statins and the cytochrome P450 (CYP450) system. The recent withdrawal of the calcium channel antagonist bepridil has highlighted the importance of the CYP 450 system in the genesis of unfavourable drug interactions[3].

However, although not discussed in the review, drug–drug interactions are not necessarily always deleterious. Drugs with the potential to produce interactions mediated by the cytochrome P-450 system include simvastatin. Since drugs such as diltiazem and nifedipine are inhibitors of cytochrome CYP3A4[3] they will potentially increase circulating concentrations and hence the cholesterol lowering effect of statins metabolized via this route.

Observational epidemiological studies suggest that risk of CHD is associated with serum cholesterol levels down to at least 3 mmol·L⁻¹ with no evidence of a threshold below which a lower cholesterol is not associated with a reduced risk[4]. As yet, there is no direct randomized evidence of the effects on CHD of larger cholesterol reduction beyond that produced by standard dose statins. However, a further reduction in cholesterol of 0·5 mmol·L⁻¹ beyond that currently achieved might be expected to further reduce CHD by approximately 20%.

SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) will address this issue in individuals at high risk who will be treated with high dose (80 mg) simvastatin. Since simvastatin is metabolized via CYP3A4, inhibition of this enzyme by drugs such as diltiazem or nifedipine might be expected to increase plasma levels approximately fourfold. Under these circumstances a 20 mg dose of simvastatin would have the equivalent effect on cholesterol lowering as a dose of 80 mg. Indeed, a recent study has demonstrated potentiatation of the cholesterol lowering effect of simvastatin in a group of diltiazem-treated patients[3].

Moreover, in the short-term there was no difference in the side effects and withdrawal from simvastatin therapy in the group taking diltiazem. The benefits of potentializing simvastatin levels by co-administration of drugs that inhibit CYP3A4 would have to be weighed against the potential for increased side effects. However, in a recent study of high dose simvastatin only a single case of myopathy was observed in a subject taking 160 mg of simvastatin daily[6]. Co-administration of cardioactive drugs which may increase levels of statins via effects on CYP3A4 may allow for greater reductions in cholesterol without additional cost. Grapefruit juice also inhibits cytochrome CYP3A4[7], so perhaps, for patients on statins metabolized by CYP3A4, a glass of grapefruit juice at breakfast will lead to further reductions in cholesterol and CHD. Such potential interactions require further study, but are not necessarily deleterious.

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Electron beam computed tomography: on its way into mainstream cardiology?

The hotline editorial by Sechtem on electron beam CT (EBCT)[1] was timely in view of the rising interest in this imaging modality. However, while there are clearly many difficulties in utilizing EBCT in current medical practice Sechtem’s review failed to highlight the potential usefulness of a negative EBCT scan. In patients with new onset of chest pain, EBCT may be a useful first investigation since a calcium score of zero has an extremely high negative predictive value for significant stenosis of any major vessel[2–4]. This may be particularly useful in the emergency department setting where a negative EBCT scan has been shown in two recent studies to predict which patients can safely be discharged (with a negative predictive value of 100%)[5–6]. This strategy may be most cost effective in patients with atypical chest pain because they have a low pre-test likelihood for ischaemic disease and therefore a reasonable likelihood of having a calcium score of zero[7].

In the editorial Sechtem makes a number of comparisons between traditional non-invasive tests (such as treadmill exercising, stress echo-cardiography or stress thallium) and EBCT. However one of the major advantages of traditional tests over EBCT that was not mentioned is their dynamic physiological nature in contrast to the static anatomical nature of EBCT. Thus dynamic data relating to the workload required before the onset of ischaemia can provide valuable information regarding severity of symptoms as well as optimization of therapies.

Interestingly, in addition to the human calcium regression study mentioned by Sechtem, Williams et al. have reported decreased histological plaque calcium with statin use in monkeys[8]. In contrast when Stary induced regression of atherosclerotic lesions in rhesus monkeys through a low cholesterol diet, he noted that calcification remained in lipid depleted residual lesions[9]. So it is not clear if calcium
resorption is a reflection of more effective lipid lowering by statins or an effect of these drugs through other mechanisms.

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References

Provisional vs primary stenting during percutaneous coronary intervention

We read with interest the paper by Knight and colleagues entitled ‘Stent implantation reduces restenosis in patients with suboptimal results following coronary angioplasty’ [1]. This small but well-designed study demonstrated a benefit of stent deployment for a ‘suboptimal’ result (15–50% residual stenosis) after balloon angioplasty; the restenosis rate in the stent group was 24% and in the balloon group 53%. An ‘optimal’ balloon angioplasty result (defined as <15% residual stenosis) was attained in only 16 (11%) of the 143 patients enrolled in the study. The restenosis rate appeared low in these patients (14%), although this represented only two of the 16 patients so the confidence limits are wide.

We were surprised to see this study described as supporting ‘A plea for provisional stenting’ in the accompanying editorial by Rupprecht and Meyer [2]. On the contrary, when nine out of 10 patients need stent deployment if this strategy is employed, one wonders whether elective stent stenting of all lesions (in vessels ≥ 3.0 mm diameter) should be performed. This approach was evaluated in the larger OPUS study [3] which demonstrated a reduction in the composite end-point of death, myocardial infarction or target vessel revascularization at 6 months, from 14.9% in those treated by balloon angioplasty with provisional stenting (for lesions visually>20%) to 6.1% in those treated by primary stent deployment. Another approach of performing angiography 24 hours post-angioplasty and stenting those lesions which had deteriorated was evaluated in the small OCBAS study [4]. Although the results were encouraging, the strategy is too cumbersome and expensive to gain widespread clinical acceptance.

Despite the major problem of dealing with in-stent restenosis, available randomized trial data support a high rate of stent deployment during coronary interventional procedures. A strategy of provisional stenting does not greatly reduce the rate of stent utilization, and does not reduce patient treatment costs [5]. Newer stent designs and deployment strategies (e.g. direct stenting without predilatation) [5,6] may further shift the balance in favour of routine stent deployment.

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