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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

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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).

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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

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× 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