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Review

Cholesterol Lowering Guidelines: From Whence We Came and Where We Are Now

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ABSTRACT

Treatment guidelines have proliferated in cardiology, although most guideline recommendations are not supported by clinical trial evidence. What is considered to be a normal cholesterol level has progressively declined over the past 50 years, with the increasing realization that "normal" is far from optimal and that lower is better. The first important United States and Canadian cholesterol guidelines were published in 1988, and recommended diet for 6 months to be followed by consideration of bile acid sequestrants or nicotinic acid. Over the ensuing 25 years guidelines have changed rapidly and dramatically in response to a large number of definitive clinical trials, usually with statins. Low-density lipoprotein cholesterol targets have moved progressively lower, and in some guidelines, have been abandoned entirely. The concept of selecting patients for treatment according to the absolute risk reduction expected from treatment on the basis of clinical trial data seems to be a rational approach. For secondary prevention, some patients are still untreated or undertreated, presenting an opportunity for improving outcomes.

RÉSUMÉ

Les lignes directrices sur les traitements se sont multipliées en cardiologie, mais la plupart des recommandations qu'elles contiennent ne sont pas appuyées par des données probantes recueillies dans le cadre d'essais cliniques. La valeur considérée comme un taux de cholestérol normal a diminué progressivement au cours des 50 dernières années, alors que l'on réalisait de plus en plus que la valeur « normale » était loin d'être optimale et qu'il était préférable de l'abaisser encore. Les premières lignes directrices importantes sur le cholestérol aux États-Unis et au Canada ont été publiées en 1988 et préconisaient un régime alimentaire pendant 6 mois suivi d'un traitement éventuel par des chélateurs des acides biliaires ou par l'acide nicotinique. Au cours des 25 années suivantes, la teneur des lignes directrices a changé de façon rapide et radicale en réponse aux résultats de plusieurs essais cliniques déterminants, portant en général sur les statines. Les cibles de cholestérol à lipoprotéines de basse densité ont vu leur importance diminuer progressivement, jusqu'à être totalement abandonnées dans certaines lignes directrices. Le concept de sélection des patients à traiter reposant sur la réduction du risque absolu attendue du traitement en se fondant sur les résultats des essais cliniques semble être une approche rationnelle. Pour ce qui est de la prévention secondaire, il existe une possibilité d'améliorer l'évolution de l'état de santé des patients puisque certains demeurent encore non traités ou sous-traités.

Nothing is different but everything's changed.

—Paul Simon, *Once Upon a Time There Was an Ocean*

Creating rules for others to follow has been a human impulse since the dawn of history. Rules, laws, and conventions are necessary for a well functioning society, but also reflect the culture and beliefs of the time. For example, one of the 282 laws in the code of Hammurabi from ancient Mesopotamia decreed that if a doctor killed a rich patient, he would have his hands cut off, but if he killed a slave, only financial restitution was required.

A Short History of Medical Guidelines

Rules or guidelines in medicine are a very recent phenomenon. The work of Hippocrates, *On the Physician*, recommended that physicians be well kempt, honest, calm, understanding, serious, and keep their fingernails at a specified length. However, Hippocrates and Maimonides are remembered primarily for their ethical precepts and not their clinical guidelines. Published guidelines in the middle of the 20th century were usually about medical ethics. In cardiology, practice guidelines were relatively uncommon before 1980, but in recent years they have proliferated. Under the search

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term, "cardiology guidelines," PubMed lists 31 articles for 1990, 193 for 2000, 639 for 2010, and 1445 for 2017.

Clinical trial evidence was not a prominent feature of early cardiology guidelines. In a survey of official cardiology guidelines from 1984 to 2008, the authors noted that levels of evidence only began to be introduced in 1998.[1] From 1998 to 2008, of 16 guidelines that reported levels of evidence, comprising a total of 2711 recommendations, only 314 of them (11%) were supported by level of evidence A. For acute coronary syndrome, heart failure, and secondary prevention, more than 20% of recommendations were supported by level of evidence A, compared with < 1% of recommendations for valvular heart disease.

