CARDIOVASCULAR RISK PROFILE AND ANTIHYPERTENSIVE TREATMENT

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The incidence of cardiovascular disease (CVD) is still increasing globally, but prevention and treatment have improved considerably during the last 20 years. As treatment is not curative, prevention is preferable although it calls for intervention in many more subjects. In order not to treat many subjects unnecessarily, it is important to identify those at highest risk of developing CVD in the future. For this purpose, several tools for cardiovascular risk estimation have been developed. In Europe, the most widely used scoring systems are SCORE [1] in subjects without known CVD or diabetes, and the cardiovascular risk stratification chart of the European Society of Hypertension (ESH) [2] in subjects with hypertension. However, many of these risk scores will, in general, overestimate the cardiovascular risk [3] because improved primary and secondary cardiovascular prevention has reduced both the incidence of myocardial infarctions and case fatalities [4] in many Western countries.

The SCORE system as a basis for strategies of prevention

Like the ESH, the European Society of Cardiology (ESC) has focused on CVD prevention, as reflected in their guidelines for clinical practice [5]. In subjects without known CVD, type 2 diabetes, type 1 diabetes with microalbuminuria, or very high levels of individual risk factors, the risk of developing fatal atherosclerotic events is calculated using the SCORE system, available in chart form (Figure 1) or as an interactive tool (HeartScore) on the ESC website (on-line version or PC-based program) (http://www.escardio.org/Policy/prevention/tools/health-toolkit/Pages/HeartScore.aspx). HeartScore is based on data from European population surveys, and national versions are available in several countries. Absolute risk of cardiovascular death within 10 years < 1% is defined as low risk; 1–4% risk is defined as moderate; 5–9% as increased, and ≥ 10% as high. Generally, there are two SCORE chart versions: for populations with low (Belgium, France, Italy, Luxemburg, Portugal, Spain, and Switzerland) or high CVD risk. In addition, each of the SCORE charts is based either on total cholesterol or the total cholesterol/HDL--cholesterol ratio. The treatment goals for blood pressure as well as other cardiovascular risk factors depend on this risk stratification, but there are no universal thresholds for initiation of drug treatment. For subjects with a 10-year risk of cardiovascular death < 5%, in addition to not smoking, BMI < 25 kg/m², and 30 minutes of moderate exercise daily, the following goals are recommended: Blood pressure < 140/90 mm Hg; total cholesterol < 5 mmol/l; low-density lipoprotein (LDL)-cholesterol < 3 mmol/l; and blood glucose < 6 mmol/l. These thresholds are arbitrary for blood pressure as well as for cholesterol as the association between blood pressure [6] as well as cholesterol [7] and the risk of developing CVD are also present at lower values. In general, drug treatment is not recommended in this low-moderate risk group if treatment goals are not met. Subjects at high risk (≥ 10%) have the same treatment goals as patients with known CVD or diabetes: Blood pressure < 130/80 mm Hg; total cholesterol < 4.5 (4.0) mmol/l; and LDL--cholesterol < 2.5 (2.0) mmol/l. In this high-risk group, drug treatment is recom-

mended if treatment goals are not met. In subjects with increased risk (5–9%), a less aggressive approach is allowed.

The impact of age on risk calculation

Age is the most important risk factor in the SCORE and may therefore lead to undertreatment in younger subjects and overtreatment in older subjects. To avoid undertreatment in younger subjects, it is recommended to use a relative risk chart or to calculate the absolute risk as if the subject were 60 years old. To avoid overtreatment in the elderly, caution is recommended with drug treatment if age is the major/sole reason for the increased cardiovascular risk. The actual cardiovascular risk may be higher than indicated in the SCORE chart (Figure 1) if some cardiovascular risk factors not included in the SCORE model are present (family history of premature CVD, physical inactivity, abdominal obesity, and others).

