**Almanac 2013—stable coronary artery disease**

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**CORONARY HEART DISEASE IN DECLINE**

Epidemiological data from Europe, the USA and elsewhere in the developed world show a steep decline in coronary heart disease (CHD) mortality during the last 40 years1. Concern about levelling of mortality rates in younger adults2 has been somewhat alleviated by data from The Netherlands showing that in men aged <55 years, rates of decline have again accelerated, increasing from only 16% in 1993-1999 to 46% in 1999-20073. A similar pattern was observed in young women with rates of decline of 5% and 38% during the same time periods. This is encouraging, particularly in the context of data from Denmark and the UK showing declining mortality and also a sharp fall in standardized incidence rates for acute myocardial infarction indicating that coronary prevention, as well as acute treatments, has contributed to recent mortality trends4,5. Meanwhile an Australian study reminds us that myocardial infarction is but one of several manifestations of cardiovascular disease by reporting that decreasing incidence and recurrence rates for hospitalized CHD from 2000 to 2007 have also been seen for cerebrovascular and peripheral arterial disease6.

However, the epidemiological news is not all good, and data from the UK show that the pernicious relationship between socioeconomic status (SES) and CHD has shown no tendency to go away in recent years, the gradients between top and bottom SES quintile groups for hospital admissions remaining essentially unchanged across the age range7. Whether this has contributed to the almost 3-fold risk of myocardial infarction associated with stillbirth and 9-fold risk associated with recurrent miscarriage in a recent German study is unclear because the investigators made no adjustment for SES8. Nor is it clear if SES has contributed to the persistent ethnic differences in both US and UK studies of CHD mortality although other factors appear also to be important. Thus, African–American men have greater exposure to CHD risk factors than Caucasians and, when adjustment is made for this, their susceptibility to CHD is no greater, although mortality rates are twice as high9. For African-American women, incidence and mortality rates are higher than their Caucasian counterparts. These findings suggesting that exposure to risk factors contributes to ethnic differences in the incidence of CHD are to some extent reflected in a recent report from the Health Survey for England in which 13,293 Caucasian and 2,120 S Asians consented to mortality follow-up10. Physical inactivity was more frequent in S Asians compared with Caucasians (47% vs 28%) and explained >20% of their excess CHD mortality. Certainly, the emerging consensus is that the excess CHD mortality among UK S Asians is driven almost entirely by their increased susceptibility to disease and not by increased case-fatality rates11.

**DIAGNOSIS OF STABLE CORONARY ARTERY DISEASE**

The recent AHA/ACC guideline update12 emphasized the importance of individualizing the diagnostic workup based on the estimated probability of coronary artery disease. In this respect, it mirrored an earlier National Institute of Clinical Excellence (NICE) guideline on chest pain diagnosis13, but there were important differences in the recommendations for non-invasive testing, the new AHA/ACC guideline preferring the exercise ECG as the initial diagnostic approach for most patients, (NICE had previously counselled against use of the exercise ECG based on its relatively poor diagnostic performance) with pharmacologic radionuclide, cardiac MRI or stress echocardiography testing in reserve for patients unable to exercise. Recommendations for cardiac CT coronary angiography (CTCA) were cautious, and invasive angiography was recommended for diagnostic purposes only if the results of non-invasive testing suggested a high likelihood of severe 3-vessel or left main coronary artery disease, and

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the patient was willing to undergo revascularizations. In general, therefore, the AHA/ACC guideline update was less prescriptive than the earlier NICE guideline, perhaps partly because it put less emphasis on the cost effectiveness of its recommendations.