In 2011 in the United States, the Institute of Medicine published guidelines for guideline development, the main features of which are listed in Table 1.[2] Do most guidelines meet these criteria? In a report on 114 randomly selected guidelines published between 2006 and 2011, fewer than half met more than 50% of the Institute of Medicine standards.[3] The authors noted that no improvement in guideline quality had occurred since a report published in 1999. Substandard guidelines might contribute to guideline nonadherence.

A more important cause of nonadherence might be the proliferation of guidelines. Does each related specialty in each country or geographic region need a separate set of guidelines on, for example, hypertension? And when multiple sets of guidelines conflict,[4] despite a common evidence base, does confidence in guidelines suffer?

Despite these shortcomings of guidelines, adherence to them has been shown to improve outcomes in many common conditions, including acute coronary syndromes,[5,6] atrial fibrillation,[7] and diabetes prevention.[8]

Normal Cholesterol Levels

In the 1963 table of normal laboratory values published in the *New England Journal of Medicine*, normal total cholesterol was listed as 150-280 mg/dL (3.9-7.3 mmol/L).[9] Normal values of serum sodium, potassium, and blood glucose are still exactly the same as they were in 1963—so what has happened to "normal" cholesterol? Adverse consequences can be expected when serum sodium or potassium levels stray outside of the normal range, but what was accepted as the normal range for total cholesterol was nothing more than the average range at that time in history in one country.

Table 1. Institute of Medicine recommendations for guideline development

The Institute of Medicine recommends that guidelines:
- Be based on a systematic review of the existing evidence
- Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups
- Consider important patient subgroups and patient preferences, as appropriate
- Be on the basis of an explicit and transparent process that minimizes distortions, biases, and conflicts of interest
- Provide a clear explanation of the logical relationships between alternative care options and health outcomes
- Provide ratings of the quality of evidence and the strength of the recommendations
- Be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations

Clinical trials of cholesterol-lowering from that era were never definitive, mainly because none of the available treatments were safe and effective at lowering low-density lipoprotein cholesterol (LDL-C). The most interesting part of these trials from the modern perspective is the high levels of baseline cholesterol; mean total cholesterol in primary prevention trials of various diets ranged from 6.0 to 7.0 mmol/L and in secondary prevention, from 6.5 to 8.3 mmol/L.[10-16] In none of these studies were baseline cholesterol levels used to select patients; these were the usual adult cholesterol levels of that era.

During 2011-2014, mean serum total cholesterol level for United States (U.S.) adults averaged 5.0 mmol/L,[17] and for Canadian adults, 5.1 mmol/L.[18] A gradual decline in cholesterol levels in adults has occurred over the past 50 years in most Western countries, and over the past 20 years this trend has accelerated with increasingly widespread statin use. To put current cholesterol levels in perspective, evidence from premodern societies, although scant, suggests that 3.2 mmol/L could be considered a "normal" total cholesterol for humans.[19] Data from clinical trials of cholesterol-lowering, primarily with statins, show that lowering LDL-C reduces cardiovascular (CV) events, with no lower limit yet detected beyond which further LDL-C-lowering does yield further event reduction.[20]

A Short History of Cholesterol Guidelines

The first report of the expert panel of the National Cholesterol Education Program (NCEP) in the United States was published in 1988, just before the era of statins.[21] The expert panel opined that a total cholesterol level < 200 mg/dL (5.2 mmol/L) was "desirable," a level of 200-239 mg/dL (5.2-6.2 mmol/L) was borderline, and a level of 240 mg/dL (6.2 mmol/L) or above was considered high. Dietary therapy was the primary treatment, with drug therapy to be considered after 6 months. Dietary therapy was recommended for patients with coronary disease or 2 other risk factors if LDL-C was 130 mg/dL (3.4 mmol/L) or higher, with a goal of reducing LDL-C to < 130 mg/dL. Drugs of first choice were bile acid sequestrants or nicotinic acid.

The report of the Canadian Consensus Conference on Cholesterol was also published in 1988, and many of its conclusions and recommendations were similar to those of the NCEP expert panel.[22] A total cholesterol goal of ≤ 5.2 mmol/L was set for patients with hypercholesterolemia, with diet being the primary therapy, and drugs to be considered after 6 months.

