Identifying Patients for Nonstatin Therapy

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Statins are first-line therapy for reducing atherosclerotic cardiovascular disease (ASCVD) risk. Some patients remain at high ASCVD risk despite maximizing statin therapy. Ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs) have been shown to reduce ASCVD events in randomized trials and may be of benefit in selected high-risk patients with cardiovascular disease (CVD) or familial hypercholesterolemia (FH). Number-needed-to-treat (NNT) to prevent one ASCVD event can help identify groups of patients who may gain a net benefit from added nonstatin therapy. Patient groups with NNTs <25 (in whom PCSK9 mAbs may approach cost effectiveness with discounting) include extremely high-risk patients (those with CVD with FH, polyvascular disease, or recurrent ASCVD events) with low-density lipoprotein cholesterol (LDL-C) levels ≥ 70 mg/dL, very high-risk patients (those with CVD with diabetes [and no polyvascular disease], chronic kidney disease, or acute coronary syndromes, or CVD or FH with poorly controlled risk factors) with LDL-C levels ≥ 100 mg/dL, and high-risk patients (those with CVD or FH with well-controlled risk factors) with LDL-C ≥ 130 mg/dL. Ezetimibe, which is generic in the United States, is reasonable for patient groups with NNTs <30, the level considered reasonable by most patients. This includes extremely high-risk patients with LDL-C levels ≥ 130 mg/dL, or very high-risk patients with LDL-C ≥ 190 mg/dL. All guidelines recommend statin therapy for the prevention of ASCVD.

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KEY WORDS

Atherosclerotic cardiovascular disease • PCSK9 monoclonal antibodies • Nonstatin therapy • Cholesterol-lowering therapies

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guideline emphasizes maximizing statin therapy, with high-intensity statin therapy recommended for higher-risk patients (those with clinical atherosclerotic cardiovascular disease [ASCVD] who are up to age 75 years, patients who have low-density lipoprotein cholesterol (LDL-C) level ≥190 mg/dL, or diabetics who are aged 40 to 75 years with ≥7.5% 10-year ASCVD risk).[1] If safety is an issue, or in those with clinical ASCVD aged >75 years, moderate-intensity statin therapy is recommended. In lower-risk primary prevention, moderate- or high-intensity statin therapy is considered reasonable. Regular monitoring of LDL-C levels is recommended to assess response to therapy and adherence to lifestyle and drug therapy.

Considerations for Adding Nonstatin Therapy

When does more need to be done once a patient is on maximally tolerated statin therapy? In patients who remain at high risk despite maximal statin therapy, the 2013 ACC/AHA cholesterol guideline recommends consideration of nonstatin agents that are shown to reduce ASCVD risk in randomized trials. When the 2013 guideline was completed, trials of niacin and fenofibrate showed that these drugs did not clearly reduce cardiovascular events when added to statin therapy, and could be harmful.[2-4] Recent randomized outcome trials of ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs) are beginning to provide the evidence to guide nonstatin treatment decisions.

Results from these trials support the net benefit paradigm introduced in the 2013 ACC/AHA cholesterol guideline.[5] Net benefit is a key consideration when the margins of benefit may be less, there are significant safety considerations, or either drug cost or access are an issue. To date, there have been no significant safety concerns with ezetimibe or the PCSK9 mAbs, alirocumab and evolocumab.[6-8] Ezetimibe has recently become generic in the United States. However, cost and access to PCSK9 mAbs continue to limit their use. Therefore, the potential for net benefit (and thereby the number of ASCVD events prevented) has important consequences in terms of cost effectiveness and willingness to pay. Net benefit depends on the ASCVD risk of the patient and the baseline LDL-C level, which is a result of genetic and lifestyle factors, statin intensity, and magnitude of reduction of LDL-C with the therapeutic intervention (Figure 1).

Recent trials of ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs) are beginning to provide the evidence to guide nonstatin treatment decisions.

