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Risk factors and target organ damage: is there a special case for pre-hypertension?

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Abbreviations

DBP Diastolic blood pressure

PWV Pulse wave velocity

SBP Systolic blood pressure

Individualised cardiovascular risk assessment is a challenging task. In the care for our patients we are guided by two complementary tools. The first tool builds upon the concept of cardiovascular risk factors, and numerous scoring systems from national and international societies are being used in clinical practice [1-3]. Needless to say that high blood pressure, hypercholesterolaemia, diabetes, and smoking are well established cardiovascular risk factors, and this list is certainly not complete. The risk factor concept works well on a population basis and helps to estimate an individual's risk, but risk scores cannot take all possibly relevant factors including diet and the genetic background into account and will therefore only provide a probability for developing disease. The second tool bases on the cardiovascular continuum, which was originally proposed by Dzau and Braunwald in 1991 [4]. The concept proposes a development from underlying risk factors via intermediate phenotypes such as endothelial dysfunction to advanced disease with target organ dysfunction and organ failure. Assessment of intermediate cardiovascular phenotypes will therefore help to identify patients who are already in the process of developing clinically overt cardiovascular disease, but also those subjects who, maybe despite having a number of cardiovascular risk factors, do not have evidence of early disease and are therefore less likely to proceed to myocardial infarction or stroke.

Numerous studies have shown that increased vascular stiffness is a clinically useful intermediate cardiovascular phenotype. Carotid-femoral pulse wave velocity (PWV) is a well validated tool to assess vascular stiffness. PWV has been found to be determined by blood pressure, age and diabetes [5], and PWV independently predicts outcome in cardiovascular diseases including renal failure [6] and hypertension [7]. The 2007 ESH/ESG Guidelines for the Management of Arterial Hypertension recommend measurement of carotid-femoral PWV to assess a patient's cardiovascular risk and to guide treatment decisions [8]. Similar associations with blood pressure have been found for other intermediate cardiovascular phenotypes including carotid intima-media thickness and left ventricular hypertrophy. In this issue of *Journal of Hypertension*, Norton *et al.* [9] examined the relationship between pre-hypertension and markers of early target organ damage including PWV in

a population sample of African ancestry. Pre-hypertension was found to be associated with target organ damage, but was not an independent predictor thereof.

The concept of pre-hypertension is relatively new and was formally introduced in the seventh edition of the US Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [10] to account for the higher chance of developing hypertension in subjects with pre-hypertension [11,12] and for the increased cardiovascular risk in this group [13]. This concept, although with some important modifications, has also been introduced to European guidelines. Most importantly, the ESH/ESC guidelines avoid the term "pre-hypertension" but differentiate into optimal (systolic blood pressure [SBP] <120 mmHg and diastolic blood pressure [DBP] <80 mmHg), normal (SBP 120-129 mmHg and/or DBP 80-84 mmHg) and high normal blood pressure (SBP 130-139 mmHg and/or DBP 85-89 mmHg) [8]. This is in line with the concept of a continuous relationship between blood pressure and cardiovascular risk, and subjects with normal blood pressure are indeed at lower risk than those with high normal blood pressure [13].

In the study by Norton *et al.* [9], subjects were grouped into those with optimal blood pressure (<120/80 mmHg), pre-hypertensive blood pressure (120-139/80-89 mmHg) and hypertension. The finding of an association between target organ damage and blood pressure category is reassuring, but the fact that pre-hypertension did not independently predict target organ damage when adjustments for age, gender, diabetes and other covariates were made, is surprising at first glance. It is even more surprising against the background of the Strong Heart Study [14] which suggested an independent association of pre-hypertension with early markers of target organ damage such as left ventricular hypertrophy. In fact, the notion that arterial distensibility is impaired not only in patients with established hypertension but also in subjects with borderline hypertension (a concept which is not fully up-to-date, but overlaps to some degree with the concept of pre-hypertension) has already been described by Aristimuño and Suarez in 1984 [15].

A number of reasons may explain the negative findings in the present study [9]. First, Norton *et al.* [9] have missed the opportunity to subgroup the pre-hypertensive subjects into those with high normal and normal blood pressures. However, such further subgrouping would have reduced the power of the study considerably. Interestingly, the continuous relationship between, for example, blood pressure and urinary albumin to creatinine ratio clearly demonstrates that subjects at the higher end of the normotensive range may have a greater prevalence of early target organ damage compared to those at the lower end of the pre-hypertensive blood pressure range. Secondly, as acknowledged by the authors, not all of the covariates have been assessed with the same precision or were in fact not available in all subjects. An example for the former is the definition of diabetes ($\text{HbA}_{1c} > 6.1\%$) which is a reasonable definition in epidemiological studies on diabetes, but compared to the precision of blood pressure measurement or echocardiography in the present study, it is certainly one of the weaker variables in the model. With regard to the latter, for example data on PWV were not available in 111 out of 882 participants for technical reasons including presence of bradycardia or obesity, and only 399 participants had a valid echocardiogram. Thirdly, although the authors present a number of carefully performed multivariate analyses, statistical adjustment for complex biological interactions is not always possible, and the lack of a statistically independent association does not necessarily exclude biological significance. Nevertheless, the models in the present study [9] also adjust for waist circumference and are therefore more comprehensive than models in a previous study [14]. Fourthly, little is known about differences in intermediate cardiovascular phenotypes between subjects of different ethnic origin. For example, PWV seems to be increased in African Caribbeans compared to Europeans [16], and similar differences may account for the inconsistent findings between the study by Norton *et al.* [9] and previous reports [14].

Most importantly, however, we should be careful not to confuse the risk factor concept with the concept of the cardiovascular continuum, particularly in cross-sectional studies. Pre-hypertension is a cardiovascular risk factor which will, in some patients and over time, lead to early and ultimately to advanced cardiovascular disease. Compared to other risk factors, in an otherwise healthy subject high normal blood pressure is a rather weak risk factor, and we should not be too surprised to see that this risk factor is not (yet) causing target organ damage on its own.

The data by Norton *et al.* [9] do not affect clinical practice. Indeed they support the present strategy not to treat pre-hypertension in the majority of patients. In this respect, Norton *et al.* reassure us that pre-hypertension on its own is not associated with early markers of target organ damage and a conservative approach to these subjects is fully justified. On the other hand, high normal blood pressure is treatable, and in subjects at high overall cardiovascular risk, such as subjects with diabetes or renal disease, pre-hypertension is a modifiable risk factor even if not independently associated with target organ damage in the present study.

A number of open questions remain, and most of these questions can only be answered by prospective studies. The relationship between blood pressure category and target organ damage demonstrates the validity of these measures in subjects who are not (yet) hypertensive even if this relationship is not independent of other variables. The present study [9] contains a rich source of data that should be followed up longitudinally. It will be extremely interesting to see if the group of pre-hypertensive subjects will over time experience more profound changes in PWV, indices of left ventricular hypertrophy and dysfunction, and albuminuria compared to patients with optimal blood pressure.

We will also have to learn how to manage patients with evidence of early target organ damage who have "soft" risk factors such as pre-hypertension, mildly elevated lipids or some degree of

overweight in the absence of "hard" classic risk factors. Studies examining the effect of medical and lifestyle intervention in such patients are warranted, and assessment of PWV, carotid intima-media thickness, echocardiography and albuminuria seem to be appropriate intermediate cardiovascular phenotypes for this purpose.

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