Cholesterol guidelines have evolved quickly and dramatically since 1988 in response to a cascade of clinical trials, usually involving statins, as shown in Figure 1. These trials showed that cholesterol-lowering reduced CV events in at-risk subgroups, beginning with coronary patients with hypercholesterolemia, then in primary prevention subgroups, and finally in several trials showing that more LDL-C-lowering was preferable to less. LDL-C levels in treated patients have decreased from considerably above 2.6 mmol/L in early statin trials to approximately 0.8 mmol/L in recent trials testing proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors.[23]

How have guideline committees responded to this tidal wave of clinical trial data over the past 3 decades? One

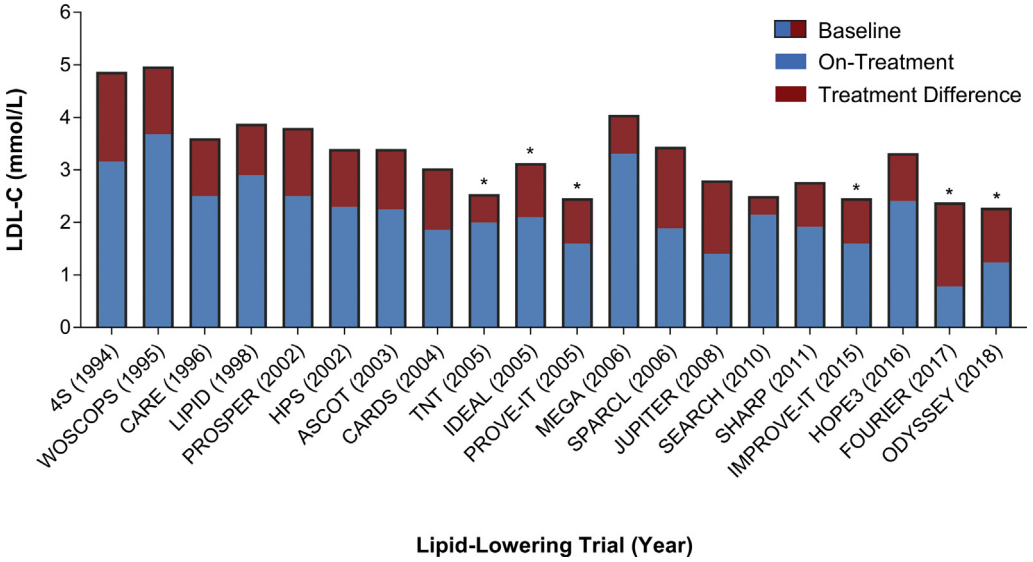

Figure 1. Major trials of cholesterol-lowering drugs 1994-2018. **Bars** represent low-density lipoprotein cholesterol (LDL-C) at baseline. The **blue** component of the bar is the LDL-C during treatment in the active treatment group, or the more intensively treated group. The **red** component of the bar is the difference in LDL-C between treatment groups, or the difference between baseline and active treatment in some trials. **Asterisks** represent trials in which patients were already taking statins at baseline. Note that across this 25-year time period, baseline LDL-C and LDL-C levels during treatment have decreased. ASCOT, **A**nglo-**S**candinavian **C**ardiac **O**utcomes **T**rial; CARDS, **C**ollaborative **A**tor**v**astatin **D**iabetes **S**tudy; CARE, **C**holesterol **a**nd **R**ecurrent **E**vents; FOURIER, **F**urther Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk; HOPE3, **H**eart **O**utcomes **P**revention **E**valuation 3; HPS, **H**eart **P**rotection **S**tudy; IDEAL, **I**ncremental **D**ecrease in **E**ndpoints Through **A**ggressive **L**ipid Lowering; IMPROVE-IT, **Imp**roved **R**eduction of **O**utcomes: **V**ytorin **E**fficacy **I**nternational **T**rial; JUPITER, **J**ustification for the **U**se of Statins in **P**revention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin; LIPID, **L**ong-Term **I**ntervention With **P**ravastatin in **I**schaemic **D**isease; MEGA, **M**anagement of **E**levated Cholesterol in the Primary Prevention **G**roup of **A**dult Japanese; ODYSSEY, Long Term, Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy; PROSPER, **Pro**spective **S**tudy of **P**ravastatin in the **E**lderly at **R**isk; PROVE-IT, **Pr**avastatin **o**r Ator**v**astatin **E**valuation and **I**nfection **T**herapy; 4S, **S**candinavian **S**imvastatin **S**urvival **S**tudy; SEARCH, **S**tudy of the **E**ffectiveness of **A**dditional **R**eductions in **C**holesterol and **H**omocysteine; SHARP, **S**tudy **H**eart **a**nd **R**enal **P**rotection; SPARCL, **S**troke **P**revention by **A**ggressive **R**eduction in **C**holesterol **L**evels; TNT, **T**reating to **N**ew **T**argets; WOSCOPS, **W**est **o**f **S**cotland **Co**ronary **P**revention **S**tudy.