Net clinical benefit can be quantified as the absolute risk reduction (ARR) benefit minus the potential for adverse effects. Number-needed-to-treat to prevent one ASCVD event (NNT) is simply 1/ARR. NNT is easily understood by clinicians, patients, and payers. In general, clinicians consider an NNT of approximately 50 to be reasonable to consider a preventive therapy, whereas patients consider an NNT of approximately 30 to be reasonable.[9] Thus, NNT can provide the basis for shared decision making by patients and clinicians. Payer approval of PCSK9 mAb prescriptions may be guided by cost-effectiveness consideration, which is largely based on consideration of absolute patient risk and relative risk reduction from therapy.[10]

Consideration of NNT facilitates an understanding of which patients may benefit the most from added nonstatin therapy; however, this information can be simplified for the busy clinician. Based on careful consideration of the NNTs,

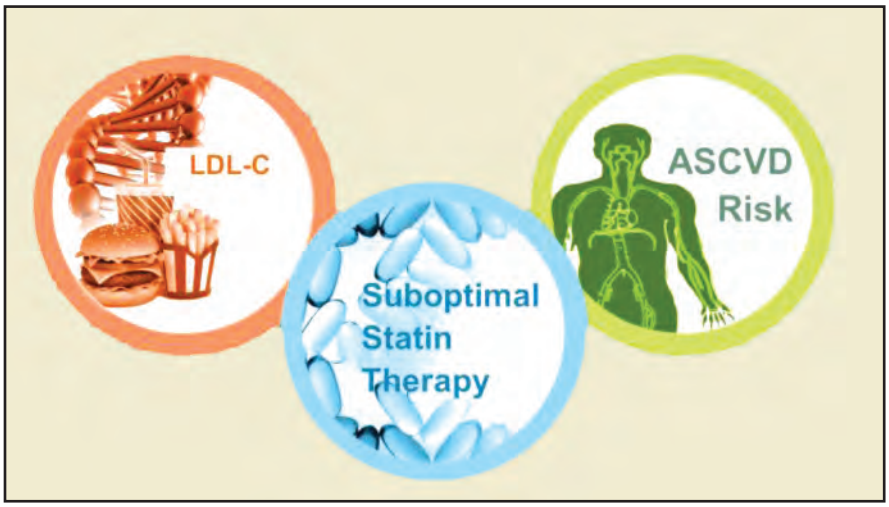

Figure 1. The potential for net benefit (and therefore the number of atherosclerotic cardiovascular events [ASCVD] events prevented) has important consequences in terms of cost effectiveness and willingness to pay. Net benefit depends on the ASCVD risk of the patient and the baseline low-density lipoprotein cholesterol level, which is a result of genetic and lifestyle factors and statin intensity.

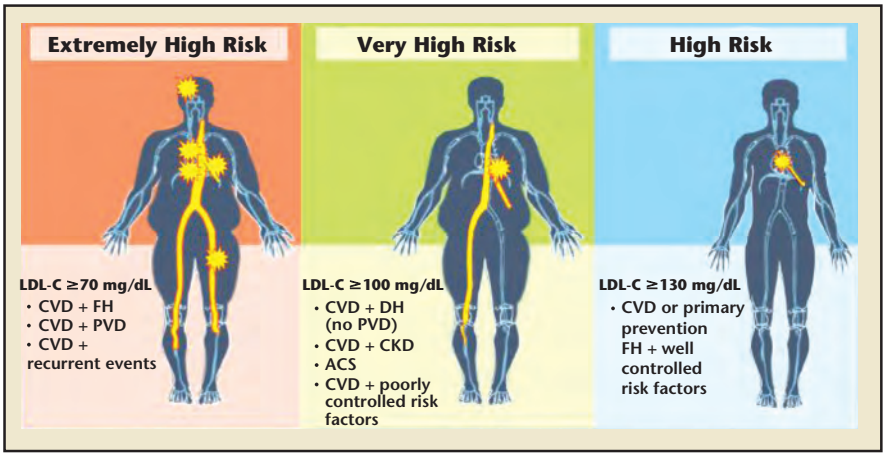

Figure 2. Target nonstatins based on risk and LDL-C. ACS, acute coronary syndrome; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PVD, polyvascular disease or peripheral arterial disease.

we identify three patient groups and LDL-C thresholds that should aid in the identification of patients most likely to benefit from adding ezetimibe or a PCSK9 mAb (Figure 2).

