SPECIAL REPORT

Divergent paradigm shifts in national, European and American cardiovascular prevention guidelines

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INTRODUCTION

In the last two years, both European and American guidelines for cardiovascular risk management have been updated. In both continents, but particularly in the US, these updates were more than trivial. In addition, continental separation in which evidence is considered admissible, and how epidemiological evidence is translated into guidelines, is becoming apparent. This separation is important and requires reflection on both sides of the Atlantic to judge whether we are on the right track to sensible and optimal cardiovascular risk management. Also, the updates cause discussion between medical professionals, which is already occurring in the Netherlands between cardiologists and other professionals caring for cardiovascular patients. These discussions may not always benefit patients.

In this commentary, we will summarise and discuss recent developments in cardiovascular prevention paradigms, and how these translate into guidelines. The focus will be on drug therapy for lipid and blood pressure management. We will place these developments in perspective with regards to the national Dutch guidelines. Finally, we will ask ourselves whether we are to choose the 'European' or the 'American' style of cardiovascular prevention.

DEVELOPMENTS IN EUROPE

In 2012, The European Society of Cardiology (ESC) presented its updated guidelines on cardiovascular disease (CVD) prevention.[1] The writing task force liberally allowed all types of epidemiological evidence, extrapolations from such evidence, and expert opinion, and consistently reported classes for recommendation and levels for evidence.

The prevention approach in the ESC guidelines is based on generic risk categories, which include the following:

- *Very high risk*: patients with previous cardiovascular events, signs of atherosclerosis (detected by, for example, stress testing or carotid ultrasonography), diabetes mellitus (DM) with at least one additional risk factor or target organ damage (e.g. microalbuminuria), severe renal insufficiency and, finally, individuals with a calculated ten-year mortality risk of 10% or more;
- *High risk*: patients with a markedly elevated single risk factor, DM without additional risk factors, moderate renal insufficiency, or a ten-year mortality risk of 5-10%;
- *Moderate risk*: patients with a ten-year mortality risk of 1-5%;
- *Low risk*.

This use of explicit generic risk categories differs from the previous 2007 ESC guidelines, where separate, less explicit considerations regarding risk were given for patients with hypertension and dyslipidaemia.[2] The 2007 version also did not qualify those with pre-clinical signs of atherosclerosis to automatically be at 'very high risk', which may have a huge impact, depending on how liberally physicians and patients decide to perform/undergo for example carotid intima-media-thickness (IMT) measurements or coronary calcium assessments. The 2012 version suggests 'consideration' of carotid ultrasonography and coronary calcium testing in those at *moderate risk*, although it fails to explain how exactly information from these tests should be incorporated in treatment decisions.

For hypertension management, the 2012 guideline recommends immediate treatment in all patients at 'high' or 'very high' risk, with a universal target of 140/90 mmHg. Importantly, the guideline also recommends treatment in all other patients at 'moderate' risk (e.g. ten-year CVD mortality risk >1%) if lifestyle measures fail to normalise blood pressure after a few months' time. In both the 2007 and the 2012 guidelines, treatment of 'high-normal' blood pressure (systolic 130-140 mmHg) is implicitly suggested for all patients with DM and microalbuminuria, as well as those with CVD.

For lipid-lowering drugs, the 2007 guideline recommended statins for all patients with previous CVD, DM with signs of target organ damage, 'marked hyperlipidaemia', and those at >5% mortality risk, with a generic low-density lipoprotein (LDL) target of 2.5 mmol/l, and an optional target of <2.0 mmol/l 'if feasible'. The 2007 guideline was not very clear about non-statin antihyperlipidaemic drugs. In the 2012 version, lipid management recommendations became significantly more aggressive. Treatment is suggested, for example, even in healthy low-risk (<1% ten-year risk) subjects with an LDL of >4.9 mmol/l, as well as in moderate (1-5%) risk individuals with an LDL >2.5 mmol/l. It also calls for 'immediate drug intervention' in all individuals at 'very high risk' who have an LDL of >1.8 mmol/l, even if they are asymptomatic. In daily practice, this implies, for example, immediate statin therapy in all patients with an increased carotid IMT. Treatment targets are the same as threshold LDL levels. Finally, the 2012 guideline implicitly recommends the liberal use of non-statin drugs if lipid targets are not reached with maximum tolerated statin doses.

Taken together, the ESC has maintained its traditional strategy of allowing the full range of types of epidemiological evidence, extrapolations from such evidence, and expert opinion to nurture the guideline recommendations. Risk thresholds for drug treatment have become very low (e.g.: >1% mortality risk per ten years, signs of pre-clinical atherosclerotic disease). In terms of treatment targets, the central hypotheses are simple: lower is better, both for blood pressure and, in particular, for cholesterol. For the latter, all means of lowering LDL cholesterol to its lowest possible level seem justified. The ESC 2012 guideline is beyond doubt the most aggressive to date.