Lifestyle modification

In all subjects, intervention should include recommendations of lifestyle changes. Although lifestyle interventions have been demonstrated to reduce blood pressure, they have not yet been demonstrated to prevent cardiovascular complications in patients with hypertension and should therefore not delay initiation of drug treatment in subjects at high risk for developing CVD. As the risk of developing CVD is multifactorial, the management of patients with hypertension should not be restricted to factors affecting blood pressure, but should also include a recommendation of smoking cessation. However, several lifestyle changes have been shown to reduce blood pressure: Weight loss [8], increased physical activity [9], salt restriction, daily fish oil [10], dietary approaches introduced by DASH diet [11], and reduced alcohol intake. These lifestyle changes will be sufficient in many subjects to reduce the cardiovascular risk and may prove to have an enormous impact on CVD prevention on a population scale.

The risk chart of the European Society of Hypertension

The ESH risk chart (Figure 2) [2] uses the terms "low", "moderate", "high", and "very high" to indicate an approximate risk of cardiovascular morbidity and mortality in the following 10 years, which is somewhat analogous to the increasing level of total cardiovascular risk estimated by the Framingham or SCORE models. However, the additional use of cardiovascular morbidity is especially relevant for patients with hypertension who have increased risk of detrimental non-fatal stroke. Similar to the ESC recommendations, the key messages in the ESH risk chart [12] are: 1) All definitions of hypertension are arbitrary because the risk of CVD decreases continuously with decreasing blood pressure down to an optimal blood pressure below 120/70 mm Hg (Figure 2); 2) As hypertension is only one of several interacting cardiovascular risk factors, the absolute cardiovas-
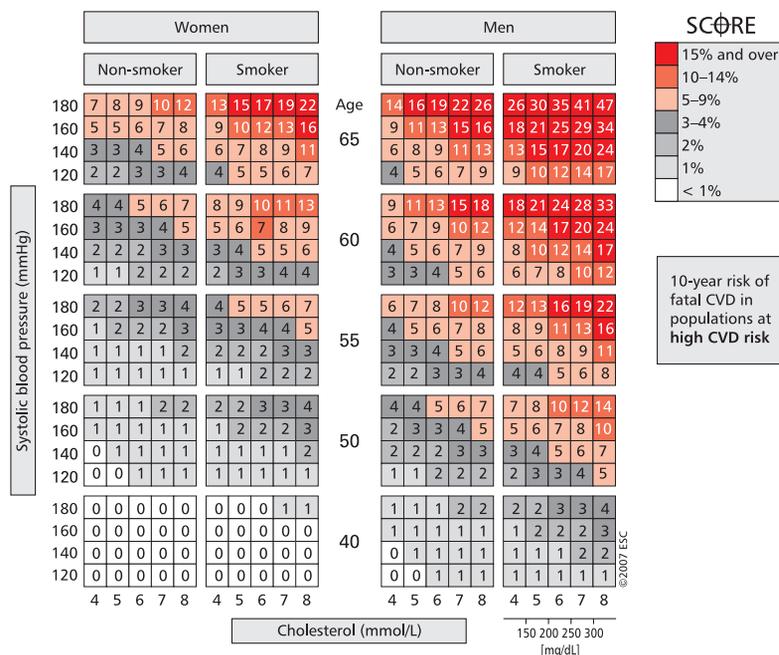

Figure 1. The absolute 10-year risk of fatal cardiovascular events as predicted by age, gender, smoking habits and serum cholesterol in subjects without diabetes or cardiovascular disease (CVD)

Blood pressure (mm Hg)					
Other risk factors, OD or disease	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥ 180 or DBP ≥ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1–2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 risk factors, MS, OD or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

Figure 2. The added absolute 10-year risk of fatal or non-fatal cardiovascular (CV) events as predicted by blood pressure, traditional CV risk factors, the metabolic syndrome (MS), subclinical CV organ damage (OD), diabetes and CV or renal disease; HT — hypertension; SBP — systolic blood pressure; DBP — diastolic blood pressure

cular risk is dependent on all the risk factors; and 3) Treatment indications and goals are determined by the absolute cardiovascular risk and are thereby dependent on cardiovascular risk factors, subclinical cardiovascular damage, and CVD.

