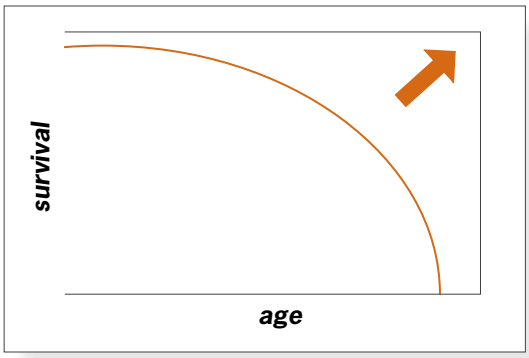
UPFRONT

THE MANNER OF OUR DYING

Preventive health care aims to prevent premature deaths and delay the onset of the suffering caused by illness and disease (compression of morbidity). This is on the understanding that everyone is entitled to a normal life span and that anyone not achieving this has been cheated of the missing years.[1] In essence the aim is to move the survival curve towards a rectangle (Figure 1).

Figure 1: Survival curve



While we put upper age limits in place for diagnostic procedures, such as cervical smears, the theory and rhetoric of preventive healthcare has not yet addressed the problem of how medicines for disease prevention should be applied to those who have already exceeded an average life span. In the context of a rapidly ageing population, there is an urgent need to think the issues through.

Unfortunately there are too few clinical trials in older populations. Sensitivity about ageism means that preventive medicines are often applied in older groups on the basis used for younger populations. The two groups are vastly different. Multiple co-existing diseases are the rule in older populations and the risk of harm from treatment is greater.

THE NEW EPIDEMICS

In the developed world, improved social conditions, immunisation and successive generations of antibiotics have been hugely successful in stemming the epidemics of infectious disease. Individuals saved from death due to overwhelming bacterial infection are now living long enough to develop other diseases producing a new 'epidemic', this time of cardiovascular disease. Now cardiovascular disease prevention is pursued and guidelines are applied regardless of age.

However if death is to be prevented at any age from any cause, epidemic will follow epidemic. Eventual mortality is certain, so the questions is what then will be the next most common cause of death and illness – the next 'epidemic'? Our bodies have a finite functional life. If various systems wear out at a similar rate, by introducing preventive treatments in the older populations aimed at reducing the risk of a particular disease, are we simply changing the cause of death rather than prolonging life?

Several factors are influential. Firstly, single disease perspectives result in trial designs that look at outcomes for single diseases in a situation where complexity is the rule.

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These single disease perspectives imply that successful interventions for the index condition should be made widely available to all those with that risk factor, irrespective of the overall effect on population mortality and morbidity. Secondly, sensitivities about ageism make us feel awkward about looking at things from a different perspective when dealing with an older population. Finally there are huge commercial gains to be made by pharmaceutical companies if statistically effective interventions in relatively small population groups can be widened to larger populations.

Research estimates of differences in the absolute risk of an adverse outcome enable us to understand the potential benefits of particular treatments. In older people, the likelihood of morbidity due to multiple and compounding diseases increases and the absolute risk of dying is increased, simply because the time of death is proportionately closer. This may magnify the apparent effect of a single intervention for a specific condition while overall survival is only minimally affected.

Notwithstanding this, treatment can be justified in terms of postponement of morbidity even when there is no change in mortality. However the difficulties associated with single disease perspectives also apply here. The use of statins for cardiovascular disease prevention provides a case study for examining these issues further.

THE EVIDENCE FOR LIPID LOWERING TREATMENTS IN OLDER AGE

The framework for lipid modification at younger ages is extrapolated for those over 75. The largest trial conducted in this group is the PROSPER trial with over 5000 participants, between 70 and 82 years old, and followed up for an average of 3.2 years.[3] It is used as the basis of most recommendations for lipid lowering treatments in older populations.