DEVELOPMENTS IN THE UNITED STATES

The US has separate guidelines for lipid management and for hypertension. Both have been recently updated, and shared remarkable similarities in a novel general approach to admission of only high-grade epidemiological evidence.

Cholesterol guidelines

In November 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) updated the 2001 Adult Treatment Panel (ATP) guideline on the treatment of cholesterol.[3] The previous version largely followed the traditional cholesterol hypothesis, and interpreted the clinical trial evidence solely in this context: higher LDL means higher risk, and the more LDL is lowered, the more effective risk reduction will be.[4] Hence, LDL lowering to specific targets was central in the recommendations, and the choice for the type of statin was determined mainly by its LDL-lowering potential.

Work on the new guideline started in 2008 and more strictly and uniquely focused on evidence from large randomised clinical trials (RCTs) to address two main questions: (1) does evidence from RCTs support a specific treatment goal for LDL or HDL cholesterol? and (2) what are the risk-benefit profiles of specific cholesterol-lowering drug regimens?

For the first question, the task force concludes there is insufficient evidence from robust RCTs to support either LDL or HDL treatment targets. For the second question, the new guideline identifies four patient categories for which RCT evidence supports benefit from statins:

- Patients with established clinical cardiovascular disease;
- Patients aged 40-75 years with DM and an LDL between 1.8 and 4.9 mmol/l;
- Adults with an LDL of 4.9 mmol/l and higher;
- Adults 40-75 years with an LDL ≥1.8 mmol/ and a calculated ten-year CVD event risk of 7.5% or higher.

These four groups were chosen because they are congruent with eligibility criteria of statin trials with clinical endpoints, and the specific treatment strategies used in these trials now prevail over LDL targets obtained from meta-regression analyses of on-treatment LDL levels versus event risk. The recommendations thus focus not on LDL cholesterol, but on specific first-line treatment strategies in patient groups that showed benefit in clinical trials. Further, the guideline explicitly encourages a 'risk discussion' between the physician and the patient, resulting in a shared decision to start or defer statin therapy.

What follows is a recommendation to consider high-intensity statins (atorvastatin 40-80 mg, rosuvastatin 20-40 mg) in Category 1 patients up to 75 years old, in Category 3 patients and (optional) in Category 4 patients. Moderate-intensity statin therapy (simvastatin or pravastatin 20-40 mg, low-dose atorvastatin or rosuvastatin, or 40 mg of fluvastatin or lovastatin) is advocated for Category 1 patients older than 75 years, for Category 2 patients, and (optional) for Category 4 patients.

Moderate-intensity statins are considered 'reasonable' for those with a 5.0 to 7.4% ten-year event risk. Statins are explicitly discouraged for patients on haemodialysis or in class II-IV heart failure, as clinical trial evidence does not support a net benefit in these patients. Monitoring LDL levels is only recommended to assess adherence, not to guide treatment to any particular LDL goal. Of note, this approach effectively rules out non-statin lipid-lowering drugs from the recommendation, simply because evidence with clinical endpoints is lacking. This contrasts with the 2001 guideline, which recommended statins, bile acid sequestrants or nicotinic acid for lipid lowering.[4]

Blood pressure guidelines

In January 2014, the longest ever awaited cardiovascular prevention guideline was finally released: the 8th Joint National Committee hypertension guidelines (JNC8).[5] Like the American cholesterol guidelines, the methodology focus shifted from non-systematic literature review of all types of epidemiological studies, to systematic review of randomised clinical trials and adoption of a strict protocol to translate this evidence to recommendations. Another similarity was that the JNC8 committee, as did the ACC/AHA committee, phrased critical questions that guided the recommendations:

- Does antihypertensive therapy at specific blood pressure thresholds improve health outcomes?
- Do randomised clinical trials support blood pressure treatment targets?
- Do various antihypertensive drug (classes) differ in benefit or harm?

The JNC8 guideline no longer addressed hypertension definitions, but strictly focused on evidence-based treatment thresholds and treatment targets. Also, the choice of drugs was more directly based on trial evidence, rather than on generic considerations of drug class properties, which previously resulted in the recommendation to use thiazide-type diuretics as first-line treatment in most patients.[6] Finally, JNC8 no longer uses risk categories, which is in line with the strategy to focus more exclusively on RCTs to guide recommendations: no RCT has ever used absolute baseline risk as an inclusion criterion.