Net Clinical Benefit and NNT

NNT is 1/ARR. ARR captures two important factors: the absolute risk of the patient and the relative risk reduction from therapy. The ARR is calculated from the absolute risk of the patient multiplied by the relative risk reduction from therapy. For example, if the absolute difference in cardiovascular event rates between two therapeutic approaches, or absolute risk reduction is 4% or 0.04, then NNT is 1/0.04 or 25. With this example, for every 25 patients receiving the evaluated treatment, one cardiovascular event would be prevented. NNT can be similar for two very different groups of patients depending on their baseline risk and intensity of therapeutic intervention: an extremely high-risk patient with a very high LDL cholesterol level who is treated with a modest LDL-C–lowering drug like ezetimibe, or a high-risk patient with a moderately high LDL-C level who is treated with a very effective LDL-C–lowering drug such as a PCSK9 mAb (Tables 1-3).

Relative Risk Reduction From LDL Cholesterol-lowering Therapies

In the Cholesterol Treatment Trialists' (CTT) meta-analysis of the statin trials, each 39-mg/dL (1 mmol/L) reduction in LDL-C is associated with a 22% reduction in the relative risk of major cardiovascular events (MACE) (Figure 3).[11] These trials were relatively long term (about 5 years). In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial,[6] ezetimibe further reduced LDL-C from 70 mg/dL to 54 mg/dL; the modest 7% relative risk reduction in MACE over 6 years was consistent with the relative risk reduction expected from the CTT meta-analysis. In contrast, the relative risk reduction in primary endpoint of MACE of 15% in the Further Cardiovascular Outcomes

TABLE 1

5-year NNT for High-risk Patients With 45% 10-year ASCVD Risk

Initial LDL Cholesterol	Ezetimibe LDL Cholesterol ↓20%	PCSK9 mAb LDL Cholesterol ↓50%	PCSK9 mAb ↓65%
190 mg/dL (4.9 mmol/L)	21	8	6
160 mg/dL (4.1 mmol/L)	24	10	7
130 mg/dL (3.4 mmol/L)	30	12	9
100 mg/dL (2.6 mmol/L)	39	16	12
70 mg/dL (1.8 mmol/L)	56	28	22

Clinicians usually consider an NNT ~50 reasonable and patients usually consider NNT ~30 reasonable.
ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein; mAb, monoclonal antibody; NNT, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9.

TABLE 2

5-year NNT for High-risk Patients With 30% 10-year ASCVD Risk

Initial LDL Cholesterol	Ezetimibe LDL Cholesterol ↓20%	PCSK9 mAb LDL Cholesterol ↓50%	PCSK9 mAb ↓65%
190 mg/dL (4.9 mmol/L)	32	13	10
160 mg/dL (4.1 mmol/L)	38	15	12
130 mg/dL (3.4 mmol/L)	47	19	15
100 mg/dL (2.6 mmol/L)	61	25	19
70 mg/dL (1.8 mmol/L)	88	43	33

Clinicians usually consider an NNT ~50 reasonable and patients usually consider NNT ~30 reasonable.
ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein; mAb, monoclonal antibody; NNT, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9.

TABLE 3

5-year NNT for High-risk Patients With 20% 10-year ASCVD Risk

	Percent LDL Cholesterol Reduction		
Initial LDL Cholesterol	20%	50%	65%
190 mg/dL (4.9 mmol/L)	48	19	15
160 mg/dL (4.1 mmol/L)	57	23	18
130 mg/dL (3.4 mmol/L)	71	28	22
100 mg/dL (2.6 mmol/L)	92	37	28
70 mg/dL (1.8 mmol/L)	131	65	50

Clinicians usually consider an NNT ~50 reasonable and patients usually consider NNT ~30 reasonable.
ASCVD, atherosclerotic cardiovascular disease; LDL, low-density lipoprotein; NNT, number-needed-to-treat.

Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial[7] (cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization) conducted just over 2 years falls short of that expected from the CTT meta-analysis. The relative reduction of the secondary composite endpoint of "harder" clinical events of cardiovascular death, myocardial infarction, and stroke of 20% conforms more closely to the CTT meta-analysis. Several explanations for the attenuated relative risk reduction observed in FOURIER have been proposed, foremost among them FOURIER's 2.2-year median duration. However, it is more likely that baseline LDL-C levels played a strong role.