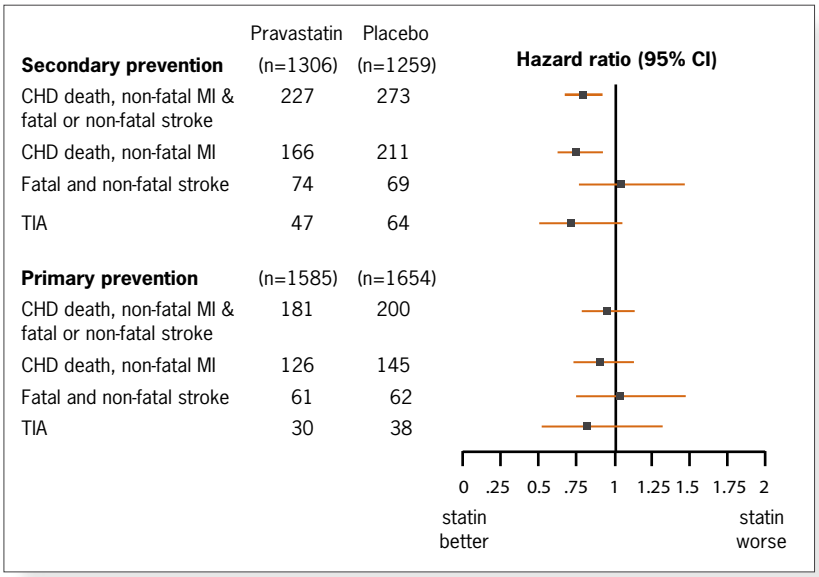
There is modest but clear prevention of cardiovascular mortality and morbidity using the primary composite endpoint of CHD death or non-fatal MI (absolute risk reduction 2.1%, NNT 48). Figure 2 shows the primary and secondary outcomes underpinning the claims for the benefits of pravastatin over placebo for preventing cardiovascular morbidity and mortality. For women, the results showed no benefit over placebo for any outcome. There is also no demonstrable benefit in primary prevention yet the conclusions are that the strategy for cardiovascular risk management in middle aged people should also be applied to elderly individuals.

If the detail of the paper is examined, the other morbidity and mortality data are illuminating. Despite a change in cardiovascular composite outcomes, there is no change in all cause mortality (Figure 3). Looking at mortality and morbidity from other causes, rates of cancer diagnosis and death were increased in the treatment group compared with placebo. This did not quite reach significance for death but did for new diagnosis of cancer (NNH 59).

The efficacy of a treatment might be justified in terms of postponement of morbidity even when there is no change in mortality, in the PROSPER paper, when the scrutiny of treatment outcomes is extended beyond a single disease model, this argument does not hold. The increase in new cancer diagnoses counters any arguments of compression of morbidity. The more

Figure 2: Major cardiovascular outcomes, according to primary or secondary prevention status of participants

The primary endpoint of the study is reproduced for comparative purposes.



likely hypothesis for this effect, which is not seen in trials of younger patients, is substitution of cause of death.

