do not seem to be substantial (table). Because all guidelines recommend prompt initiation of drug treatment in patients with hypertension stage II or III, estimates of total cardiovascular risk in this setting might not have a major effect on therapeutic decisions, but rather on the expectations of benefit. In patients with hypertension stage I, with the notable exception of the Joint National Committee 8, the other guidelines take cardiovascular risk estimates into some account, by recommending the initiation of drug treatment when the risk is increased generally on the basis of target organ damage or established cardiovascular disease. Future studies should focus on stage I hypertension and clarify what is the most accurate and cost-effective approach to stratify cardiovascular risk and to estimate the expected benefit of treatment in these patients.

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Heparin monotherapy for percutaneous coronary intervention?

The efficacy and safety of percutaneous coronary intervention (PCI) has been substantially enhanced by refinements in antithrombotic treatments. Ischaemic complications were reduced by as much as 50% with addition of platelet glycoprotein IIb/IIIa inhibitors (GPIs) to early regimens of aspirin and heparin. However, use of these potent platelet inhibitors was accompanied by increased risk of haemorrhagic complications, which are associated with increased mortality, morbidity, and costs. Development of antithrombotic drugs therefore focused on reducing risks of haemorrhagic events while maintaining protection against ischaemic complications. In several trials in patients undergoing PCI, substitution of the direct thrombin inhibitor bivalirudin for the combination of heparin and a GPI consistently reduced the incidence of major bleeding by about 40%. Although occurrence of the composite ischaemic endpoints of those trials was not significantly increased by bivalirudin, there seemed to be more frequent periprocedural myocardial infarctions in several studies and rates of acute stent thrombosis were significantly higher with bivalirudin than with heparin in patients with ST-elevation myocardial infarction (STEMI). However, long-term mortality was not increased with bivalirudin and this drug largely supplanted the combination of heparin plus a GPI during PCI.

Advances in interventional practices have the potential to alter the balance between bleeding and ischaemic risks. Ticagrelor and prasugrel—potent and rapidly acting inhibitors of the platelet ADP receptor—reduce ischaemic events when used instead of clopidogrel in patients with acute
coronary syndromes. Although no trial has explicitly tested whether these drugs remove the need for use of a GPI with heparin, GPI use has nonetheless decreased. Radial, rather than femoral, arterial access is becoming more common during PCI, thus reducing the risk of vascular-site haemorrhage and the need for pharmacological measures to control bleeding. Newer stent designs with thinner metallic struts eluting second-generation antiproliferative drugs seem to be associated with lower rates of stent thrombosis. With changing interventional treatments, recent trials have re-examined bivalirudin compared with heparin-based regimens. Some of these trials took the position that routine GPI use is no longer needed during contemporary PCI, comparing bivalirudin instead with heparin monotherapy (with GPs used in either group only provisionally for ischaemic complications). In a large trial of this design among patients with STEMI, bivalirudin did not reduce bleeding complications and was associated with higher rates of stent thrombosis, myocardial reinfarction, and repeat revascularisation compared with heparin.

In The Lancet, Matthew Cavender and Marc Sabatine shed some light on seemingly disparate results with bivalirudin in a meta-analysis of randomised trials of bivalirudin versus heparin regimens during coronary stenting. They included 16 trials of nearly 34,000 patients with STEMI, non-ST-segment-elevation acute coronary syndromes, or urgent or elective PCI. They appropriately stratified the trials according to the strategy for use of GPs: bivalirudin monotherapy versus heparin plus planned GPI; bivalirudin monotherapy versus heparin monotherapy, or bivalirudin versus heparin with planned GPI in both groups. Ischaemic complications of PCI were more frequent among patients assigned to receive bivalirudin-based regimens compared with heparin-based regimens (risk ratio [RR] 1·09, 95% CI 1·01–1·17; p=0·0204), a finding that was consistent regardless of the clinical indication for PCI or the strategy for use of GPs. However, the effect of bivalirudin on bleeding risk was significantly affected by the strategy for concomitant GPI use. In trials in which GPs were used routinely with heparin, bleeding was reduced by bivalirudin (RR 0·53, 95% CI 0·47–0·61). In trials comparing bivalirudin with heparin monotherapy, there was no significant difference in bleeding rates (RR 0·78, 95% CI 0·51–1·19); the single sizeable trial of that design to show reduced haemorrhage risk with bivalirudin (ISAR-REACT 3) used a heparin dose (140 U/kg bodyweight) that was much higher than that used in interventional practice (50–70 U/kg).

Findings from this meta-analysis suggest that routine use of bivalirudin offers little advantage over heparin among patients undergoing PCI, at least in settings in which ticagrelor or prasugrel are frequently used and vascular access is primarily through the radial artery. The reduction in haemorrhagic events noted with bivalirudin in earlier trials seems to have been due primarily to sparing of the use of GPs, and cannot be expected when compared with heparin monotherapy. Moreover, rates of myocardial infarction, revascularisation, and stent thrombosis were reduced by heparin versus bivalirudin, independently of concomitant GPI use. However, the comparison between bivalirudin and heparin monotherapy was driven primarily by the results of two large studies: a UK single-centre study and a Chinese trial that has not yet been published in a peer-reviewed journal. Moreover, these two trials enrolled patients with STEMI and might not be representative of outcome in settings where ticagrelor and prasugrel are not indicated. Definitive and broader conclusions regarding the efficacy of bivalirudin versus heparin must therefore await results of the multicentre 6800-patient MATRIX trial, which is expected to be completed by the end of 2014 (NCT01433627).
Dyslipidaemia in perspective

Dyslipidaemia as the original cause of atherosclerotic vascular disease has returned to centre stage, 20 years after the results of the 4S study\(^1\) were published in The Lancet in 1994. The 4S study heralded the beginning of the great success of statins, now the most widely prescribed class of drugs in the history of medicine. The three Series papers in this issue of The Lancet on the consequences of perturbed lipoprotein metabolism for vascular disease are an education on their own.\(^2\)\(^-\)\(^4\) The authors provide balanced and thorough overviews on what is known and, most importantly, still unknown in the specialty.

LDL cholesterol\(^1\) has been at the core of atherogenesis for so long in our collective memory that few clinicians have any doubt about its causal role in heart disease. Most clinicians regard familial hypercholesterolaemia to be the best example of that association, and are convinced by the Oxford meta-analysis showing that statins exert their beneficial effects through lowering of LDL cholesterol concentrations.\(^1\)\(^-\)\(^4\) The massive power of the large lipid genetics consortia and their mendelian randomisation approach in dyslipidaemia have further cemented the role of LDL cholesterol as a cause of atherosclerotic vascular disease.\(^7\)

Nevertheless, not every question has been fully answered, including why has it not been shown convincingly with any other class of drugs that reduction of cardiovascular events follows LDL cholesterol lowering as closely as it does with statins. Despite cholestyramine and partial ileal bypass surgery with a cholesterol absorption inhibitor (IMPROVE-IT [NCT00202878]) and a monoclonal antibody targeting PCSK9 (ODYSSEY Outcomes [NCT01663402], FOURIER [NCT01764633], SPIRE I [NCT01975376], and SPIRE II [NCT01975389]), with success defined as results close to the CTT regression line (ie, a relation that would show event reduction). Such findings should convince sceptics and would make investigation of where the association ends possible; this point is unlikely to be at zero, but will probably be well below 25 mg/dL (0·65 mmol/L), the true physiological LDL cholesterol concentration.

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