The most widely discussed recommendation of the JNC8 guideline is to increase the systolic blood pressure threshold and treatment target for antihypertensive treatment from 140 to 150 mmHg in all patients above 60 years of age. For patients with DM or chronic kidney disease, the committee also concluded that the former more strict target of 130/80 mmHg was insufficiently supported by clinical trial evidence, and so this target was also raised to 140/90 mmHg in the 2014 update. Finally, the updated guideline explicitly discourages the combination of an ACE inhibitor and an angiotensin-receptor blocker.

SYNTHESIS AND DISCUSSION

Table 1 summarises critical differences between the most recent European and US cardiovascular prevention guidelines. In addition, a third column is added to highlight the position of the multidisciplinary Dutch Cardiovascular Risk Management (CVRM) guideline, which was issued in 2011, and included representatives of all major clinical disciplines (family medicine, internal medicine, cardiology, neurology, etc.) in its writing committee.[7]

Taken together, both the European and the US guidelines employ more complex criteria for primary prevention than the Dutch guidelines, which mainly look at calculated ten-year event risk and whether LDL cholesterol and systolic blood pressure (SBP) are above a threshold level above which treatment efficacy is believed to be proven beyond reasonable doubt.

Not only are the European and US guidelines more complex than the Dutch guidelines, they are also significantly more aggressive, albeit in different ways. The ESC guidelines are aggressive in that even patients at very low ten-year mortality risk of ≥1% (corresponding to event risks of approximately 2 to 4% [7]) are considered eligible for antihyperlipidaemic treatment if their LDL exceeds 2.5 mmol/l. The LDL treatment threshold is even lower at 1.8 mmol/l for patients with an estimated risk of ≥5%. With regard to hypertension, if we assume an average relative risk reduction of 30% for antihypertensive treatment for healthy individuals with a 3% ten-year event risk, the corresponding ten-year number needed-to-treat (NNT) to prevent a single event is approximately 100 (1000 per year!).

In terms of eligibility criteria for primary preventive treatment, the US Guidelines are even more aggressive than those from Europe. All patients with an LDL ≥1.8 mmol/l and an estimated ten-year *event* risk of ≥7.5% 'should be treated', and statins are considered 'reasonable' for those with a 5 to 7.5% event risk. Although the *event* risk thresholds are thus generally higher than the corresponding *mortality* risk thresholds from the US guidelines, the LDL threshold is considerably lower for a large number of individuals. For hypertension, no absolute risk threshold is advocated, and a non-smoking 40-year-old female with a favourable lipid profile, but a blood pressure of for example 150/90 mmHg, would qualify for treatment, even though the ten-year event risk is substantially lower than 1%. For this category of not-too-rare patients, the maximum NNT raises to extreme heights, as shown in *table 1*. In comparison, implementation of the Dutch CVRM guidelines is generally associated with ten-year NNTs of <20.

This remarkable difference in NNTs between the Dutch and the recent international guidelines is not primarily based on differences in interpretation of the cardiovascular

Table 1. *Comparison of updated European, US, and Dutch National guidelines for cardiovascular risk management*

	European ESC Guidelines	**US Guidelines (ACC/AHA and JNC8)**	**Dutch CVRM Guidelines**
Main criteria for treatment	Established CVD, pre-clinical CVD, DM, 10-year *mortality* (†) risk	Established CVD, DM, LDL-cholesterol, 10-year CVD *event* risk	Established CVD, 10-year CVD *event* risk
Cholesterol			
Risk threshold for patients without CVD	- All patients with LDL ≥4.9 mmol/l; - LDL≥2.5 mmol/l and 10-y † risk >1% - LDL≥1.8 mmol/l, and 10-y † risk >5% or complicated DM or (preclinical) CVD	- All patients with LDL ≥4.9 mmol/l; - DM and LDL ≥1.8 mmol/l; - LDL ≥1.8 mmol/l and 10-y event, risk ≥7.5% ('reasonable' for >5%)	10-y event risk ≥20% and LDL >2.5 mmol/l (DM is considered a separate category with risk estimation based on adding 15 years to age)
Treatment target	LDL 1.8-2.5 mmol/l	None	LDL 2.5 mmol/l
Recommended drugs	Statin or any other lipid lowering drug	Statins only; high vs low intensity	Statins, others discouraged
Blood pressure			
Risk threshold for patients without CVD	10-y † risk ≥1% and BP ≥140/90 mmHg (130/90 for CVD and complicated DM)	- Adults ≥60-y and BP ≥150/90 mmHg - Adults <60-y and BP ≥140/90 mmHg	10-y event risk ≥20% and SBP >140 mmHg
Treatment target	130-140 mmHg	140 mmHg (150 if age ≥60-y)	140 mmHg
Recommended drugs	All major drug classes	All major drug classes	Thiazide-type, calcium blockers, ACE inhibitor.
Estimated maximum 10-year NNT for hypertension treatment	100	>200	20

