Death as a measure of clinical outcome: appropriate only in the otherwise immortal?

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For once I had had a little time to read the journals, and had taken the opportunity to look at various meta-analyses and large studies into the outcome of various trials of primary and secondary prevention. I was feeling that at last we had some fundamental guidance as what to do and expressed my pleasure in this to Charles.

'Charles,' I said, 'After all my groans, I'm sure you'll be glad to hear me say that medicine is getting easier in one respect.'

'Go on,' he said.

'We are now getting good guidance about what long-term preventative treatment we should give to prevent illnesses or their recurrences, particularly in cardiovascular diseases. These studies involve several thousands of patients, so we do now know where we stand.'

'Are many centres involved?'

'Yes,' I said.

'That means that simple outcome measures have to be used. What are they?'

'Usually specific events and deaths related to the condition, and overall mortality. I must confess that I am always suspicious of the results when they concentrate on these events.'

'Self-fulfilling prophesies,' he suggested.

'Of course to a certain extent you're right. The same might apply to condition-related deaths, but overall mortality does allow for the hazards, as well as the benefits, of treatment. I look for net lives saved, and regard all disease-specific outcomes merely as explanations for the benefit gained.'

'Couldn't have put it better myself,' he said. He then reflected, 'But aren't we all going to die, Coe?'

'Yes, but what's that got to do with it?'

'Life can only be saved in the otherwise immortal.'

'You're not saying that reduction in overall mortality is to be treated with the same suspicion as the intended effects of treatment?'

'No, I wouldn't go as far as that, but let's think about its implications, for example, for a 50-year-old man when moderate hypertension is diagnosed. As is so often the case, it's easiest to follow the arguments if one puts the extremes first. Let's start with the young person wearing a safety helmet. For the period at risk, when they're actually riding their bike or their horse, they are effectively immortal (although even that isn't quite true – d'you remember the distinguished show jumper, Caroline Bradley, who fell off her horse, dying of a subarrachnoid haemorrhage?). Here the concept of saving life is entirely valid and the mechanism real to the individual. It's easier to see how a crash helmet prevents a skull fracture, than how a pill prevents a stroke.'

'Yes, but the chances of an otherwise fit man of 50 with hypertension dying of an unrelated condition are relatively small.'

'Let's go to the elderly, where the chances of dying of something else are high. The limit to life might be accepted but disability abhorred.'

'Yes, the fear of a serious stroke is often greater than of death.'

'So then the realistic aim is ability not immortality.'

'Yes, but what about the middle-aged man, found to have moderate hypertension.'

'What do the trials show?'

'A relative risk reduction consistent at about 30%, with an absolute benefit of the order of 1 to 5% over five years in otherwise low-risk groups.'

'That's what I guessed. A friend of mine is thinking of doing a study to see what people would regard as a reasonable prospect, so I asked around a few of my friends who came up with a 10-20% chance of benefit.'

'That's expecting a lot, isn't it?'

'Yes, but don't forget, as I said before, a pill doesn't as obviously protect against death as a crash helmet and they are also thinking about employability, life insurance, more visits to you people, and a very natural reluctance to go on pills for the first time in their life.'

'So they are prepared to take the risk?'

'Yes.'

'Although one recent paper might be read as suggesting otherwise[1], intervention in low-risk groups might save hundreds of premature deaths, and money for the health service.'

'Yes, although in general, successful treatment has at best a neutral effect on health expenditure, prevention of cardiovascular disease in the mid-fifties would allow money to be spent elsewhere and benefit the Exchequer's income.'

'How can we overcome the problem?'

'One could try a vicarious argument'

'What do you mean?' I asked.

'You might try asking, "Would you be prepared to take a tablet as your contribution to preventing several hundred early deaths a year, and save the health service and the country a lot of money?" This would be most likely to work in the better educated.'

'The lowest risk group! Any other ideas?'

'Yes, so let's think about cigarette smoking. What would you say to a fit heavy smoker of 50 who he said he would stop smoking on retirement on his 65th birthday, but was prepared to accept the risk of lung cancer and heart attacks until then?'

'I would tell him he might be doing irretrievable damage to his bronchial tree, which would not be reversed by stopping at 65.'

'Could you apply the same approach to blood pressure? Has hypertension the same permanent effect on the coronary arteries as smoking has on the bronchial tree?'

'I understand that treatment of hypertension started in the elderly does reduce strokes but the benefits to the coronary tree and in terms of heart failure are much less clear cut.'

'So perhaps, your trialists should be encouraged to use permanent damage to the vascular tree as the outcome measure,' he suggested. 'Infrequent random events really are more likely to happen to somebody else, and using a more predictable outcome puts you in a much stronger position to give advice. This applies particularly where you are entirely responsible for discovery of "abnormality"'. He continued, 'Furthermore, this approach might enable you to say that blood pressure should be measured early in adult life in everyone. Alternatively, you might recognise a group of people in whom opportunistic measures of blood pressure should never be made, because at most you would give them general advice on diet and exercise, which should be given to everyone ...'

'But if you don't take the blood pressure you might miss unsuspected severe hypertension.'

'How often in a truly asymptomatic healthy non-attender? Once in a lifetime?' he suggested.

I could not deny it.

'Hard cases make bad law.' He continued, 'It is better than one man should die than ...'

'Than many suffer from iatrogenic morbidity.'

'Well said.'

Coemgenus

Reference

1 McConnachie A, Hunt K, Emslie C *et al*. 'Unwarranted survivals' and 'anomalous deaths' from coronary heart disease: prospective survey of general population. *BMJ* 2001;**323**:1487–91.