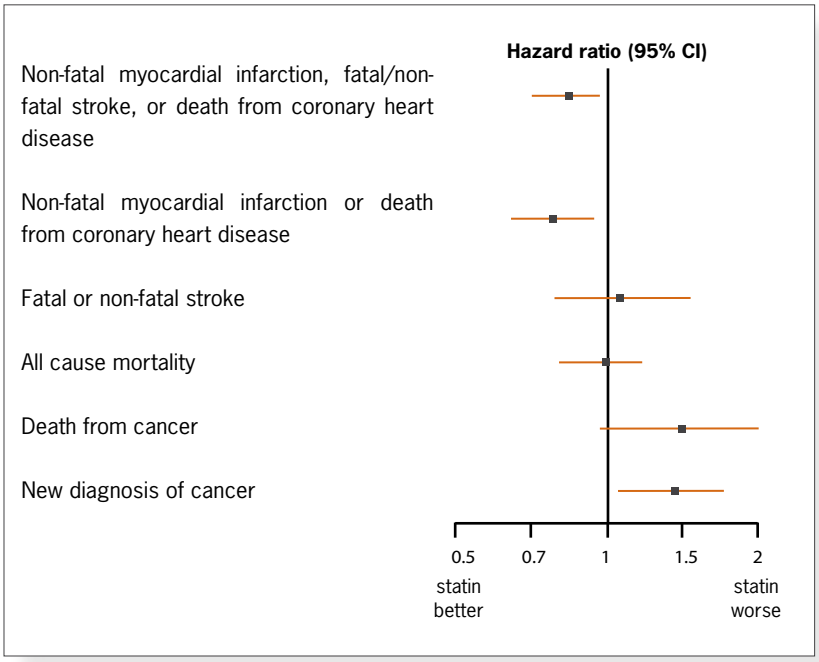
This is a phenomenon which is unprecedented. The prevention of untimely death is a valid pursuit of medicine up to a point. Thus when we vaccinate children in infancy we are selecting out a cause of death for them, but in this case justifiably, because deaths from infectious disease tend to occur prematurely. It is only when we start selecting out causes of death, rather than extending life, that this endeavour becomes questionable.

Many patients fear the manner of their dying more than death itself and many regard coronary heart disease as a 'good way to go' in old age.[5] In prescribing medicines to prevent particular diseases, we may select for another cause of death unknowingly and certainly without the patient's informed consent. This is fundamentally unethical, undermining the principle of autonomous choice and the concept of *'primum non nocere'*. An older patient who has elected to *'reduce the risk of heart attack'* may make a different decision when told '*you will not extend your years of life and you will increase your risk of being diagnosed with and dying of cancer'*

Clinical decisions about prescribing for disease prevention carries additional responsibilities.[6]
Preventive treatments do not relieve suffering directly, but are designed to reduce some future risk of suffering and are usually initiated by the suggestion of the physician rather then a patient request. Compared with initiation of treatment to relieve suffering, a degree of persuasion is involved in starting preventive treatments.[7] As clinicians we must therefore be reasonably certain they will fulfill their promise. There are harms other than the side effects of the actual treatments, not the least of which is the shadow cast over a currently healthy life by the threat of disease. One might argue that this particular harm is magnified as mortality looms closer. These considerations may explain the evident discomfort of general practitioners and their apparent reluctance to follow guidelines for cholesterol measurement and lipid lowering agents in those aged 75 years or over, compared with those under 75.[8] While every treatment decision is an individual one, guidance for populations is based on population data. The PROSPER study has been acknowledged as the best available evidence for the effects of statins for prevention of cardio- and cerebrovascular disease in old age. We cannot ignore it.

The best interests of the older person, who has paid a lifetime of taxes, might be to invest that money in health care that will genuinely relieve their suffering. Cataract and joint replacement surgery, and personal care of those with dementia, provide obvious examples. A different model is required for assessing medicines for prevention in old age. One that includes duration of life extension, duration of treatment and takes account of mortality and morbidity, due to all causes as well as the harms attributable to treatment. Some preventive

Figure 3: Outcome



interventions that have benefits across a range of conditions will likely be of similar benefit in older populations as in younger populations using this model (flu vaccination, exercise, smoking cessation). Some may be of more benefit in older populations, some like statins, will be of less benefit.

Patients and physicians are entitled to all the information they require to make decisions with such profound consequences. The current international single disease models of research, analysis and guidelines make this unlikely. Evidence for older populations cannot be squeezed uncomfortably into models designed to best assess the benefits and harms of treatment in younger populations. Our current models of quality usually relate to 'doing something'. A better model would acknowledge confidently when not to use medicines – when best practice is 'not doing'. If we continue using the current framework the benefits will accrue only for pharmaceutical companies with increasing profits from an ageing population consumed by epidemics rather than enjoying their long life.

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