ESC = European Society of Cardiology; US = United States; ACC = American College of Cardiology; AHA = American Heart Association; JNC8 = Eight Joint National Committee; CVRM = cardiovascular risk management; CVD = cardiovascular disease; DM = diabetes mellitus; LDL = low-density lipoprotein cholesterol; NNT = number needed to treat.

prevention literature. In fact, little doubt was expressed by the working committee of the Dutch guidelines that antihypertensives and statins would be effective in patients at substantially lower risks than the 20% event-risk threshold. Rather, the CVRM guideline is based on a maximum NNT that was generally considered acceptable from both an individual and a societal perspective. Also, the Dutch guideline committee was hesitant to conclude that very long-term treatment was proven safe in young low-risk patients. Here, thus, the Dutch and the international guidelines seem to part. International guidelines increasingly focus on what is effective, Dutch guidelines maintain a traditional focus on what is effective and reasonable in terms of anticipated absolute benefit. Why the international guidelines move towards more aggressive approaches is unclear. The focus on absolute benefit has lost none of its virtues, at least in our opinion.

What has been the response to the international guidelines? Somewhat surprisingly, the updated ESC guidelines received very few comments in the literature. The response to the US updates has been significantly more intense. The ACC/AHA cholesterol guideline has been criticised for holding on to a too strict definition of 'evidence' by only including epidemiological evidence coming from randomised clinical trials.[8] Concerns have also been raised that the risk prediction tool used in the ACC/AHA guideline is inaccurate.[9] It has further received major criticism for lowering the threshold for statin treatment.[10,11] Patients with an LDL as low as 1.9 mmol/l would be considered for statin treatment if their ten-year event risk exceeds only 5%, even if this risk is mainly defined by age, smoking and blood pressure. In the US only, over 45 million middle-aged Americans would qualify for statin treatment, which corresponds to one in every three American adults.[9] Worldwide, over a billion (1000 million) non-diseased individuals would qualify for statins if the ACC/AHA cholesterol guidelines were fully implemented.[11] Popular media, such as the New York Times, called upon people in good cardiovascular heath to ignore the cholesterol guidelines for this same reason of excessive NNTs.[www.nytimes.com/2013/11/19/opinion)

The updated JNC hypertension guidelines were only a few weeks old when we wrote this manuscript, but fierce responses have already been published. Only days after JNC8 was officially released, a minority from the JNC panel published a comment stating that they disagreed with raising the SBP target from 140 to 150 mmHg in patients older than 60 years.[12]

Within the Netherlands, there is less concern over updates in European or US cardiovascular guidelines. The Dutch Society of Cardiology (NVVC), however, has made a noticeable move to endorse the National CVRM guidelines in 2011, but also the ESC guideline, even though the recommendations have very different implications for patients and healthy individuals qualifying for primary prevention. To date, it is unclear whether Dutch cardiologists indeed feel we should collectively move towards the much more aggressive prevention strategies propagated by the ESC guidelines.

Our personal view is that both the US and the European guidelines contain positive elements that are noteworthy, but both are problematic in other respects.

The ESC guideline correctly maintains a focus on absolute risk thresholds for initiating preventive drug treatment, but the threshold has become extremely low, exposing many patients to treatments that provide only very small absolute risk reductions. Also, the lack of focus on clinical trial evidence has allowed a very liberal strategy towards for example non-statin antihyperlipidaemic treatment, which we feel is problematic.

The US guidelines shift the weight of attention to randomised clinical trial evidence. Although randomised clinical trials are arguably more objective, they are affected by significant selection bias, and trial data availability is largely determined by the pharmaceutical industry. The rational and far more common approach is sensibly weighing different types of evidence, giving credits to the objectivity of RCT, but also acknowledging the added value of observational studies and meta-regression analyses. Disqualifying this approach has had profound effects. For example, the fact that no clinical trial selected patients based on absolute risk calculation precluded the use of baseline risk in the JNC8 guidelines. By not allowing absolute baseline risk estimation to the selection process for antihypertensive treatment, the JNC8 guideline effectively recommends antihypertensive treatment for a large proportion of the adult population. Another example that follows from admitting only trial evidence is that although the 150 mmHg treatment goal for patients over 60 years may make sense for this group at large, compelling evidence from observational and meta-regression analyses strongly calls for extra caution in the oldest old, particularly those who are frail.[13]

In conclusion, international cardiovascular prevention guidelines are becoming more and more aggressive, but methods for weighing the evidence have become increasingly dissimilar. Guideline paradigms are shifting, but not all in a similar direction.

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