**MANAGEMENT OF STABLE CORONARY ARTERY DISEASE**

The recent NICE guideline recommended initial treatment with a short-acting nitrate and a β-blocker and/or a calcium channel blocker for control of angina plus aspirin and a statin for secondary prevention. Lifestyle measures were also emphasized. For patients with continuing symptoms cardiac catheterization with a view to revascularization was recommended, additional antianginal treatment (long-acting nitrates or one of the newer agents) only being indicated for patients unsuitable for revascularization. It was further recommended that the mode of revascularization (percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG)) should best be determined by a multidisciplinary group, a recommendation that has also been emphasized by European guideline groups, bearing in mind the potential for prognostic benefit from CABG in patients with complex multivessel and left main stem disease, particularly those with diabetes. For patients with symptoms adequately controlled with medical treatment, the guideline recommended discussion of the potential for prognostic improvement with CABG. Those patients prepared to proceed to CABG might then be offered diagnostic cardiac catheterization to rule out complex multivessel and left main stem disease, which a recent meta-analysis reported in as many as 36% (18.5-48.8%) of cases of stable coronary disease selected for cardiac catheterization.

**SECONDARY PREVENTION OF STABLE CORONARY DISEASE**

The scope for improving secondary prevention in patients with stable coronary artery disease has been emphasized in two recent reports. In The multinational REduction of Atherothrombosis for Continued Health (REACH) Registry, 20 588 symptomatic patients were analyzed for ‘good control’ of cardiovascular risk factors, defined as three to five of systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg, fasting glycaemia <110 mg/dL, total cholesterol <200 mg/dL, non-smoking. Only 59.4% had good control of risk factors at baseline, but this was associated with lower mortality (OR 0.89; 95% CI 0.79 to 0.99) at 36 months, compared with poor control. In the UK ASPIRE-2-PREVENT survey, 676 patients with CHD (25.6% women) had the following rates of major risk factors: smoking 14.1%, obesity 38%, physical inactivity 83.3%, blood pressure ≥130/80 mmHg, total cholesterol ≥4 mmol/L and diabetes 17.8%, leading the authors to conclude that there is considerable potential for reducing cardiovascular risk in these patients and thereby improve prognosis.

**Clopidogrel.** The availability of low-cost generic clopidogrel prompted a NICE review of its cost effectiveness which recommended it should now supersede aspirin in certain high-risk groups, namely patients with multivascular disease, peripheral vascular disease and myocardial infarction. However, clopidogrel is metabolized by enzymes in the hepatic cytochrome P450 (CYP) system, and variability in its antiplatelet activity may occur because the activity of these enzymes is influenced by common genetic variations, and also by a number of commonly used drugs. Several studies have reported loss-of-function alleles in CYP2C19 that result in reduced activation of clopidogrel and a modest lowering of antiplatelet activity which have been associated with an increased risk of cardiovascular events in some meta-analyses. Conversely, gain-of-function alleles have been associated with reduced cardiovascular risk among clopidogrel-treated patients. A recent meta-analysis, however, has commented on the tendency of small studies to bias conclusions about the way genetic variants influence clinical outcomes, and in larger studies of clopidogrel therapy with ≥200 outcome events found no effect of loss-of-function alleles on cardiovascular risk. At present, therefore, there seems to be no compelling indication for genetic testing to guide clopidogrel treatment although the topic remains a subject of ongoing debate. Also debated is the interaction of clopidogrel with some commonly used drugs, particularly proton pump inhibitors (PPI) and amlodipine. A recent meta-analysis of studies of PPIs in patients treated with clopidogrel found clear evidence of reduced platelet activity but although clinical outcomes appeared adversely affected by the interaction, the authors urged cautious interpretation, pointing out the heterogeneity caused by retrospective studies. When analysis was restricted to prospective studies of PPIs and clopidogrel, adverse clinical consequences could no longer be demonstrated (OR 1.13 (0.98 to 1.30)). Similarly, the clinical impact of amlodipine on responsiveness to clopidogrel remains uncertain. Certainly, there is evidence of interaction, and in one
study of 1258 patients receiving clopidogrel, amlo-
dipine administration was associated with higher on-
treatment platelet reactivity only in those patients with a
loss-of-function P450 (CYP) genotype (249±83 vs
228±84 P2Y12 reaction units), and this was associated
with a higher incidence of cardiovascular events (4.6%
vs 0.6%)27. However, in a more recent randomized tri-
al, platelet function in 98 patients with stable coronary
erve disease taking clopidogrel was similar regardless
of amlodipine therapy28. At present, therefore, there is
no guideline recommendation about concomitant prescrip-
tion of these drugs in patients taking clopidogrel.