response has been to continue to lower LDL-C targets; for example, the LDL-C target of 70 mg/dL (1.8 mmol/L) was introduced in 2004 as a therapeutic option for very high-risk patients, going beyond the 2001 NCEP recommendations,[24] but has since been adopted as a much broader target. The most recent American Association of Clinical Endocrinologists/American College of Endocrinology guidelines establish 5 levels of risk from low to extreme with 5 corresponding LDL-C targets, from 130 mg/dL (3.4 mmol/L) to 55 mg/dL (1.4 mmol/L).[25]

In addition to fixed numerical targets, some guidelines have introduced a percent reduction in baseline LDL-C, either as a component of the target, or as a stand-alone goal. For example, the current Canadian guidelines recommend a target LDL-C of < 2 mmol/L or a $> 50\%$ reduction in LDL-C for intermediate- or high-risk patients. For patients with a LDL-C > 5 mmol/L, a $> 50\%$ reduction is recommended as a stand-alone target.[26] The evidence supports percent reduction as superior to fixed LDL-C targets. In a study specifically comparing them, percent LDL-C reduction added incremental prognostic value over statin dose and attained LDL-C levels, but attained LDL-C level did not provide incremental prognostic value over statin dose and percent LDL-C reduction.[27]

The most recent European guidelines also include a percent reduction goal.[28] They go further however, and for the first time question the value of numerical targets: "lowering LDL-C beyond the goals that were set in the previous EAS/ESC guidelines is associated with fewer CV events. Therefore, it seems appropriate to reduce LDL-C as low as possible, at least in patients at very high CV risk."[28]

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines took the radical step of eliminating LDL-C targets.[29] Instead, 4 treatment groups were identified for which clinical trial evidence showed that statins reduced number of events. High- or moderate-intensity statin treatment was recommended for all patients without contraindications. High-intensity treatment was defined as a drug and dose that reduced LDL-C by $\geq 50\%$, and moderate-intensity treatment as that yielding a 30% to $< 50\%$ reduction.

The National Institute for Health and Care Excellence in the United Kingdom recommends a specific statin, atorvastatin, at either the 10 mg or 80 mg dose, depending upon the level of risk.[30] The Kidney Disease: Improving Global Outcomes guideline makes the important point that LDL-C is not an accurate predictor of CV risk in patients with chronic kidney disease, and should not be used to determine who should receive lipid-lowering treatment.[31] The Kidney Disease: Improving Global Outcomes guideline also recommends a statin, with or without ezetimibe, for all adults aged 50 years or older with chronic kidney disease, and for those aged 18-49 years with a 10-year CV risk $> 10\%$.

In addition to these approaches embodied in different guidelines, proposals have been advanced for patient selection criteria for cholesterol-lowering treatment. Ridker and colleagues suggested that the ACC/AHA algorithm incorporate groups that have been shown to derive clear benefit in 5 major primary prevention trials.[32] These investigators pointed out that for primary prevention, the ACC/AHA guidelines and trial-derived selection criteria identified groups that overlap only partly. Trial-based patient selection also does not force treatment consideration for most elderly participants, whose 10-year risk almost automatically exceeds 7.5%. At the other extreme, it has been advocated that age alone be used to select individuals for statin therapy; that is, simply to treat everyone beginning at age 55 years.[33] This approach is cost-effective because it does not require laboratory measurement of lipids or drug titration to targets.

