Who wants to be normal?

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Is the average elderly Norwegian at high risk of cardiovascular disease after 60 years of age? Will most of these men and women need health care or even drug treatment in order to lower serum lipids and/or blood pressure? Well, according to the present guidelines of the European Heart Association (1), this actually seems to be the case. Hartz et al (2) show that in Tromsø, Norway, the vast majority of men >60 years, and females >70, have a 10-year risk of fatal cardiovascular disease exceeding 5%, the suggested limit for intervention. We can argue about the exact figures, including the (unpublished) confidence interval of the 5% limit, but the main message is clear: it is normal to be at 'high' risk. And what is true for Norway would be true for most other European countries.

However, many clinicians will find this definition of normality hard to accept. Some will object simply on the basis of semantics: the 'average' can never be equal to 'high'. Some will feel that it is unethical to turn the majority of seemingly healthy citizens into patients requiring medical treatment and surveillance. When it comes to long-term pharmacological treatment, many doctors are still wondering whether all-cause mortality is significantly lowered by drug treatment and whether study participants were representative of their own patients in clinical practice. Some will argue that the necessary societal expenses could be better used for other purposes, unless each person covers all the costs for screening and treatment. Some will say that

it is normal to die if you are old. However, most elderly people will be glad to postpone death and disability, if an efficient option is available.

Certainly, in secondary prevention, the efficiency of drug treatment is evident (3). Virtually all of us agree to treat average or high serum cholesterol and blood pressure in patients with established cardiovascular disease, although the evidence from randomised controlled trials is stronger for statins than for antihypertensives. After myocardial infarction, the prescription of low-dose aspirin and beta-blockers is also based on solid evidence, as is the use of ACE inhibitors in high-risk patients. And in the Heart Protection Study, simvastatin prevented 1 of 4 strokes in subjects with a prior cerebrovascular event irrespective of pre-existing coronary disease. Substantial evidence also suggests that patients with diabetes should have lower than ’normal’ levels of blood pressure and LDL cholesterol. Among the Tromsø population studied by Hartz et al (2), roughly one third of the ’high’ risk subjects belonged to this secondary prevention group, i.e. people with self-reported cardiovascular disease (myocardial infarction, angina pectoris, stroke or internittent claudication) or diabetes.

In primary prevention, however, things are a bit more complicated (3). It is still uncertain if total mortality is decreased by drug treatment in subjets in the lower range of ’high’ initial risk of cardiovascular death. Even more uncertain is whether aggressive treatment is more effective than a less aggressive one, with regard to the dose and number of drugs. These uncertainties apply to both mild hypertension and dyslipidaemia. Before telling the average citizen that long-term medication is beneficial it would therefore be preferable to have a more solid scientific base than what we have today. In primary prevention, it is particularly important to scrutinize the validity of the European SCORE risk charts in this aspect. Computer-based score systems and standardization of risk factor measurements may further improve risk evaluations at the

individual level, for example if waist circumference and HDL cholesterol are included in the model.

Age as a risk factor poses a particular problem. Much evidence suggests that in the elderly, antihypertensives are more effective and statins equally effective as in younger people. As the absolute cardiovascular risk is higher, the absolute benefit may therefore increase with age, possibly well above 70 years. However, a beneficial effect on total mortality in the elderly has been shown for antihypertensives but not for lipid lowering. Drug treatment patterns among the Tromsø population study suggest that there is (compared with European guidelines) a very large underprescription of antihypertensives and, in particular, lipid-lowering drugs after the age of 65. Hartz et al (2) suggest that the validity of the guidelines for elderly individuals be carefully re-evaluated.

However, let us, for a moment, leave all these uncertainties and accept the fact that the average middle-aged or elderly European, even in Mediterranean countries, sooner or later will be at high risk of stroke or cardiovascular death. The most important underlying condition, atherosclerosis, affects to a high degree the coronary arteries of virtually everyone who has passed the age of 60, even in Southern Europe (4). Although advanced atherosclerosis is a typical consequence of ageing today, early human autopsy studies and animal experiments suggest that it is not an inevitable process (5). An international autopsy study in the 1960s comparing middle-aged men in four countries revealed a marked difference, depending on the degree of urbanisation (6). Other free-living mammals are apparently not affected by advanced coronary atherosclerosis unless they are fed a diet not available in their natural habitat, and atherosclerosis promotion and regression in animal experiments are highly responsive to dietary manipulation, in particular one that is in concert with the animal's natural diet (5).

Others and we have found reasonably good evidence that human populations with lifestyles resembling that of our pre-agricultural ancestors have no or little cardiovascular disease, despite sufficient numbers of elderly (5, 7). Clinical studies strongly suggest that both stroke and coronary heart disease were absent before urbanisation in such populations (7, 8). Cardiovascular risk factor levels have been remarkably beneficial and very different from those among Western populations, most consistently with regard to blood pressure and the metabolic syndrome (5). The lowest levels of blood pressure (typically 110/70±15/10 mm Hg) and serum cholesterol (typically 3±1 mmol/L) have been noted in hunter-gatherers with very high intakes of meat. Furthermore, in several recent dietary intervention trials, Jenkins et al (9) have obtained effective lowering of LDL cholesterol with cereal- and dairy-free, plant based diets, in fact as effective as with statin treatment. Possibly, the common denominator is avoidance of foods that are new to the human species.

Our concept of normality obviously depends on whether we believe that these recent but common risk profiles are unavoidable or not. If all citizens were smokers, we would certainly not object to classify the average risk of fatal lung cancer as high, even if the 10-year risk in that case would be less than 5%. We would then use non-smokers as the norm despite their absence in our own population.

Hence, it seems obvious that there is a large potential to prevent cardiovascular disease in Europe. Smoking abstention, regular physical activity, and healthy diets are important steps towards this goal, as firmly stated in the European guidelines (1). At the societal level, healthy lifestyles need to be strongly promoted and subsidized. With regard to diet, increasing evidence suggests that the prevailing concepts may need considerable modification before food becomes an efficient tool in the prevention and treatment of cardiovascular disease. Although randomized dietary trials are difficult to perform, the enormous amonut of money spent so far in randomised

drug trials (the recently published ASCOT study was estimated to a worth of 300 billion Euros) must sooner or later be equalled in the search for optimal dietary modification. We believe that our evolutionary legacy may provide a reference standard in that search (5, 8, 10, 11).

In summary, the study by Hartz et al adds to the evidence that the majority of Europeans should take their future risk of cardiovascular disease seriously. The European guidelines are a valuable starting point for clinicians to be much more active in this process, as long as the the position of the guideline writers has not been undermined by better arguments. I think it would be a mistake to adjust the guidelines only because they show that few of us are healthy.

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