk patients LDL-C ≥100 mg/dl High-risk patients LDL-C ≥130 mg/dl Moderate-risk patients LDL-C ≥190 mg/dl No discount $/=- $274,000–$302,000 QALY |
| NNT <50 | Very high-risk patients LDL-C ≥70 mg/dl High-risk patients LDL-C ≥100 mg/dl Moderate-risk patients LDL-C ≥160 mg/dl No discount $/=- $290,000–$302,000 QALY |

*Cost per quality-adjusted life year (QALY) gained (assuming undiscounted acquisition cost of $14,000/yr and 50% relative risk reduction with PCSK9 mAb $C15). All costs in U.S. dollars. Ezetimibe recently became generic. Cost-effectiveness analyses unavailable.

Abbreviations as in Table 1.

CLINICAL PERSPECTIVE

Applying this metric, the addition of ezetimibe for an additional 20% reduction in LDL-C would seem reasonable at the NNT <50 level for very high-risk patients with LDL-C ≥130 mg/dl or high-risk patients with LDL-C ≥190 mg/dl (Tables 1 and 2, Central Illustration). At the NNT <30 level, ezetimibe therapy would be reasonable only for very high-risk patients with LDL-C ≥160 mg/dl. Thus, ezetimibe seems most likely to provide a meaningful risk reduction benefit only for patients with heterozygous FH, or those at high risk who are unable to tolerate or are less responsive to higher-intensity statin therapy.

A 50% or 65% reduction in LDL-C results in lower 5-year NNTs (Table 1). On the basis of a 5-year NNT ≤50, clinicians might consider the addition of a PCSK9 mAb reasonable for very high-risk patients with LDL-C ≥70 mg/dl, high-risk patients with LDL-C ≥100 mg/dl, and moderate-risk patients with LDL-C ≥160 mg/dl (Tables 1 and 2). At the NNT ≤30 level, a PCSK9 mAb would be reasonable in very high-risk patients with LDL-C ≥100 mg/dl, high-risk patients with LDL-C ≥130 mg/dl, and moderate-risk patients with LDL-C ≥190 mg/dl. To inform the clinician-patient discussion, consideration of adverse events is needed to estimate the potential for net benefit. Ezetimibe appears to have no serious adverse effects, and therefore the NNT likely reflects the potential for net benefit. Bile acid sequestrants were recommended in the ACC pathway for consideration as a second-line agent after ezetimibe in patients with a history of untreated heterozygous FH, or those at high risk who are unable to tolerate or are less responsive to higher-intensity statin therapy.

These findings largely validate the patient categories used in the ACC nonstatin clinical pathway. They also provide strong support for the use of absolute risk and LDL-C thresholds for informing the decision to add a nonstatin, providing quantitative information that can guide decision making within the context of
highest doses. It seems reasonable as part of shared decision-making to mention that the potential for adverse cognitive events for PCSK9 mAbs is relatively low (1-year NNH $= 186$ for the broad category of neurocognitive events) and may be confined to the highest doses of PCSK9 mAbs. The 5-year NNH for neurocognitive events on the basis of formal neurocognitive testing is unknown at this time, pending the results of ongoing trials. However, the risk of potentially severe adverse events is likely far outweighed by the potential for an ASCVD risk reduction in higher-risk patients.

Additional considerations in the clinician-patient discussion include evidence from randomized trials that the additional drug reduces ASCVD events when added to background statin therapy, patient perceptions of benefits and harms, patient preferences for additional preventive treatment, route of administration, convenience and medication storage, insurance copayments, and whether the additional drug will jeopardize adherence to other evidence-based therapies (1,3). A case example is provided in Table 3.

