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What do we gain from the sixth coronary heart disease drug?

Not much: guidelines must consider cost effectiveness

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From air travel to patient safety to coronary heart disease prevention, people strive to reduce risk to zero. We know that zero risk is unattainable, yet we pursue perfection. It may be useful to hold perfection as an ideal,[1] but there can be great harm in trying to achieve it because near perfection often imposes near infinite costs. The closer we get to perfect risk reduction, the more likely it becomes that we could have got a better bang for our preventive buck somewhere else. This applies across all activities—and needs to be heeded in health care as anywhere else.

For example, air travel is already much safer than most other forms of travel, so £10m ($17m; €14m) spent on road safety would save far more life years than £10m put into tightening airport security. Yet since September 11 much new spending has gone into airport security. In health too we often see a rush to perfection without regard for costs. Here are three examples. Firstly, universal precautions to prevent worksite transmission of HIV to healthcare workers have been widely implemented, yet cost from £76 000 to £1.2m per quality adjusted life year (QALY).[2] Secondly, because we worry about the harm caused by health care, huge investments are being proposed for error reporting systems, electronic patient records, physician order entry, barcode point of care, and many other safety related changes—even though their cost effectiveness is unknown.[3 4] Thirdly, the United Kingdom adopted guidelines[5] on the use of statins for primary and secondary prevention of coronary heart disease that would have required either a 20% increase in drug costs or termination of more beneficial interventions.[6]

In health care, cost remains something of a dirty word, and including evidence about costs in clinical guidelines remains controversial. But costs are not just cash. Advocates of evidence based medicine advise doctors to think of costs as "other treatments you can't afford to do if you use your scarce resources to do this one," noting that "when internists borrow a bed from their surgical colleagues in order to admit a medical emergency tonight, the opportunity cost includes tomorrow's cancelled surgery."[7]

No healthcare system has the human and financial resources to deliver every test and treatment that offers even minimal potential benefit to every patient. Every system limits the tests and treatments available in some way. Clinical practice guidelines can summarise the research evidence and prescribe reasonable limits to care for typical patients. Guidelines do not replace clinical judgment—and proponents of evidence based medicine do not claim that they should.[7] Appropriate use of guidelines can replace implicit, undocumented, and highly variable limits to care with explicit, clear, consistent ones—this is surely both more just and more efficient. The only alternative to setting priorities—an infinite budget for health care—is neither realistic nor desirable.

The paper in this issue by Marshall (p 1264) tackles the question of whether national treatment guidelines should consider cost effectiveness through an example, modelling the incremental cost effectiveness of commonly combined preventive treatments for coronary heart disease.[8] In accordance with standard economic evaluation methods, cost effectiveness is first modelled for each treatment individually, to determine the efficient order in which to apply the treatments. Incremental cost effectiveness is then determined by applying the treatments in order of their (individual) cost effectiveness and calculating the extra cost and extra benefit of each additional treatment. Like the celebrated paper about the sixth stool guaiac,[9] the calculation reveals surprisingly high costs per coronary event prevented for the sixth drug (clopidogrel when added to aspirin, three antihypertensive agents, and simvastatin).

Marshall's work shows that £100 000 can either prevent one coronary event or many more. It will prevent only 1.2 events if used (in accordance with current UK guidelines[10]) to prescribe simvastatin (after aspirin and antihypertensive agents) in patients at a five year risk of a coronary event of 15%. If used for aspirin the same £100 000 could prevent either 12.7 events (in patients at 5% risk) or 28.6 events (in patients at 10% risk). Marshall has not calculated QALYs, but if he did the trade off could be more than 50:1, since lower risk patients tend to be younger and so gain more high quality life years for each event avoided than patients at 30% risk.

Marshall did not model stroke risk, but including it would only steepen the trade off between treatments, since aspirin is much more cost effective in stroke prevention than simvastatin or clopidogrel (based on drug costs and published estimates of effectiveness).[11 12] Marshall modelled bleeding complications from aspirin by reducing the estimated coronary events

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avoided with aspirin, which effectively equates these complications with coronary events. While imperfect, this adjustment is a reasonable approximation and shows successfully that aspirin is the most cost effective treatment despite complications. Indeed, by adjusting for complications only for aspirin, Marshall has been conservative: clopidogrel increases the incidence of rash and diarrhoea,[13] and statins in primary prevention have not consistently reduced the incidence of myocardial infarction or stroke and have not reduced all cause mortality, possibly because of undetected serious adverse events.[14]

Should these results persuade clinicians? Should national guidelines be amended to offer preventive measures in order of incremental cost effectiveness? Absolutely, because any other action guarantees less gain in health for whatever is spent. Across the entire NHS, following the current guidelines would waste billions of pounds and prevent fewer coronary events than if cost effectiveness were used to guide treatment. Evidence based clinical guidance must include incremental cost effectiveness, to prevent the pointless and profligate pursuit of perfection.

Rebecca N Warburton *assistant professor*
(rnwarbur@uvic.ca)

School of Public Administration, University of Victoria, Victoria, BC, V8W 2Y2 Canada

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Risk factor scoring for coronary heart disease

Prediction algorithms need regular updating

Global risk assessment has become an accepted component of clinical guidelines and recommendations in cardiovascular medicine. The aim is to provide a valid estimate of the probability of a defined cardiovascular event over a period of five or ten years in individuals free of clinical manifestations of cardiovascular disease at the time of examination. The information available for global risk assessments commonly consists of individual risk factor measurements and a basic assessment of concurrent clinical conditions. The aim of the resulting absolute level of predicted risk is to determine the intensity of clinical intervention. What do we know about the validity of the population data from which the individual risk factor measurements are derived?

The Framingham Heart Study and the Framingham Offspring Study were the first epidemiological studies that prospectively collected population based data on the association between risk factors and the occurrence of fatal and non-fatal coronary and other cardiovascular events in a systematic and sustained fashion.[1] Hence, when the New Zealand Guidelines Group first used global cardiovascular risk assessment as a tool for identifying patients in need of antihypertensive drug treatment,[2] risk equations based on the experience of the Framingham sample were the only accurate data source readily available. Others followed the approach of using absolute, rather than relative, risk estimates as clinical treatment decision aids, and within a couple of years the Framingham risk equations had pervaded most clinical guidelines.

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Early reports provided reassurance by confirming that observed and predicted risk were of similar magnitude, for example in UK patients.[3] More recent comparisons revealed reasonable agreement between Framingham predicted risk and observed risk in six US cohorts of white and black people, but not in those of Japanese, Hispanic, or Native American ethnic origin.[4] The Framingham authors themselves had cautioned about generalising from their data.[1] And, indeed, an increasing number of reports suggest that this procedure is misleading under various circumstances. When applied to different populations, for example from Southern Europe,[5 6] or in studies with a more recent onset and follow up period,[7 8] the observed absolute risk is often substantially lower than predicted by the Framingham algorithms.

In this issue (p 1267), Brindle et al present their findings for men who participated in the 10 year follow up of the British Regional Heart Study.[9] They report that the Framingham prediction equations overestimate the risk of coronary mortality by 47% and of fatal plus non-fatal coronary events by 57%. Likewise, a recent report from the PRIME study group

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