Cholesterol guidelines have evolved dramatically since 1988. The pool of individuals shown in clinical trials to benefit from cholesterol-lowering has increased substantially. Reassuringly, statins have been remarkably safe,[20] and are now comparatively inexpensive, making them cost-effective for lower-risk subgroups. Guidelines have thus expanded to include more patients. Combination cholesterol-lowering regimens that include a PCSK9 inhibitor are capable of lowering LDL-C levels to well below 1 mmol/L.

Specific Numerical LDL-C Targets

Early cholesterol guidelines contained specific cut points for initiation of treatment and as treatment targets; specifically, 190, 160, 130, 100, and 70 mg/dL (4.9, 4.1, 3.4, 2.6, and 1.8 mmol/L).[4] These numbers are not on the basis of any clinical trial evidence. The evidence indicates that statins reduce CV events in a linear fashion across a broad range of LDL-C down to a level < 1.3 mmol/L.[20,34] There is nothing magical about the target numbers. In a post hoc analysis from the **F**urther Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk (FOURIER) trial, evolocumab reduced the risk of the primary end point by 20% (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.60-1.07) in the 2034 patients with a baseline LDL-C < 1.8 mmol/L and by 14% (HR, 0.86; 95% CI, 0.79-0.92) in those with a baseline LDL-C ≥ 1.8 mmol/L.[35,36] High-risk patients with an LDL-C < 1.8 mmol/L benefit from further LDL-C reduction.

The strategy of treating to a specific LDL-C target has been recommended for many years in various guidelines, but until recently had not actually been rigourously tested in an adequately powered clinical trial. In the Standard vs Int**e**nsive Statin Therapy For Hypercholesterole**m**ic **P**atients With D**ia**betic Retinopa**thy** (EMPATHY) trial, 5042 patients in Japan were randomized to either standard therapy targeting an LDL-C level of 100-120 mg/dL (2.6-3.1 mmol/L) or to more intensive therapy, targeting an LDL-C < 70 mg/dL (1.8 mmol/L).[37] The LDL-C range of 100-120 mg/dL is in accord with cholesterol guidelines in Japan. After a median follow-up of approximately 3 years, the CV event rate was reduced, but not significantly, in the intensive group (HR, 0.84; 95% CI, 0.67-1.07). However, less than half of the patients in the intensive therapy group actually attained the LDL-C target of < 70 mg/dL (1.8 mmol/L), and in an analysis restricted to patients who actually achieved their LDL-C goals, a large reduction in CV events was seen (HR, 0.48; 95% CI, 0.28-0.82).

The failure of physicians to get more than half of patients to goal during 3 years of treatment within the strict confines of a clinical trial suggests that the whole strategy of treating to a target is impractical and flawed. Because Japanese physicians tend to prescribe smaller doses of statins (and other drugs) compared with physicians in most other countries, it is possible that a higher proportion of patients might have attained their target if the trial had been performed elsewhere. Nevertheless, in the absence of any credible evidence that the treating to target approach works, it seems reasonable that guideline committees stop recommending it.

Selecting Patients for Cholesterol-Lowering Treatment

Physicians have gradually learned to treat the level of CV risk instead of treating the level of cholesterol, despite the difficulties in accurately assessing risk. A more precise approach to patient selection involves the calculation of absolute risk reduction (ARR).[38,39] ARR can be calculated for an individual if one knows the baseline LDL-C level, the baseline level of risk, and the amount of LDL-C reduction with treatment. With statins, each mmol/L reduction in LDL-C reduces CV events by 22%.[20] Statins reduce LDL-C as a percentage of the baseline level, so that a 50% LDL-C reduction will reduce risk more when baseline LDL-C is high compared with low.

