The patient had a sibling who was mismatched for one HLA-haplotype and was able to provide bone-marrow stem cells instead of the matched unrelated donor.

Natural rubber latex, the sap of the Brazilian rubber tree, is used to produce rubber, a material now used widely in the household and in medical practice. Immediate hypersensitivity reactions to latex were first reported in 1979,[1] but the incidence of allergy to latex has probably increased in the last decade as a result of widespread use of rubber gloves by health-care workers to prevent microbial spread.[2,3] Epidemiological studies show that 2–15% of health-care workers are allergic to latex.[4]

Anaphylactic reactions in individuals who have an allergy to latex are common during the perioperative period, reflecting the breach of tissue barriers and parenteral administration of drugs and fluids through latex-containing syringes and tubing. Consequently, there has been an attempt to increase the awareness of anaesthetists in the UK, and specific guidelines have been prepared to ensure that the risk of anaphylaxis is reduced as much as possible.[5] Nevertheless adherence to these guidelines cannot guarantee the safety of any procedure and the anaesthetist involved in this case believed that the risk of general anaesthesia for a healthy volunteer donor could not be justified, a view with which we concur.

This case highlights the need to enquire specifically about latex allergy during the medical assessment of prospective haemopoietic stem-cell donors. Specific testing may be indicated, particularly in health-care workers. A history of allergy to latex should probably be regarded as an absolute contraindication to stem-cell donation by a volunteer donor.

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1 Nutter AF. Contract urticaria to rubber. *Br J Dermatol* 1979; 191–98.
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Are drugs interchangeable?

Sir—Curt Furberg and colleagues (Oct 2, p 1202)[1] highlight the dangers of the use of evidence about the efficacy, safety, and cost-effectiveness of one drug to justify the prescription of a related but less well-studied drug. However, they miss the point when they ascribe responsibility for this to the marketing strategies of individual drug companies, the fact that prescribing habits are determined by uncritical market forces, and deficiencies of the drug-licensing process.

The regulatory agencies are charged solely with ensuring that licensed products are safe and that they justify any claims that their manufacturer may make about them. That drugs are often licensed on the basis of evidence of benefit on surrogate markers is questionable,[2] but the fact that a drug is licensed surely does not mean that it should necessarily be prescribed. The only inference should be that it, like similarly licensed drugs, is worthy of consideration. The choice of drug remains the responsibility of the attending physician, because he or she knows the peculiar characteristics of the patient, and of the health-care system, because it is responsible for overseeing clinical governance.

Furberg and colleagues' assertion that the appropriateness of a drug can only be decided after thorough evaluation in large randomised trials is certainly true. As they correctly state, however, such evidence is commonly absent when a drug is first launched. Physicians nonetheless prescribe such drugs, so one can hardly blame pharmaceutical companies for marketing them. The problem is not confined to newly licensed drugs.[3]

Evidence-based prescription,[3,4] like evidence-based medicine,[5] is only possible if inidividual physicians stay up to date with the latest trials[2] and the results of these are appropriately distilled and disseminated as local guidelines by drugs and therapeutics committees or national institutions such as the National Institute for Clinical Excellence.

Testing drugs against the best available therapy is expensive. There is always the possibility that older treatments may prove more effective or cost-effective. The producers of "me-too" drugs obviate the need for testing by stressing their drug's similarity to the reference drug and instead try to convince the prescriber to prescribe on the basis of either lower cost or unproven ancillary properties. If the drug companies could be convinced that any new drug will not achieve widespread use unless proven to be superior to existing therapies, more effort would be expended in providing evidence to justify the drug's use. Although in the short term a better tested and hence quite possible more expensive therapy may be used, in the longer term the benefits of such a strategy would be more effective and result in less wasteful drug prescribing with manifest benefits for doctors, the National Health Service, and most importantly the patients.[4,5]

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1 Furberg CD, Herrington DM, Psaty BM. Are drugs within a class interchangeable? *Lancet* 1999; **354:** 1202–04.
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Sir—Curt Furberg and colleagues[1] raise important questions about the interchangeability of drugs within therapeutic classes. However, that they confine their evidence solely to observational before-and-after data from New Zealand,[2] with respect to the switch from subsidised simvastatin to fluvastatin, does their paper an injustice.

Thomas and Mann's study[2] has been criticised on a number of grounds. Mortality data were not reported because patients treated on simvastatin before the switch would have to survive to remain in the cohort, and since no such restriction occurred after switching to fluvastatin, deaths after the switch should have been excluded. Because this study was an uncontrolled before-and-after trial meant that potential bias was introduced by the unmasking of clinicians, who admitted and then assessed patients, and of the evaluators who extracted and assessed the data. Additionally, the data before the switch were obtained from the hospital computer system (of incomplete reliability), whereas the data after the switch were collected systematically and with care.