In the FOURIER trial, the relative risk reductions in MACE and ASCVD events after year 1 were higher than in the first year, although they still fell short of the magnitude expected from the mean 62-mg/dL (1.6 mmol/L) reduction in LDL-C from 92 to 30 mg/dL (relative risk reduction 20% for MACE in year 2 vs the 35% relative risk reduction expected from the CTT meta-analysis of statins).[7] However, the relative risk reductions observed in two PCSK9 mAb efficacy trials in which mean baseline LDL-C was approximately 120 mg/dL (evolocumab over 11 mo and alirocumab over 18 mo) had relative risk reductions of 50%, although confidence intervals were wide.[12,13] Further insight into the importance of baseline LDL-C comes from the Studies of PCSK9 Inhibition and the Reduction of

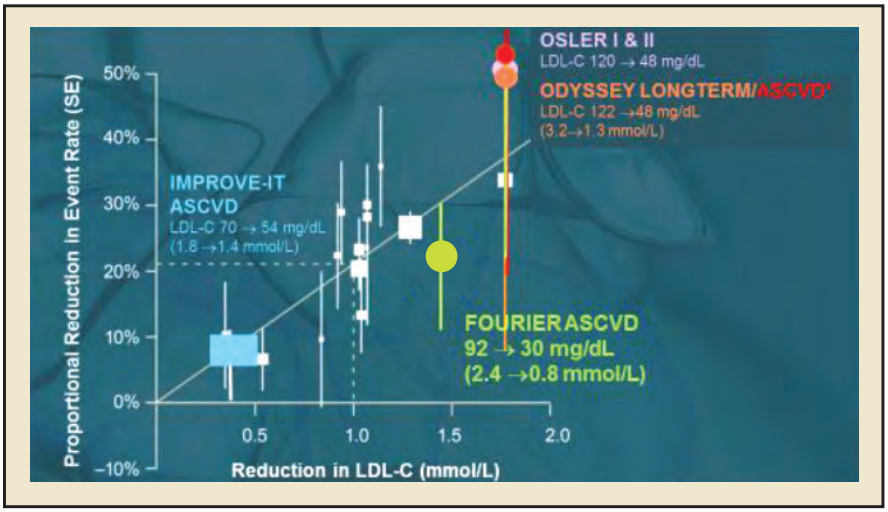

Figure 3. PCSK9 mAbs for CVD event reduction. *Applied FOURIER inclusion criteria to LONG TERM. ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol mAb, monoclonal antibodyPCSK9, proprotein convertase subtilisin/kinexin type 9. Data from CTT Collaboration. *Lancet.* 2005;366:1267-1278; Cannon CP et al. *N Engl J Med.* 2015;372:2387-2397; Robinson JG et al. *N Engl J Med.* 2015;372:1489-1499; Sabatine MS et al. *N Engl J Med.* 2015;372:1500-1509; The HPS2-THRIVE Collaborative Group. *N Engl J Med.* 2014;371:2003-2012; The ACCORD Study Group. *N Engl J Med.* 2010;362:1563-1574; AIM-HIGH. *N Engl J Med.* 2011;365:2255-2267; Sabatine M et al. *N Engl J Med.* doi 10.1056/NEJMoa1615664; Robinson JG et al. Presented at ACC 2017. Poster number 1203-305.

Vascular Events (SPIRE)-2 trial of bococizumab, a humanized PCSK9 mAb that did not move forward in development due to loss of efficacy from the formation of neutralizing antibodies that reduced its LDL-C lowering capacity.[14] Baseline LDL-C in SPIRE-2 was 134 mg/dL, (higher than in FOURIER or ODYSSEY OUTCOMES) and the trial was terminated after a median 1 year of follow-up. Notably, the SPIRE-2 relative risk reductions in MACE (nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina requiring urgent revascularization, or cardiovascular death) of 21% at 1 year were greater than for FOURIER after a median of 2.2 years (Figure 4). These findings support a log linear association between LDL-C lowering and cardiovascular event reduction (Figure 5). Thus, the greatest reductions in risk will occur in higher-risk patients with higher baseline LDL-C levels.