As illustrated by the SCORE (Figure 1), a large proportion of patients with hypertension will not be at high absolute risk of cardiovascular death. However, some of these patients may be at high risk of non-fatal cardiovascular events, non-fatal stroke in particular. The ESC guidelines for antihypertensive treatment follow, to a large extent, the ESH guidelines, but they are somewhat more restrictive regarding initiation of antihypertensive drug treatment.

Special considerations
The following three groups of patients are often debated: Hypertensive patients at low added risk, subjects with high normal blood pressure and several additional cardiovascular risk factors or subclinical cardiovascular damage, and normotensive patients with CVD.

Hypertensive patients at low added risk (20% of the middle-aged, healthy population [12])
In patients with grade 1 hypertension without other cardiovascular risk factors, the ESH primarily recommends lifestyle changes, but, if hypertension persists after six months, antihypertensive drug treatment is recommended not based on clear scientific evidence but based on the fact that the patients will eventually develop additional risk factors, and on the assumption that early prevention is better than late [13]. However, the ESC guidelines do not recommend antihypertensive drug treatment in patients with grade 1 hypertension and SCORE < 1%, due to their low cardiovascular risk. As the SCORE often underestimates the risk for non-fatal stroke in women, the risk associated with not treating middle-aged women with hypertension and SCORE < 1% should be carefully considered. Before making this decision, it is crucial to assess all cardiovascular risk factors and to follow these patients because, over time, the 10-year absolute risk of cardiovascular death will increase above 1% thus requiring drug treatment. This risk of undertreatment in middle-aged women may explain the relatively high number of cardiovascular deaths in 40-year-old women in the Västerbotten Intervention Program of northern Sweden [3].

Subjects with high normal blood pressure (15% of the middle-aged, healthy population [12])
Healthy subjects with high normal blood pressure have only slightly elevated cardiovascular risk compared to healthy subjects with optimal blood pressure (< 120/80 mm Hg) [14]. However, a large proportion of cardiovascular events occur in this rather large group, and, since risk assessment is often perceived as complicated, they deserve special attention. In subjects with high normal blood pressure and SCORE < 5%, no diabetes and no sign of subclinical cardiovascular damage, lifestyle advice is recommended by the ESC [5] and ESH [2]. In subjects with high normal blood pressure and diabetes, these societies recommend lifestyle changes as well as antihypertensive drug treatment. In the intermediate group of subjects with high normal blood pressure and SCORE ≥ 5% or with high normal blood pressure and high added cardiovascular risk due to the presence of any three other cardiovascular risk factors, metabolic syndrome or subclinical cardiovascu-

lar damage, they recommend lifestyle changes and the consideration of antihypertensive drug treatment. However, antihypertensive treatment in subjects with high normal blood pressure and diabetes or in subjects at high added risk has never been demonstrated to reduce major cardiovascular events [13], but is likely to reduce subclinical cardiovascular damage [2] and is thereby assumed to reduce cardiovascular risk [13]. By measuring subclinical cardiovascular damage, it is also possible to target and monitor treatment on a more individual basis [15]. As blockage of the renin-angiotensin-aldosterone system is associated with regression of subclinical cardiovascular damage without metabolic side effects, typical treatment will include an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II-receptor blocker (ARB) [16].

Normotensive patients with CVD
Despite little evidence, the ESH recommended in their 2007 guidelines [2] antihypertensive drug treatment, especially ACE-inhibitors or ARBs, in patients with CVD or renal insufficiency independently of blood pressure. However, the clear scientific evidence for more aggressive treatment in patients with CVD is lacking [13], and post-hoc analyses from the OnTarget-study [17] have demonstrated a worse prognosis in patients reaching a very low blood pressure, indicating a threshold for how far blood pressure may be reduced in patients with CVD. Therefore, the ESH have modified their rather aggressive recommendation for a treatment goal just below 130/80 mm Hg [13] which is also used by the ESC [5]. The first line of antihypertensive drug treatment is dependent on the type of CVD. In diabetes with microalbuminuria or renal insufficiency, ACE inhibitors or ARBs should be included in the treatment.