Novel lipid-lowering drugs in clinical translation. Conventional lipid-lowering therapies, even when
combined with LDL-apheresis, are often insufficient to
treat to guideline targets patients with familial hyper-
cholesterolaemia (FH), an autosomal dominant disorder
of lipid metabolism associated with accelerated
 coronary disease35. There is, therefore, considerable
interest in novel therapies currently under investiga-
tion, particularly lomitapide, an oral inhibitor of mi-
crosomal transfer protein and monoclonal antibodies
against PCSK9. A phase II study of lomitapide in ho-
mozygous FH showed a 50% reduction in LDL-cho-
lesterol and, although gastrointestinal side effects were
common, a useful role for the drug seems likely in the-
se homozygous patients36. PCSK9 inhibitors have also
produced 50-60% reductions in LDL-cholesterol values
in clinical studies when added to statins and ezetimibe,
but unlike lomitapide, are probably mainly effective in
heterozygotic FH because they act through interferen-
ce with LDL receptors which are dysfunctional or com-
pletely absent in homozygotes37,38. The expectation is
that application of these new drugs will allow most pa-
tients with FH to achieve target concentrations of LDL
cholesterol. An important component of FH manage-
ment involves identification of other affected family
members, and cascade screening using genetic testing
has been reported as cost effective39. However, recent
evidence suggests that polygenic disorders account for
an appreciable proportion of FH cases40, and this will
limit the effectiveness of cascade screening to relati-
vies of mutation-positive (monogenic) cases. In other
patients, with cholesterol levels consistent with an FH
genotype, more conventional primary care strategies41
should remain the screening tool of choice, at least for
the time being.

REvascularisation In Stable CAD

Percutaneous coronary intervention. The COURAGE
trial was a game-changer, showing that coronary sten-
ting in patients with stable angina did not improve
cardiovascular outcomes compared with optimal me-
dical therapy (OMT) while quality-of-life benefits were
short-lived\textsuperscript{42,43}. Now available is a meta-analysis comparing contemporary medical therapy and PCI in eight randomized trials involving 7229 patients with stable CAD\textsuperscript{44}. Again, cardiovascular outcomes between the groups were similar during follow-up for an average 4.3 years with no significant clinical benefit for PCI, risks of death (8.9\% vs 9.1\%) and non-fatal MI (8.9\% vs 8.1\%) being nearly identical with medical therapy, while differences in unplanned revascularization (21.4\% vs 30.7\%) and persistent angina (29\% vs 33\%) were small and insignificant. The data support recent guideline recommendations for treatment of stable angina (see above), and have been used to challenge those clinicians who continue to offer PCI to patients not receiving OMT\textsuperscript{45}. However, FAME-II has now provided some support for an early interventional approach in a randomized comparison of OMT and PCI using drug-eluting stents guided by fractional flow reserve (FFR)\textsuperscript{46}. The study was stopped 17 months earlier than planned because the composite endpoint (all-cause mortality, non-fatal MI, urgent revascularization) occurred in 4.3\% of the PCI group compared with 12.7\% of the non-PCI (OMT) group. Relief of angina was also more effective in the PCI group. Already, PCI guided by FFR has become a recommended strategy in stable coronary artery disease but some feel this is premature\textsuperscript{47}. Thus, the treatment difference in FAME-II was driven solely by a reduction in urgent revascularization (49 in the OMT alone group; 7 in the FFR-PCI group (HR=0.13, 95\% CI 0.06 to 0.30), while the 33 deaths and non-fatal MIs were distributed fairly evenly between the groups. Moreover, the majority of patients undergoing ‘urgent’ revascularization lacked objective findings of high-risk ischaemia or threshold biomarker elevations, raising concerns of biased selection of patients for invasive management during follow-up. Nevertheless, the argument in favor of interventional management as an initial strategy in stable angina has undoubtedly been strengthened by FAME-II, but final answers to the debate may have to await the findings of the ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA Trial; ClinicalTrials.gov number, NCT 01471522), comparing effects of revascularization (PCI or CABG) combined with OMT, with OMT alone on cardiovascular death, or MI in patients with stable CAD, and objective evidence of myocardial ischaemia.