We are disappointed that Furberg and colleagues disregard these features and the substantial criticism of

Thomas and Mann's paper.[3–5] There is no evidence that Furberg et al have undertaken a systematic compilation and critical appraisal of the literature relevant to this topic to form their view.

Thomas and Mann tabulated but failed to comment on a key possible reason behind the reported increase in cholesterol concentrations: the possible subtherapeutic dosing of patients with the substituted drug (fluvastatin). This fact suggests not so much difficulties with fluvastatin but with how it was prescribed (ie, how prescribers substituted one drug for another). Thomas and Mann have subsequently stated "many of the factors that led to under-dosing these patients have been corrected", and that "positive changes have subsequently taken place to improve access of patients to statins, ensure the appropriate education of prescribers, and funding for patient monitoring on switching drugs" (personal communication).

We therefore believe that Thomas and Mann's study does not necessarily show "how arguments based on the class effect concept may be misleading" or that "to assume that all drugs of a class are interchangeable may therefore be dangerous". Indeed, whereas in some cases changing medicines might be dangerous, this is certainly not proven. There are potentially large benefits from proven freeing up of health resources, which can be used to improve health status in other spheres.

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1 Furberg CD, Herrington DM, Psaty BM. Are drugs within a class interchangeable? *Lancet* 1999; **354:** 1202–04.
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5 Wierzbicki AS, Crook MA, Reynolds TM, Jackson G. Thrombotic vascular events after change of statin. *Lancet* 1999; **353:** 845.

Sir—Curt Furberg and colleagues[1] raise many issues about evidence-based medicine and the extent to which it is applied. They make valuable points about how safety testing and drug equivalence in clinical trials should be shown.

In cardiology, particular attention is given to three classes of drugs. With β-blockade, the disadvantages of certain early compounds are described, but Furberg and colleagues do not mention that the early trials that showed benefits with β-blockade were done with the unselective β-blocker timolol.[2] Nowadays, atenolol, a 1β selective antagonist, is commonly used for these effects, which are assumed to be class based.

In the case of calcium channel blockers (CCBs) concern has been expressed about short-acting agents, although meta-analyses have not shown any difference.[3] Mibefradil was a novel agent that blocked T-type voltage-gated calcium channels compared with L-channels blocked by the other dihydropyridines (most CCBs) and benzylalkylamines (verapamil). Mibefradil was not pharmacologically equivalent to other CCBs and its adverse effects, including arrhythmogenesis, were shown in clinical trials. Of more concern was that the safety testing with this drug was inadequate and the licensing authorities did not identify the interactions with other cytochrome P450 3A4 metabolised agents commonly used in patients with coronary disease, including some statins, before general release.

Furberg and colleagues' comments about comparative trials of statins are controversial and some of their statements are inaccurate and unwarranted. Firm evidence exists for the three fungally derived statins. Fluvastatin has been shown to reduce coronary events in a placebo-controlled study[4] and to be beneficial in regression studies. The report of atherothrombotic events cited by Furberg et al has been heavily criticised on the grounds of small numbers and imperfect methodology.[4] Data on safety and lipid reduction but not as yet on event reduction, exist for atorvastatin.[5] Little data are available for cerivastatin.

In evidence-based medicine, a continuum exists from those who are prepared to assert class effect after a single mortality trial to others who believe that drugs proven in mortality-based studies have to be used at trial doses in similar populations. Where one stands on this continuum is a matter of individual clinical judgment. However, common sense suggests that if three or more compounds are beneficial in mortality studies, have very similar pharmacological characteristics, and have identical multiple surrogate endpoint data, a class effect may well exist for other drugs that show similar properties across the range of surrogate endpoints. A balance has to be struck between the requirement for absolute proof for each compound in mortality studies (at substantial ethical cost) and the inhibition of innovation by a different form of monopolistic marketing lock-in. Multiple compounds stimulate efficacy and price competition, can reduce health-care costs and increase access for patients to possibly superior compounds with slower development timescales before formal proof of their efficacy becomes available.

Evidence-based medicine is a difficult concept to practice and each physician needs to think carefully about how they stand on the issue with each drug.

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1 Furberg CD, Herrington DM, Psaty BM. Are drugs within a class interchangeable? *Lancet* 1999; **354:** 1202–04.
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Authors' reply

Sir—We agree with Garfield Drummond that cost should not be a surrogate marker for best clinical practice. However, we feel that widespread use of unproven "me-too" drugs is a consequence of inadequate regulatory policies coupled with aggressive marketing strategies—not merely a reflection of attending physician's tailoring of therapy. A physician's conviction about the merits of a "me-too" drug for a specific patient, which may be in part the result of marketing influences, should not replace objective data on clinical benefits and risk of various treatment options.

Wayne McNee and colleagues and we have different views with respect to the concept of class effect. Members of a drug class are not interchangeable without convincing scientific evidence, and, thus, we cannot understand their decision to replace simvastatin, a statin with proven mortality and morbidity benefit, with fluvastatin, an unproven