In response: Surrogate measures should be abandonded

Kevin S Channer

Kevin S Channer
MD FRCP, Consultant Cardiologist, Royal Hallamshire Hospital; Honorary Professor of Cardiovascular Medicine, Sheffield Hallam University

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Epidemiological studies have shown that cardiovascular diseases are associated with characteristics and conditions that increase the risk of adverse events. Some of these risk factors can be modified by changes in lifestyle or through drug therapy. Doctors and patients have been encouraged to change the risk by aiming at a target. Then, by regular monitoring, it is possible to see how close or how far away from the ideal position the treatment or strategy has reached. Regular monitoring helps bind doctor and patient together in a management contract – both are working in unison for a common goal. But it is disheartening for the patients and worrying for the doctor if the target is never reached. The concept of target-driven strategies has now been questioned – the latest new idea is that fixed doses of drugs should be given irrespective of the monitored endpoint. Indeed, some commentators advocate a polypill containing fixed doses of drugs which have been shown in large randomised trials to be effective in reducing cardiovascular risk in large populations of patients.[1] This is a community medicine approach – a population approach akin to cleaning up the water supply.

In his article, Peter Winocour challenges the whole idea of fixed treatment schedules. He advocates individualised treatment aimed at surrogate endpoints ('targets'). He believes that dose titration is more valid, but he does not convince me.

Firstly, he claims that the large numbers of studies were not representative of all patient subgroups. I disagree. I think that the numbers of patients involved in these clinical trials are now so large and the results so consistent with each other that the results are genuinely generalisable.[2] Secondly, the effect on risk of increasing the level of total cholesterol, systolic and diastolic blood pressure is linear. This has been shown in major meta-analyses.[3] These are continua within the population and there is now a clear recognition that there is not a 'normal' level of blood pressure or cholesterol. Indeed, the normal range (defined as 2 standard deviations from the mean) changes with age for both these parameters.[4] Further analyses of treatment effects have shown that the lower the blood pressure or cholesterol level, the lower the risk of an event (death, stroke or myocardial infarction). So, whatever the initial starting point, treatment has proven benefits.[5]

In secondary prevention after a myocardial infarction, the issue is straightforward. If at the age of 50 years, a man with a blood cholesterol of 5.0 mmol/l and a blood pressure of 145/80, has an infarct, then it could be argued that these two risk factors were too high for him. Clinical trials demonstrate unequivocally that if he is given a statin drug and anti-hypertensive therapy, either with a beta-adrenoceptor blocker or an angiotensin-converting enzyme (ACE) inhibitor, then he will subsequently have a lower cardiovascular risk than if he does not take active medication. Most of the clinical trial evidence shows relative risk reductions of between 20% and 30% for each intervention but absolute reductions in endpoints are much less. Of course, the absolute benefit will depend on his initial absolute risk, although the relative risk reduction will be the same. Thus, if his cardiovascular event rate is 3% per annum then with these treatments it will be reduced to less than 2% per annum. If his cardiovascular risk is 10% per annum then it will be reduced to less than 7% per annum. For the individual the absolute risk matters, but the clinician rarely knows exactly what the absolute risk for the individual is. The point is that if he were managed by target-directed treatment (5.0 mmol/l for cholesterol; <160/90 mmHg for blood pressure) then he would not have been given any secondary prevention treatment except aspirin, for which no target has ever been identified.

This means in practice that only some patients will benefit from the treatment by not experiencing an event. Neither doctor nor patient knows if they are the one – just like the lottery – for the patient 'it could be you!' Although the absolute risk of death may be small over the duration of the trial, nevertheless most patients with ischaemic heart disease will eventually die of it. It is possible to estimate the average extension of survival afforded by taking individual drugs from analysis of the Kaplan-Meier survival curves from the published literature.[6] Thus, giving an aspirin a day to patients with ischaemic heart disease extends their life by an average of 24 months. This average life extension is more meaningful for the patient compared with an absolute risk reduction of, say, 1% per annum.

Aspirin is a good example here because the absence of a measurable surrogate endpoint has not stopped doctors prescribing it.

Which is the better approach? There can be no doubt that the more drugs that are combined then the less benefit will accrue from later additions. The issue is whether giving the drug at a fixed dose and without measuring its effect (as with aspirin) is correct. I see no compelling argument in this paper to suggest that it is not. Especially since audit after audit shows that doctors do not routinely use appropriate drugs in secondary prevention.[7] Generally we are very poor at implementing evidence-based medicine. Strategies like the National Service Framework for Coronary Heart Disease have for the first time empowered other health professionals (pharmacists, nurses) to challenge the prescribing of secondary prevention drugs by doctors and by so doing have improved their routine prescription. The Myocardial Infarction National Audit Project (MINAP) clearly shows increases in the prescription of drugs for secondary prevention following myocardial infarction.[8]

Evidence shows that blood pressure controlled to target is difficult and rarely achieved in practice.[9] Nevertheless, with regard to risk reduction, fixed doses of aspirin, a statin, an ACE inhibitor and/or a beta blocker are more likely in population terms to be effective than dose titration to arbitrary targets. There is evidence that the more individual drugs a patient is given the worse the compliance with treatment,[10] so perhaps the multi-pill would help here.

References

1 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;**326**:1419–23.

2 Briel M, Studer M, Glass TR, Bucher HC. Effects of statins on stroke prevention in patients with and without coronary heart disease: a meta-analysis of randomised controlled trials. *Am J Med* 2004;**117**: 596–606.

3 MacMahon S, Peto R, Cutler J, Collins R *et al.* Blood pressure and coronary heart disease: part 1, prolonged differences in blood pressure: prospective observational studies corrected for regression dilution bias. *Lancet* 1990;**335**:765–74.

4 Anum EA Adera T. Hypercholesterolaemia and coronary heart disease in the elderly: a meta-analysis. *Ann Epidemiol* 2004;**14**:705–21.

5 Wilt TJ, Bloomfield HE, MacDonald R, Nelson D *et al.* Effectiveness of statin therapy in adults with coronary heart disease. *Arch Intern Med* 2004;**164**:1427–36.

6 Malkin C, Channer KS. Life saving or death prolonging? Interpreting clinical trial data and survival curves for patients with congestive heart failure. *Eur J Heart Fail* 2005;**7**:143–8.

7 Irving RJ, Oram SH, Boyd J, Rutledge P *et al.* Ten year audit of secondary prevention in coronary bypass patients. *BMJ* 2000;**321**:22–3.

8 Birkhead JS, Walker L, Pearson M, Weston C *et al.* National Audit of Myocardial Infarction Project Steering Group. Improving care for patients with acute coronary syndromes: initial results from the National Audit of Myocardial Infarction Project (MINAP). *Heart* 2004;**90**:1004–9.

9 Chobanian AV. Control of hypertension – an important national priority. *N Engl J Med* 2001;**345**:534–65.

10 Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001; **23**:1296–309.