**COST PERSPECTIVE.** Currently, the cost of the PCSK9 mAbs precludes widespread use of these drugs in patients who might benefit (20,29). The wholesale acquisition price of both alirocumab and evolocumab exceeds $14,000/year in the United States, although discounting may occur for some payers and in other countries. A cost-effectiveness analysis of PCSK9

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**Table 3**: Determining When to Add Nonstatin Therapy

<table>
<thead>
<tr>
<th>Patient LDL-C (mg/dl)</th>
<th>Very high-risk patient (≥30 10-year ASCVD risk)</th>
<th>High-risk (20–29% 10-year ASCVD risk)</th>
<th>Moderate-risk (10–19% 10-year ASCVD risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥190</td>
<td>PCSK9 mAb (NNT ≤21-28) Ezetimibe (NNT &lt;30)</td>
<td>PCSK9 mAb (NNT ≤21-28) Ezetimibe (NNT &lt;50)</td>
<td>PCSK9 mAb (NNT &lt;50)</td>
</tr>
<tr>
<td>≥160</td>
<td>Ezetimibe (NNT &lt;50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥130</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥100</td>
<td>PCSK9 mAb (NNT &lt;50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70</td>
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</tbody>
</table>


The “rule of thumb” categories of patients who are likely to experience an atherosclerotic cardiovascular disease (ASCVD) risk reduction benefit from additional low-density lipoprotein cholesterol (LDL-C)-lowering therapy, considering both clinical and cost perspective (assuming no adverse events). mAb = monoclonal antibody; NNT = number needed to treat.
TABLE 3 Case Study of a 43-Year-Old Woman With LDL-C >190 mg/dl

<table>
<thead>
<tr>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI 28.7 kg/m², blood pressure 145/86 mm Hg. No corneal arcus, normal tendon size.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting lipid panel total cholesterol 343 mg/dl, LDL-C 249 mg/dl, HDL-C 58 mg/dl, triglycerides 178 mg/dl</td>
</tr>
<tr>
<td>Fasting glucose: 102 mg/dl</td>
</tr>
<tr>
<td>Normal values: thyroid stimulating hormone, alanine aminotransferase, total protein, alkaline phosphatase, bilirubin, and creatinine</td>
</tr>
</tbody>
</table>

**Assessment**

1. **Familial hypercholesterolemia.** She meets the FH diagnostic criteria of the American Heart Association: primary elevation in LDL-C ≥190 mg/dl for adults plus a first degree relative with premature coronary heart disease (alternatively may have a first degree relative with LDL-C ≥190 mg/dl for adults or LDL-C ≥160 mg/dl for children, or positive genetic testing) (41). No evidence of secondary causes of hypercholesterolemia. The prevalence of FH is approximately 1 in 250 individuals in populations around the world, and higher in some communities (9,40).

2. **Treatment.** She is in a statin benefit group identified in the 2013 ACC/AHA cholesterol guideline (primary LDL-C ≥190 mg/dl (2). No further risk assessment is necessary (indeed, pooled cohort equations do not accurately estimate risk when LDL-C ≥190 mg/dl) (36). Start atorvastatin 80 mg, a high-intensity statin as recommended by the 2013 ACC/AHA cholesterol guideline for all adults ≥21 yrs with LDL-C ≥190 mg/dl unless there is a contraindication (2).

3. **Contraception.** The patient and her partner were counseled to continue effective contraception to avoid the potential risk of fetal harm from statin therapy.

4. **Life-style.** She was encouraged to continue a heart-healthy diet, to have regular physical activity, to control weight, and to continue to avoid exposure to tobacco.

5. **Follow-up.** Lipid panel at 3 months. No need to retest liver function tests because baseline ALT was normal.

**Follow-Up Visit**

J.V. returns for her 9-month follow-up visit. Her LDL-C after 3 months on atorvastatin 80 mg was 147 mg/dl, a 41% reduction from baseline. She was counseled on adherence to life-style and medication. At the 6-month follow-up visit, her LDL-C was 142 mg/dl, a 43% reduction from baseline. LDL-C today is 149 mg/dl on atorvastatin 80 mg/dl. She has no musculoskeletal symptoms, missed no doses of atorvastatin (she uses a weekly pillbox), and is as adherent as she is able to with her life-style.

**Assessment**

1. **Familial hypercholesterolemia.** Her 15-yr-old son has an LDL-C of 180 mg/dl and has been started on a moderate-intensity statin (45). Her 12-yr-old daughter has an LDL-C of 130 mg/dl and has been started on a moderate-intensity statin (45). There are no other affected family members.

2. **Additional LDL-C lowering.** She was engaged in a clinician-patient discussion. She would likely benefit from additional LDL-C lowering to reduce her burden of atherosclerosis for several reasons: 1) due to her lifetime exposure to high LDL-C levels; 2) the delay in starting atorvastatin in her 40s; and 3) the increased ASCVD risk observed in African-American women and men (46).

