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Cardiovascular Disease Prevention: What Makes an Intervention Worthwhile?

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In the context of medical practice, it is always pertinent to consider what makes a given intervention worthwhile? The misconceptions on which such decisions were based, the ironic and sometimes ethical dilemmas which ensued and the challenges they still pose are amply demonstrated by the profession's struggle to formulate guidelines for the prevention of cardiovascular diseases. Whilst accepting that such decisions must ultimately depend on the prevailing circumstances (individual socioeconomic priorities), in the past such recommendations were largely concerned with modifying a composite of correctable individual risk factors, based on what was known about the relative risk reduction (RRR) likely to be achieved. These risk factors included smoking, sedentary life style, hypertension, hypercholesterolaemia and obesity. Moreover, recommendations were commonly based on equating the clinical significance of modifying corresponding surrogate markers whatever the means (or drug).

The latter assumptions notwithstanding, recognising and understanding the importance of absolute risk reduction (ARR) over a given period of time, and its reciprocal, the number needed to treat (NNT), has been a major new advance. Since these two interdependent parameters convey a much fairer idea as to how worthwhile a given intervention might be in relation to others, they are also an aid to setting priorities. Deciding whether to consider an intervention as worthwhile under any given set of circumstances then becomes somewhat easier.

This point is abundantly illustrated when comparing RRRs and NNTs to describe coronary heart disease (CHD) event prevention following long-term intervention with statins under different circumstances in similarly aged adults. Thus, in four large-scale, randomised, placebo-controlled clinical trials of outcome, groups receiving statins all experienced the same magnitude of plasma cholesterol lowering and RRR for prevention of CHD events (24-37%). On the contrary, NNT was a highly discriminating parameter. Thus, in the 4S trial involving patients with both coronary artery disease and hypercholesterolaemia, patients receiving active treatment enjoyed an NNT/year of 63 as opposed to 256 in persons with neither among participants of the AFCAPS/TexCAPS trial. In the remaining trials, among persons who all had CHD only (CARE) or hypercholesterolaemia only (WOSCOP), values for NNT/year were intermediate. Clearly, relative to persons with neither risk factor, those with both required that about four times fewer persons needed to receive statin just to prevent a single individual experiencing a CHD event. In other words, a much smaller effort had to be expended in persons at higher risk. Recourse to NNTs (but not RRRs) for different cardiovascular events, also illustrated that statins have a much more marked effect on preventing CHD than strokes; respective values for stroke prevention consistently being much greater than for CHD event prevention. Furthermore, in the same four trials calculation of the NNTs (± 95% CIs) to prevent death from any cause reveal that a reduction in overall mortality can only be inferred with confidence, among patients with both CHD and hypercholesterolaemia. NNTs also indicate how many individuals must necessarily incur the expense, inconvenience and risk of adverse effects from such drug treatment over a given period of time, just to save one person from experiencing the defined event.

Consideration of ARR has also been one of the key innovations in the new British Hypertension Society Guidelines for the management of hypertension. One
of its recommendations is a formal estimation of a subject's 10 year CHD risk in order to decide whether or not to treat a patient with mild hypertension. In this context recourse to ARR rather than RRR is certainly a laudable development, as it provides direct information about likely real benefits over time. Regrettably however, this approach does not take age into account.

As elderly patients have inherently higher risks of disease and death, treatment decisions based on risk alone will always favour the elderly. In other words, an elderly person with very mild hypertension or very mild hyperlipidaemia readily attains the 1.5% or so annual risk of events that mandates treatment. Whereas a young person, even with multiple risk factors, may not reach the same level of annual risk. If treatment decisions are to be based solely on risk, then implementing this strategy will lead to therapeutic decisions that run contrary to common sense. The problem is that knowing the baseline risk, (i.e. the risk of no treatment), is not enough. One also needs to know the benefits of treatment. In this regard, the benefit is directly related to the life expectancy. A cardiovascular death at 50 represents, say 20 years of life lost, whereas a death at 75 could represent only 5 lost years.

In the absence of a full assessment of risk and benefit (quality life years preserved), basing treatment decisions on the 10 year cardiovascular risk alone is inadequate and may lead to inappropriate and inequitable allocation of resources. There is a real danger that this policy will tend to conserve the most aged members of the population by prolonging life in the extremely elderly, whilst forgoing the prevention of premature deaths through withholding treatment in the young. The solution is to use the NNT to gain one year of life (or better still one quality adjusted life year or QALY), to evaluate the effectiveness of an intervention. This will take into account differential potential benefits accruing from the intervention in terms of remaining life expectancy (or QALYS) in the young as opposed to the elderly.

References