or febuxostat).[10,11] Enhanced understanding of pathophysiological mechanisms might lead to improved drugs, with reduced potential for side-effects compared with today's uricosurics.

Even more exciting is the idea that responding to the defects of these transporter proteins might have further beneficial effects, because they could also transport other molecules besides urate. Some studies have suggested that the association between metabolic syndrome and gout is not only caused by diet and personal behaviour.[5,7] If this association holds true, we might have a better understanding of some of the most relevant medical problems of our time.

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We declare that we have no conflict of interest.

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β blockers in non-cardiac surgery: haemodynamic data needed

Published Online November 11, 2008 DOI:10.1016/S0140-6736(08)61623-2
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Patients undergoing non-cardiac surgery are at high risk of life-threatening cardiac complications. Generally, the risk of perioperative complications depends on the condition of the patient before surgery, any comorbidities, and the invasiveness and duration of the surgical procedure. Specifically, cardiac complications can be expected in patients with documented or hidden coronary artery disease, heart failure, or aortic valve disease, and who undergo procedures that are associated with prolonged haemodynamic or cardiac stress.

The clinical importance of perioperative cardiac complications is well recognised, and several treatment strategies have been developed with the aim to safely reduce their occurrence. Most strategies use drugs, including statins and β blockers, that affect plaque stability or myocardial oxygen balance, or both.[1–4] β blockers improve myocardial oxygenation by decreasing heart rate and myocardial contractility, and promote coronary plaque stability by reducing mechanical and shear stresses.[5,6] β blockers are also thought to have anti-inflammatory effects.[7]

In today's *Lancet*, Sripal Bangalore and colleagues present a meta-analysis of 33 randomised trials of perioperative β-blocker treatment versus placebo or control treatment in patients undergoing non-cardiac surgery for several indications.[8] They conclude that β blockers result in 16 fewer non-fatal myocardial infarctions per 1000 patients treated, but at the expense of three non-fatal disabling strokes and (possibly) three fatal cardiac or non-cardiac complications.

Bangalore and colleagues acknowledge that the recent POISE trial had the greatest weight for all of the above analyses.[3] Indeed, about 80% of the deaths, myocardial infarctions, and strokes in their meta-analysis are derived from POISE, and this proportion was as high as 84% in the trials they labelled low-bias risk. Hence, a more detailed analysis of the results of POISE compared with non-POISE trials is warranted. We restricted ourselves to an analysis of the presented mortality data (table) because, whatever the judgment about the quality of the included trials, these numbers are most probably unbiased.

Our first interesting observation is that, whereas in POISE β blockers were associated with a 34% increased incidence of mortality from all causes, in the non-POISE trials the point estimate of treatment effect was con-

	All-cause mortality					Cardiovascular mortality				
	N	Deaths	OR (95% CI)	Homogeneity of ORs	Benefit per 1000 (SD)	N	Deaths	OR (95% CI)	Homogeneity of ORs	Benefit per 1000 (SD)
Total										
POISE										
β blocker	4174	129 (3·1%)	→ 1·34 (1·03–1·75)	→ 0·027	–7·7 (3·6)	4174	75 (1·8%)	→ 1·30 (0·92–1·84)	→ 0·086	–4·1 (2·7)
Control	4177	97 (2·3%)				4177	58 (1·4%)			
Non-POISE										
β blocker	1896	36 (1·9%)	→ 0·74 (0·47–1·17)		6·4 (5·0)	1866	18 (1·0%)	→ 0·70 (0·37–1·31)		4·1 (3·7)
Control	1615	41 (2·5%)				1598	22 (1·4%)			
Non-POISE total										
Non-POISE, strokes reported										
β blocker	1536	31 (2·0%)	→ 1·01 (0·60–1·69)	→ 0·017	–0·1 (5·2)	1536	16 (1·0%)	→ 1·08 (0·52–2·25)	→ 0·021	–0·8 (3·7)
Control	1346	27 (2·0%)				1346	13 (1·0%)			
Non-POISE, strokes not reported										
β blocker	360	5 (1·4%)	→ 0·26 (0·09–0·72)		38·2 (14·9)	330	2 (0·6%)	→ 0·16 (0·04–0·77)		29·7 (12·4)
Control	269	14 (5·2%)				252	9 (3·6%)			

N=number of patients. OR=odds ratio. Homogeneity of ORs=Breslow-Day test.

Table: **Analysis of mortality data from reference 8**

sistent with a reduced incidence by β blockers (although the confidence interval of treatment effect crossed the point of no difference).