3. **Families.** The patient and her partner were counseled to continue effective contraception to avoid the potential risk of fetal harm from statin therapy.

4. **Life-style.** She was encouraged to continue a heart-healthy diet, to have regular physical activity, to control weight, and to continue to avoid exposure to tobacco.

5. **Follow-up.** Lipid panel at 3 months. No need to retest liver function tests because baseline ALT was normal.

mAbs released by ICER found that for those with FH, with clinical CVD and statin intolerance, and with ASCVD and LDL-C ≥70 mg/dl, the incremental cost effectiveness ratios were $290,000, $274,000, and $202,000 per QALY gained, respectively (5-year NNT = 28, 21, and 21, respectively) (20). The ICER estimated that for PCSK9 mAbs to be cost-effective (under conventional willingness-to-pay thresholds of $50,000, $100,000, and $150,000 per QALY gained), the annual price would need to be reduced to $2,166, $5,404, and $7,735, respectively. They estimated a price of $2,177/year (an 85% discount from list price) would be required to keep from exceeding growth targets in the future gross domestic product, as suggested in state and national legislation.

ICER calculations on the basis of NNT suggest strategies for better identifying patient groups in which PCSK9 mAbs would be reasonably cost-effective. Referring to Table 1, 5-year NNTs <10 to 12 would likely be cost effective at <$150,000 per QALY gained for full-price PCSK9 mAbs—corresponding to very high-risk individuals with LDL-C ≥160 mg/dl (Central Illustration, Tables 1 and 2). This captures very high-risk patients who have the most to benefit
from PCSK9 mAb therapy—those with clinical ASCVD and FH, or statin intolerant patients with clinical ASCVD and other genetic hypercholesterolemas. However, if 50% discounting occurs, a 5-year NNT of 21 to 28 would also likely be cost effective at <$150,000 per QALY gained. This corresponds to very high-risk patients with LDL-C ≥100 mg/dl, or high-risk patients with LDL-C ≥160 mg/dl.

The ICER analysis assumed a 50% reduction in cardiovascular events on the basis of the preliminary data from shorter-term efficacy trials (20). However, this magnitude of relative risk reduction may only hold true at the higher LDL-C levels of patients who were enrolled in the 2 PCSK9 mAb efficacy/safety trials that reported the preliminary cardiovascular outcomes data—where mean LDL-C was approximately 120 mg/dl and an approximately 65% reduction in LDL-C occurred (16,17). The CTT meta-analysis suggests that smaller relative risk reductions may occur when baseline LDL-C levels are lower or percent LDL-C reductions are smaller (15). Ongoing cardiovascular outcomes trials for evolocumab and alirocumab are evaluating incremental risk reduction in LDL-C occurred (16,17). The CTT meta-analysis suggests that smaller relative risk reductions may occur when baseline LDL-C levels are lower or percent LDL-C reductions are smaller (15). Ongoing cardiovascular outcomes trials for evolocumab and alirocumab are evaluating incremental risk reduction in LDL-C occurred (16,17). Therefore the cost-effectiveness ratio may be lower than originally estimated if a <50% relative reduction in cardiovascular events is observed. Ezetimibe is anticipated to become generic in 2017 in the United States, which should substantially influence its cost-effectiveness.

**STUDY LIMITATIONS.** Determination of absolute risk for the ACC pathway patient groups was on the basis of the best evidence available from clinical trials, and few data were available for patients with baseline primary LDL-C ≥190 mg/dl. Risk prediction equations are needed for statin-treated patients with and without ASCVD derived from contemporary data that include levels of risk factor control and use of evidence-based medications (32). Although risk prediction and estimation of net benefit is probabilistic, more refined estimates may better prioritize patients for therapy and inform the clinician-patient discussion.

We used the relative risk reduction (21%) expected for a 39 mg/dl (1 mmol/l) reduction in LDL-C observed in the CTT meta-analysis for the 50% and 65% reduction in LDL-C from adding a PCSK mAb. The confidence intervals were wide in the preliminary data reported to date (Figure 1). More precise estimates await ongoing cardiovascular outcomes trials of PCSK9 mAbs.