For primary prevention, the ACC/AHA guidelines recommend consideration of treatment for subjects with a 10-year risk of $\geq 7.5\%$ and an LDL-C of 70-189 mg/dL (1.8-4.9 mmol/L).[29] Thanassoulis et al. have described a "benefit-based" approach derived from the results of primary prevention trials, and using a 10-year ARR of 2.3 as the decision point for treatment.[39] The benefit-based approach identified 9.5 million Americans not currently eligible for statin treatment because their 10-year risk was $< 7.5\%$, who had the same or greater expected benefit from statins compared with higher-risk individuals (a 10-year ARR of 2.3). Using this approach on the basis of the benefits seen in trials leads to a more precise targeting of patients who will benefit from cholesterol-lowering.

Older guidelines recommended more intensive treatment to attain lower treatment goals in patients with higher levels of risk, and less intensive treatment and easier goals for patients in lower-risk categories. Because, with the exception of simvastatin, adverse effects of statins are not closely related to dose,[40] and lower attained LDL-C levels yield more event reduction,[20] low-intensity statin therapy does not make sense for patients who tolerate higher doses.

Selecting Patients for Combined Cholesterol-Lowering Treatment

Fibrates and niacin did not reduce CV events in clinical trials of patients taking statins, and thus are no longer recommended as add-on therapy in current guidelines.[26,28-30] Ezetimibe is commonly used as add-on therapy on the basis of the results of the **Imp**roved **R**eduction of **O**utcomes: **V**ytorin **E**fficacy **I**nternational **T**rial (IMPROVE-IT),[41] in which 18,144 post-acute coronary syndrome patients were

randomized to simvastatin 40 mg/d alone or with ezetimibe 10 mg/d. After 7 years of follow-up, the primary end point was 32.7% in the combination therapy group and 34.7% in the simvastatin-alone group, a 6.4% relative risk reduction ($P = 0.016$). The number need to treat to prevent one CV event in IMPROVE-IT was 350 per year of treatment. The application to approve the simvastatin/ezetimibe combination for the reduction of CV events was rejected by the U.S. Food and Drug Administration, but was approved by the European Medicines Agency. Subgroup analyses of IMPROVE-IT showed a significant CV event reduction in patients with diabetes and in those aged 75 years or older, but none in nondiabetic patients or patients younger than 75 years of age.[42]

European and Canadian guidelines recommend that consideration be given to using ezetimibe in addition to a statin in selected patients who do not reach treatment targets with statins alone.[26,28] The ACC Task Force on Clinical Expert Consensus Documents published an "expert consensus decision pathway on the role of nonstatin therapies for LDL-C-lowering."[43] The Task Force emphasized that they did not use the rigourous methodology required for guideline development, and also recommended that ezetimibe be considered for patients with an inadequate response to statin therapy.

Two large clinical trials have recently shown that the PCSK9 inhibitors evolocumab and alirocumab not only reduce LDL-C by more that 50% but also correspondingly reduce CV events.[44,45] Because of to their high cost, PCSK9 inhibitors have been determined in studies from various groups to be far from cost-effective for most patients, as recently summarized by Annemans et al.[46] However, patients with a 10-year risk of a CV event in the range of 30% despite statin treatment have been identified from subgroup analyses of clinical trials.[47] These subgroups and their estimated levels of risk are listed in Table 2. The phrase, "highest risk-highest benefit" has been coined to define the patients likely to benefit from PCSK9 inhibitor treatment and to meet cost-effectiveness criteria.[46] This relationship is depicted in Figure 2.

Tools to Improve the Accuracy of Risk Assessment

Treatment decisions depend on accurate risk assessment, and the inaccuracy of standard risk assessment tools might be the Achilles heel that limits accurate treatment decisions. A subgroup within a population might have a risk that differs substantially from the mean risk of the entire population. Risk has shifted over time, and data from older cohorts might not accurately reflect current risk.

Table 2. Patient subgroups with a very high 10-year risk despite statin treatment

Patient category	10-year risk, %
Clinical ASCVD and diabetes	28-38
With CKD	28-43
Without CKD	26-29
Clinical ASCVD and CKD	34-35
Recent ACS (< 3 months)	32
CHD and poorly controlled risk factors	28-41
CHD and CKD	43-55
CHD and age 65 years or older	21-54
Male sex and stroke or TIA	31
CHD and baseline LDL-C ≥ 5.0 mmol/L	41

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; LDL-C, low-density lipoprotein cholesterol; TIA, transient ischemic attack.