… the relative risk reductions observed in two PCSK9 mAb efficacy trials in which mean baseline LDL-C was approximately 120 mg/dL (evolocumab over 11 mo and alirocumab over 18 mo) had relative risk reductions of 50%, although confidence intervals were wide.

Estimating NNT for Different Types of Patients

Based on a systematic review of the statin arms of cardiovascular outcomes trials and observational studies of cohorts with familial hypercholesterolemia through 2016, and the

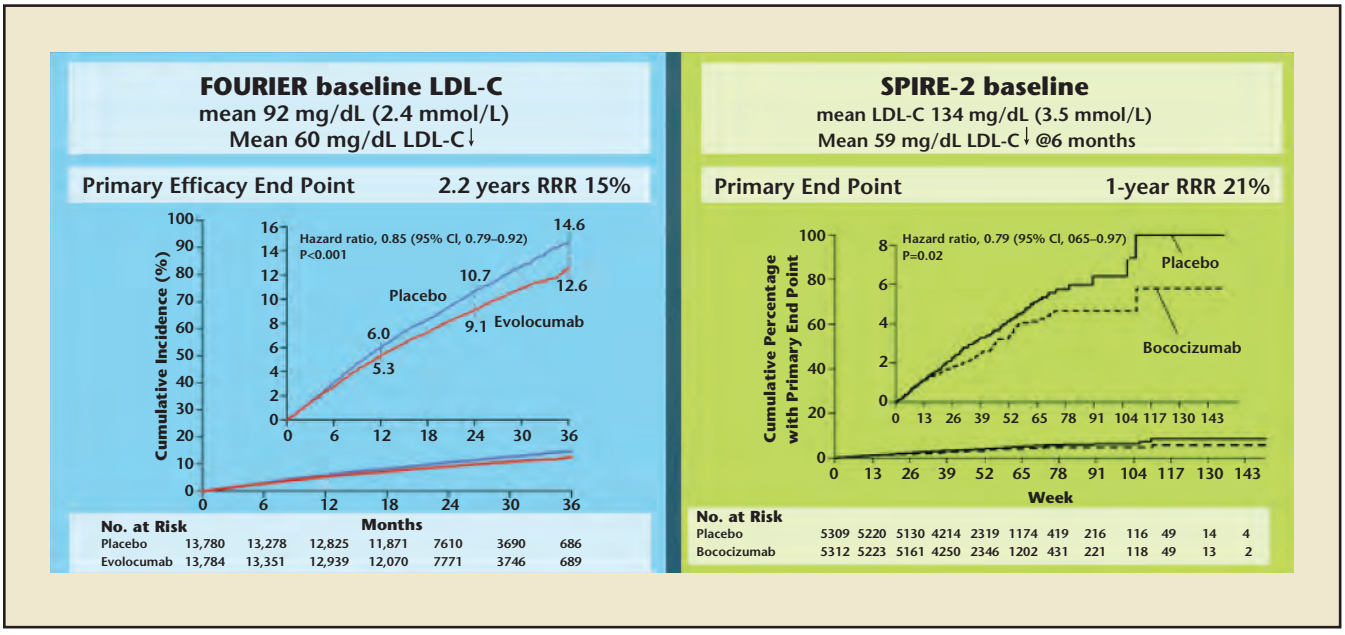

Figure 4. FOURIER 2.2 years vs SPIRE-2 1 year MACE. LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiac event; RRR, relative risk reduction. Sabatine M et al. *N Engl J Med.* 2017;376:1713-1722; Ridker PM et al. *N Engl J Med.* 2017;376:1527-1539.