Practical use of risk stratification
In general, the SCORE should be used in healthy, normotensive subjects, and the ESH risk chart in hypertensive patients. However, physicians are still reluctant to use risk stratification tools, and the differences between the ESH risk chart and the SCORE, if used as recommended by the ESC, are only small [18]. Therefore, it is more important that doctors use the risk stratification tool with which they are familiar and less important which tool they use. General assessment of subclinical cardiovascular damage in normotensive subjects with SCORE < 5% is an overwhelming task without a substantial clinical impact [19]. However, assessment of subclinical cardiovascular damage in normotensive subjects with 1% < SCORE < 5% may have some clinical impact. In subjects with high normal blood pressure, assessment of subclinical cardiovascular damage may increase the sensitivity for identifying subjects experiencing later cardiovascular events [12]. However, as approximately 80% of healthy subjects with high normal blood pressure and SCORE ≥ 5% have subclinical cardiovascular damage [19], calculation of the SCORE could be considered instead of measuring subclinical cardiovascular damage in this group.

Summary
Estimation of absolute cardiovascular risk is important for the choice of primary as well as secondary cardiovascular prevention. In general, physicians are advised to use the SCORE in apparently healthy subjects with optimal or normal blood pressure, the ESH risk stratification chart in patients with hypertension, and either one or, better still, a combination of the two instruments in apparently healthy subjects with high normal blood pressure.

References
1. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003; 24: 987–1003.
2. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007; 25: 1105–1187.
3. Stenlund H, Lönnberg G, Jenkins P, et al. Fewer deaths from cardiovascular disease than expected from the Systematic Coronary Risk Evaluation chart in a Swedish population. Eur J Cardiovasc Prev Rehab 2009; 16: 321–324.
4. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in US deaths from coronary disease, 1980–2000. N Engl J Med 2007; 356: 2388–2398.
5. Graham IM. Guidelines on cardiovascular disease prevention in clinical practice: The European perspective. Curr Opin Cardiol 2005; 20: 430–439.
6. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903–1913.
7. Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007; 370: 1829–1839.
8. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension 2003; 42: 878–884.
9. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann Intern Med 2002; 136: 493–503.
10. Geleijnse JM, Giltay EJ, Grobbee DE, Donders AR, Kok FJ. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. J Hypertens 2002; 20: 1493–1499.
11. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med 2001; 344: 3–10.
12. Sehestedt T, Jeppesen J, Hansen TW, et al. Which markers of subclinical organ damage to measure in individuals with high normal blood pressure? J Hypertens 2009; 27: 1165–1171.
13. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European Guidelines on Hypertension Management: A European Society of Hypertension (ESH) Task Force Document. J Hypertens 2009 Oct 15. [Epub ahead of print].
14. Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001; 345: 1291–1297.
15. Nilsson PM, Lurbe E, Laurent S. The early life origins of vascular ageing and cardiovascular risk: the EVA syndrome. J Hypertens 2008; 26: 1049–1057.
16. Nilsson PM, Boutouyrie P, Laurent S. Vascular aging: A tale of EVA and ADAM in cardiovascular risk assessment and prevention. Hypertension 2009; 54: 3–10.
17. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008; 358: 1547–1559.
18. Sehestedt T, Jeppesen J, Hansen TW, et al. Risk stratification with the risk chart from the European Society of Hypertension compared with SCORE in the general population. J Hypertens 2009; 27: 2351–2357.
19. Sehestedt T, Jeppesen J, Hansen TW, et al. Risk stratification is improved by adding markers of subclinical organ damage to SCORE. Eur Heart J 2010; 31: 883–891.