Data from Robinson et al.[47]

Nontraditional risk factors are potentially useful tools to increase the precision of risk prediction, such that cholesterol-lowering treatment could be targeted to patients with a high likelihood of benefit, while avoiding those truly at very low risk. The evidence for 3 popular nontraditional risk factors, coronary artery calcium (CAC) score, high-sensitivity C-reactive protein (hs-CRP), and ankle-brachial index (ABI), was recently reviewed by a panel from the U.S. Preventive Services Task Force.[48-50] The panel concluded that there is insufficient evidence at this time to recommend for or against adding CAC score, hs-CRP level, or ABI to traditional risk assessment for CV disease in asymptomatic adults to prevent CV disease events.

This general conclusion does not preclude these tests from being useful in specific types of patients. A CAC score > 100 Agatston units reclassifies a patient with a borderline risk to high-risk, and conversely, a score of 0 reclassifies the same individual to a low-risk group. Reclassification studies consistently show across different race and sex groups that CAC score provides useful risk stratification information when applied to patients for whom the question of statin treatment is uncertain.[50]

A high hs-CRP level is a marker of increased CV risk; however, the effect of hs-CRP level on risk reclassification is modest, and thus the usefulness of hs-CRP measurement in routine assessment of CV disease risk for primary prevention is limited.[50]

ABI is a well validated test to detect peripheral arterial disease; indeed, a low ABI indicates severe atherosclerosis and warrants consideration of statin treatment, even in the absence of other risk factors. However, ABI adds little value to traditional risk factor assessment.[48-50] A low ABI is uncommon in the absence of other risk factors and a normal ABI does not meaningfully reclassify a subject with risk factors to a lower risk category.

Practical Considerations

Most of the information in this article is not relevant to the day-to-day work of a practicing cardiologist because most of the patients that we see already have atherosclerosis, and according to any cholesterol guideline, should be treated aggressively. Yet, evidence suggests that many of our patients do not receive guideline-recommended treatment. In a large series of patients older than 65 years in Ontario, 33.9% were receiving optimal medical therapy, defined as a statin, a β-blocker, and either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, before percutaneous coronary intervention, but only 47.1% were receiving such therapy after percutaneous coronary intervention.[51] The proportion receiving a statin increased from 64.3% to 84.6%.

Data on persistence of treatment with a statin is worse. In an older study, more than half of patients in British Columbia who were prescribed a statin discontinued it for at least 90 days during follow-up.[51] Patients who discontinue their statin are significantly more likely to experience myocardial infarction and CV death.[52] Should we blame patients for