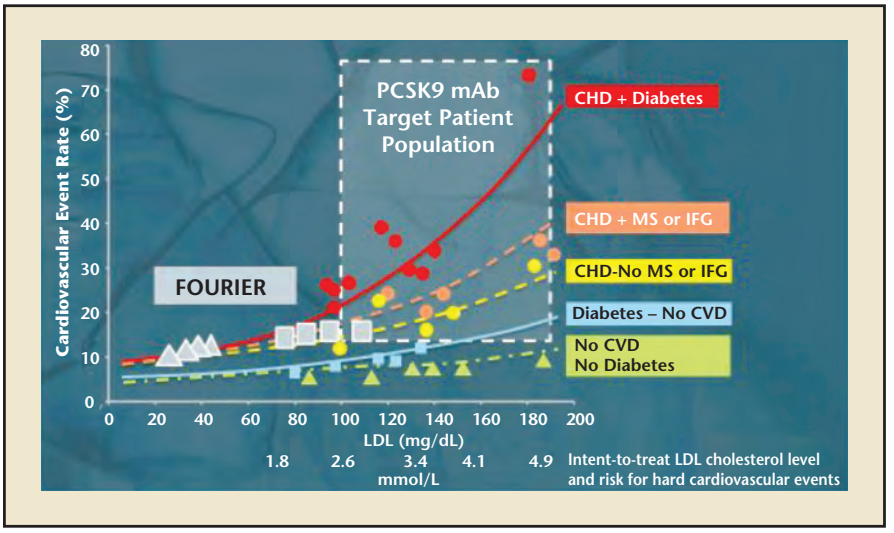

Figure 5. Largest absolute CVD risk reduction benefit in high-risk patients with higher LDL-C levels. CVD, cardiovascular disease; IFG, impaired fasting glucose; LDL-C, low-density lipoprotein cholesterol; mAb, monoclonal antibody; MS, metabolic syndrome; PCSK9, proprotein convertase subtilisin/kinexin type 9. Risk curve concept: Robinson JG, Stone NJ. *Am J Cardiol.* 2006:98;1405-1408; FOURIER median of baseline LDL-C quartiles from Sabatine M, et al. Presented ACC Scientific Sessions; March 2017; Washington, DC.

ASCVD event rates reported in recent subgroup analyses of the FOURIER trial, we have identified three groups of patients at high, very high, and extremely high cardiovascular risk (Table 4).[5,15,16] NNTs can be calculated for different levels of absolute risk, baseline LDL-C level on maximal statin therapy, and the efficacy of the LDL-C–lowering therapy.

… the greatest reductions in risk will occur in higher-risk patients with higher LDL-C levels.

Cost Effectiveness

In a 2016 analysis by the Institute for Clinical and Economic Review, patient groups with 5-year NNTs of 10 to 14 were cost effective at $150,000 per quality-adjusted life year (Table 5).[17] Five-year NNTs of 21 to 28 approach more acceptable levels of cost effectiveness with discounting.

LDL Cholesterol Goals

Several organizations recommend titrating LDL-C or non–high-density lipoprotein cholesterol (HDL-C) to various goal levels. The main problem with this strategy is that it is not based on the potential for a patient to meaningfully benefit from the therapy added to reach this arbitrarily prespecified target. For example, several guidelines recommend an LDL-C goal <70 mg/dL for a patient with clinical cardiovascular disease. Thus, a patient with cardiovascular disease with well-controlled risk factors (~20% 10-y ASCVD risk) on a high-intensity statin with an LDL-C of 75 mg/dL should have ezetimibe added to

TABLE 4

Extremely High-, Very High-, and High-risk Patients on Maximally Tolerated Statin Therapy

Extremely High Risk	Very High Risk	High Risk
CVD++ >45% 10-y ASCVD risk	CVD+ or FH + risk factors 30%-40% 10-y ASCVD risk	CVD or FH no RF ~20% 10-y ASCVD risk
CVD + FH	CVD + diabetes (no polyvascular disease)	CVD with well-controlled risk factors
CVD + polyvascular disease CVD + peripheral arterial disease	CVD + chronic kidney disease (excluding hemodialysis)	FH age 40-75 y, no or well-controlled risk factors
CVD+ recurrent CVD events	Acute coronary syndromes	
	CVD + poorly controlled risk factors	
	FH age 40-75 y + poorly controlled CVD risk factors	

ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; FH, familial hypercholesterolemia; RF, risk factor.