The differential treatment effect seems to be caused by the high mortality in POISE patients who are given β blockers (3·1% *vs* 1·9% in non-POISE trials), and not by differences in patients allocated to control therapy (2·3% *vs* 2·5%). We found similar patterns for cardiovascular mortality.

In view of these findings, detailed analysis of the cause and timing of the observed deaths is urgent, especially in patients who received β blockers. The tip of the veil was lifted by the POISE investigators, because they learnt that perioperative hypotension, bradycardia, and stroke were the main determinants of all-cause death in their trial, whereas a history of cerebrovascular disease was associated with increased risk of stroke. It cannot be excluded that the high (starting) dose of metoprolol succinate that was used in POISE might have caused an unfavourable haemodynamic condition that ultimately resulted in fatal stroke, more often so than for other β-blocker regimens, particularly in patients with a diseased cerebrovascular tree. Clearly, the β-blocker regimen in POISE was associated with an increased incidence of fatal and non-fatal stroke.

In their analysis, Bangalore and colleagues found no evidence of a differential effect of β blockers on non-fatal stroke between POISE and non-POISE trials. Hence they conclude that there could be increased risk of stroke with use of β blockers. However, absence of evidence for heterogeneity does not automatically imply sufficient evidence for homogeneity. Furthermore, the trials that were included in the analysis of stroke are not a random selection of all studies in the meta-analysis. At least, a remarkable differential effect of β blockers on all-cause and cardiovascular mortality was observed between trials with (neutral effect on mortality) and without (significant mortality reduction) available stroke data. In view of this apparent heterogeneity, we believe that an estimation of the net clinical outcome of β-blocker treatment should not be based on the sum of its effects on the components of death, non-fatal myocardial infarction, and non-fatal stroke that were presented in this meta-analysis.

There is a solid pathophysiological basis for the reduction of perioperative cardiac complications by β blockers. By contrast, a general mechanism that might explain excess cerebral complications has not been revealed. Now that the methodologically sound meta-analysis by Bangalore and colleagues has emphasised that risk of stroke might be a serious issue we call on all colleagues who are working on trials to release data about clinical conditions and perioperative haemodynamic changes that might have resulted in these complications. These data will be key for updates of treatment guidelines.

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HIV prevention research: the ecstasy and the agony

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Over the past 2 years, *The Lancet* has proactively championed HIV prevention science. It published a state-of-the-art series on HIV prevention, timed for the 2008 Mexico City International AIDS Conference,[1] and six other primary publications from key HIV-prevention trials. The two trials that showed male circumcision protected against HIV acquisition were uplifting.[2,3] Disappointingly, four other trials failed to show that the diaphragm,[4] prophylaxis for herpes simplex virus type 2,[5] an HIV vaccine,[6] and now Carraguard as a topical microbicide[7] are effective in preventing HIV. Such is the ecstasy and the agony of HIV-prevention research.

The results of the Carraguard trial, reported in *The Lancet* today by Stephanie Skoler-Karpoff and colleagues,[7] continue the discouraging wake of other coitally related topical products.[8–13] The hope was that ingredients in gels, films, or suppositories might prevent HIV transmission when inserted into the vagina before sexual intercourse, to provide a female-controlled alternative to male condoms.

Karen Tweedy-Holmes/Population Council

Carraguard applicator

The first-generation trials of topical antimicrobial agents during the 1990s focused on nonoxynol-9, because it appeared effective against HIV in vitro, had been used safely as a spermicide for half a century, and was available over the counter. However, randomised trials eventually showed that nonoxynol-9 was ineffective in preventing HIV and other sexually transmitted infections.[8,9] These trials were followed by studies to assess second-generation non-HIV specific agents, such as vaginal defence boosters, surfactants, and entry-fusion inhibitors. SAVVY vaginal gel (C31G),[11] and cellulose sulfate[12,13] have been assessed in phase III trials, with disappointing results, while trials of BufferGel and PRO 2000 are underway.

Despite certain weaknesses from the intent-to-treat perspective (eg, discontinuing women from the trial when they became pregnant), the Carraguard trial had strengths that gave hope for success. It was done by the Population Council, an organisation with a strong track record in new contraceptive products. The trial had ample funding from two large donors, and featured a creative mix of behavioural and biological interventions. Most importantly, it had an adequate number of HIV endpoints to determine efficacy; the trial was designed to measure a 33% level of protection, a more difficult