NNT and NNH have several important limitations. They represent averages on the basis of numerous assumptions and are influenced by the time horizon for risk. For younger individuals, a longer horizon might be more appropriate (33), which might make our results more conservative.

The use of 20% to define the lower absolute risk threshold in the high-risk category may not reflect the risk of patients receiving high-intensity statins. However, the achieved LDL-C level <70 mg/dl with high-intensity statin therapy in the majority of ASCVD patients in clinical trials (2) means that most will not enter the ACC pathway for consideration of nonstatin therapy.

We assumed a linear association between LDL-C and cardiovascular event reduction to extrapolate to LDL-C levels beyond those observed in Figure 1. Some evidence suggests that this might be conservative, because risk reductions might be curvilinear and thus steeper at very high LDL-C levels (34).

**OTHER PREVENTIVE THERAPIES.** The focus of this paper is on adding nonstatin therapy to further lower LDL-C in patients who are receiving maximal statin therapy, but the same concept of net benefit can be extended to other drugs that reduce ASCVD events. A number of cardiovascular outcomes trials are underway for drugs that modify other lipids or have anti-inflammatory effects. If these drugs are shown to further reduce ASCVD events when added to maximal evidence-based therapies, the relative ASCVD risk reduction can be used to estimate the absolute risk reduction (and NNT) independent of baseline LDL-C level. The adverse event rates in the trial(s) can be used to estimate NNH, which together with NNT can be used to estimate the potential for net benefit. This information can then be used to inform shared decision making as part of the clinician-patient discussion. Consideration of NNT and NNH could also be used to inform the long-term use of other preventive therapies that reduce cardiovascular events in the statin era, such as aspirin or beta-blocking agents. The NNT and NNH may also inform the intensification of antihypertensive therapy on the basis of data from the SPRINT trial (35).

**FUTURE DIRECTIONS.** Current risk prediction equations are intended for individuals without CVD who are not receiving statin therapy (36). Risk prediction equations for recurrent ASCVD events are subject to several limitations, including decades old data and a lack of statin information (32,37). Validated, easy to use risk calculators derived from contemporary data from the population under treatment are urgently
needed for predicting ASCVD outcomes among statin-treated patients and for individualized prediction of adverse events from the added therapy.

Alternative treatment paradigms on the basis of the legacy effects observed with long-term follow-up of statin trials may be established with long-term follow-up of the PCSK9 mAbs trials (38). Shorter-term intensive LDL-C lowering therapy with PCSK9 mAbs might be more cost-effective when considered over longer-term benefit, or when a broader range of ASCVD events or recurrent events are considered (39,40).

CONCLUSIONS

The addition of ezetimibe or PCSK9 mAbs to maximally tolerated statin therapy may be cost effective in very high-risk and high-risk patients, depending on baseline LDL-C levels and pricing. Estimation of NNT is determined by patient’s absolute risk and the estimated relative reduction in risk from therapy. The potential for net benefit is based on estimated NNT and NNH. For NNT $\geq$50, ezetimibe may benefit very high-risk patients with LDL-C $\geq$130 mg/dl or high-risk patients with LDL-C $\geq$190 mg/dl, and PCSK9 mAb may benefit very high-risk and high-risk patients with LDL-C $\geq$70 mg/dl. For NNT $\geq$30, ezetimibe may benefit very high-risk patients with LDL-C $>$160 mg/dl, and PCSK9 mAb may benefit very high-risk and high-risk patients with LDL-C $>$130 mg/dl.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Some patients treated with statin drugs remain at risk of ischemic cardiovascular events. The benefit and risk of adding a nonstatin agent to further lower LDL-C can be estimated on the basis of the patient’s risk, the on-treatment LDL-C level, and the additional relative reduction in risk on the basis of the percent reduction in LDL-C.

TRANSLATIONAL OUTLOOK: Prospective studies are needed to validate the effect of drug-specific algorithms on rates of ischemic outcomes when nonstatin agents are added in statin-treated patients with atherosclerosis.

REFERENCES


KEY WORDS cost, ezetimibe, nonstatins, PCSK9 inhibitors, statins

APPENDIX For supplemental figures and tables, and Supplements A to D, please see the online version of this article.