TABLE 5

Cost Effectiveness Depends on the Number of Events Prevented and Drug Cost

NNT 10-14	Very high-risk individuals with LDL cholesterol (LDL-C) ≥190 mg/dL (4.9 mmol/L) or LDL-C ≥160 (4.1 mmol/L) 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 (2.6 mmol/L) High risk patients with LDL-C ≥130 mg/dL (3.4 mmol/L)
	Depending on discount Discount ~50% (~$7700/y) / $150,000 QALY Discount ~60% (~$5400/y) / $100,000 QALY Discount ~77% (~$3200/y) / $50,000 QALY Discount ~85% (~$2200/y) to avoid exceeding growth targets US healthcare costs

Cost per QALY gained over 5 years of treatment (assuming undiscounted acquisition cost of $14,000/y and 50% relative risk reduction with PCSK9 mAb). All costs in US dollars.
LDL, low-density lipoprotein; QALY, quality-adjusted life year.
Data from Robinson JG et al.[5]

reach the goal of <70 mg/dL. This entails treating approximately 130 patients for 5 years to prevent 1 event (NNT = 130), making it an extremely low priority in this patient's care. Conversely, an extremely high-risk patient with a history of coronary heart disease and peripheral arterial disease (~45% 10-y ASCVD risk) with an LDL-C level of 68 mg/dL may be considered at goal, yet may still benefit from the addition of a PCSK9 mAb to reduce LDL-C another 65% (NNT = 22) due to high baseline risk. In contrast, a strategy using patient risk and an LDL-C threshold to treat facilitates a more straightforward consideration of the potential for benefit to the patient.

… a patient with cardiovascular disease with well-controlled risk factors (~20% 10-y ASCVD risk) on a high-intensity statin with an LDL-C of 75 mg/dL should have ezetimibe added to reach the goal of <70 mg/dL.

Putting It All Together

Maximize Statin Therapy

It is critical to ensure that the patient is taking the maximally tolerated intensity of statin therapy. In the Treating to New Targets (TNT) trial, the extrapolated 10-year ASCVD event rate for patients with CVD and diabetes was 37% for those in the moderate-intensity statin arm, vs 28% in the high-intensity statin arm.[5] Increasing atorvastatin, 10 mg, to atorvastatin, 80 mg, has a 5-year NNT of 22 and costs nothing! Of note, atorvastatin, 80 mg, was as well tolerated

MAIN POINTS

- Statins are first-line therapy for reducing atherosclerotic cardiovascular disease (ASCVD) risk. Some patients remain at high ASCVD risk despite maximizing statin therapy.
- Ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs) have been shown to reduce ASCVD events in randomized trials and may be of benefit in selected patients with cardiovascular disease or familial hypercholesterolemia (FH).
- Selected patients with cardiovascular disease or FH may benefit from the addition of a PCSK9 mAb or ezetimibe. The potential for a net ASCVD risk reduction benefit may inform this decision.

as atorvastatin, 10 mg, over the 5 years of the TNT trial,[18] based on the NNT tables (Tables 1-3).

Based on absolute risk and a very favorable NNT ≤25, in which PCSK9 mAbs approach cost effectiveness with discounting, LDL-C thresholds can be identified for extremely high-risk (LDL-C ≥70 mg/dL), very high-risk (LDL-C ≥100 mg/dL), and high-risk (LDL cholesterol ≥130 mg/dL) patients (Figure 2). Patients in these groups above the LDL-C threshold are likely to have a net benefit from the addition of a PCSK9 mAb that lowers LDL-C by 65%.

For ezetimibe, the LDL-C thresholds are substantially higher for NNTs ≤30, the level considered reasonable by many patients: extremely high risk with LDL-C level ≥130 mg/dL and very high risk with LDL-C level ≥190 mg/dL. Nonetheless, it may make sense to add ezetimibe above these thresholds, depending on the cost of generic ezetimibe that can vary from $552 to $2544/year (goodrx.com) and then reassess the need for a PCSK9 mAb depending on the achieved LDL cholesterol level.

Conclusions

Statins are the evidence-based drugs of choice for ASCVD risk reduction. Many patients remain at increased ASCVD risk, and residual risk, despite maximally tolerated statin therapy. Depending on their cardiovascular risk based on atherosclerosis burden, cardiometabolic risk factors, and LDL cholesterol levels on maximally tolerated statin therapy, selected patients with extremely high risk and very high risk of cardiovascular disease including the often under diagnosed familial hypercholesterolemia may benefit from the addition of a PCSK9 mAb or ezetimibe. ■

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