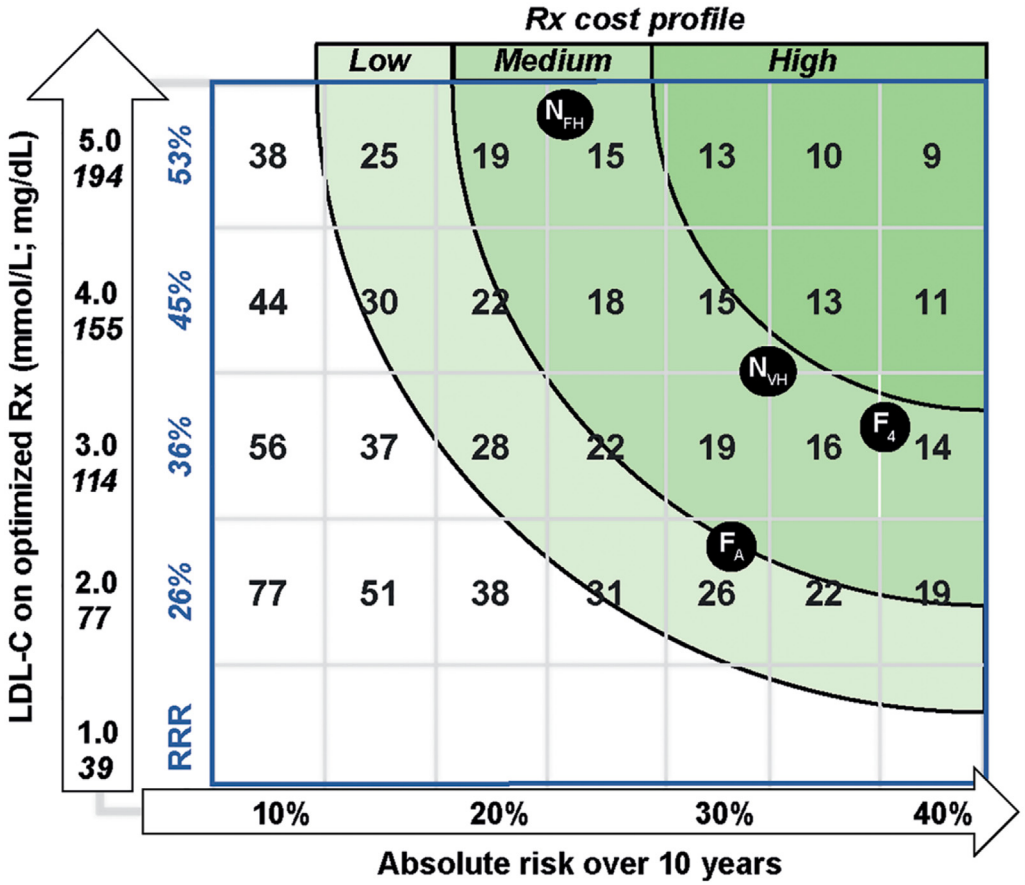

Figure 2. "Highest risk—highest benefit" strategy for proprotein convertase subtilisin/kexin 9 inhibitor use. The schematic shows low-density lipoprotein cholesterol (LDL-C) during optimum statin/ezetimibe therapy on the vertical axis and cardiovascular risk on the horizontal axis. Predicted relative risk reduction (RRR) associated with a proprotein convertase subtilisin/kexin 9 inhibitor-induced 60% decrease in LDL-C is in the first column. This is on the basis of a 22% risk reduction per 1.0 mmol/L decrease in LDL-C as confirmed in **F**urther Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk (FOURIER). Number needed to treat (NNT) is provided per 5% increment in risk and 1.0 mmol/L increment in LDL-C in the other columns. These are given for a 5-year time scale. Varying cost profiles are represented by the shades of **green**. A low-cost jurisdiction might permit NNT < 30 as an acceptable threshold; medium-cost NNT < 20; and high-cost NNT < 15. For illustration purposes, markers are provided for the approximate NNT for the average FOURIER subject (F_A; estimated annual risk 3.3%), a FOURIER subject in the top LDL-C quartile (F_4; annual risk 3.8%), and the National Institute for Health and Care Excellence-approved categories (N_{VH}: very high risk [ie, polyvascular disease or multiple events, LDL-C > 3.5 mmol/L]; N_{FH}: FH no event with LDL-C > 5.0 mmol/L). Reproduced from Annemans et al.[46] with permission from Oxford University Press.

discontinuing their statin? They learn about the potential side effects of statins from many sources, and any fears that they have will often be magnified by lurid, inaccurate information that chokes the internet.[53]

Who will tell our patients with coronary disease that the biggest threat to their health is CV disease and its complications? And that if their LDL-C is reduced by > 2 mmol/L, their risk of myocardial infarction, stroke, coronary revascularization, and CV death will all be reduced by half? Do we have something more important than this to do during the brief minutes we have with each patient? For the patient with previous coronary bypass surgery who has been happily taking a low-dose statin ever since, can we take the time to switch to high-intensity therapy? The ARR over 5 years for such a switch is 3.3 for a major CV event and an additional 4.6 for repeat revascularization.[54] Few things that we do in practice accomplish that much benefit with such little effort.

Nothing is different but everything's changed. The guidelines have changed substantially over the past 2 decades, but nothing is different about the challenges we face in terms of providing optimal cholesterol-lowering therapy to our patients, and maintaining their adherence.

Disclosures

Dr Waters has received honoraria for participation in clinical trial committees from CSL Ltd, the Medicines Company, Pfizer, Regeneron, Resverlogix, and Sanofi, and consulting fees and honoraria for lectures from Pfizer.

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