Coronary artery bypass surgery. Updated US guidelines\textsuperscript{48} have endorsed the NICE recommendation of a multidisciplinary team approach to adjudicating revascularization decisions in patients with complex coronary disease, encouraging application of SYNTAX and other scoring systems in arriving at an appropriate decision\textsuperscript{49}. The potential for CABG compared with PCI to improve prognosis in patients with left main and multivessel CAD is supported by recent cohort studies\textsuperscript{50,51}, and now available are the 5-year follow-up data from SYNTAX in which major adverse cardiac and cerebrovascular events (MACCE) were 26.9\% in the CABG group and 37-3\% in the PCI group, driven largely by lower rates of non-fatal myocardial infarction and repeat revascularization for CABG, with no significant difference in all-cause mortality and stroke compared with PCI\textsuperscript{52}. The benefits of CABG were particularly evident in patients with intermediate and high SYNTAX scores, there being no significant difference in outcomes between revascularization strategies for patients with low SYNTAX scores. Any question about the preferred revascularization strategy in patients with diabetes and multivessel coronary artery disease has now been answered by the FREEDOM TRIAL which randomized 1900 patients on OMT to either PCI with drug-eluting stents or CABG\textsuperscript{53}. After a median follow-up of 3.8 years, the primary outcome, a composite of death from any cause, non-fatal myocardial infarction, or non-fatal stroke, occurred in 26.6\% of the PCI group and 18.7\% of the CABG group. The authors concluded that CABG is superior to PCI in patients with diabetes and multivessel disease. There is less certainty about the preferred revascularization strategy in left main coronary disease, the SYNTAX investigators reporting similar outcomes for PCI and CABG, a finding consistent with other contemporary studies that identify stenting as a reasonable strategy in appropriately selected cases, even though the need for repeat revascularization is almost invariably higher compared with CABG\textsuperscript{54,55}.

Surgical technique has come under considerable scrutiny recently. Concerns about the potential adverse effects of endoscopic versus open saphenous vein harvesting have been based largely on a non-randomized cohort study of 1817 patients in whom rates of vein graft failure at 1 year were 47\% vs 38\%, and rates of death, myocardial infarction or revascularization at 3 years were 20.2\% vs 17.4\% for endoscopic versus open saphenous vein harvesting\textsuperscript{56}. This led NICE to recommend caution in use of the endoscopic technique\textsuperscript{57}, but such concerns have now been allayed by the results of two large cohort studies. In the US study of 235 394 Medicare CABG patients in the Society of Thoracic Surgeons (STS), national database mortality rates were
similar regardless of harvesting technique, while rates of harvest site complications were lower for the endoscopic technique. A UK study of 4702 CABG patients reported similar findings with no differences in inhospital mortality (0.9% vs 1.1%, p=0.71) or midterm mortality (HR 1.04; 95% CI 0.65 to 1.66) for endoscopic versus open vein harvesting.

Also under scrutiny have been the relative benefits of off-pump and on-pump CABG. Each has its proponents, but the results of randomized outcome trials have failed to show any clear advantage for off-pump CABG, the 3-year results of the Best Bypass Surgery Trial showing no significant difference in the primary composite outcome of MACCE compared with on-pump CABG, but a tendency towards higher mortality. This may reflect, at least in part, differences in graft patency rates favoring on-pump procedures, the ROOBY trial reporting rates of 91.4% vs 85.8% for arterial grafts and 80.4% vs 72.7% for saphenous vein grafts in on-pump compared with off-pump patients. Particularly disappointing has been the failure of off-pump surgery to reduce cerebral injury, but a randomized comparison of minimal (MECC) versus conventional (CECC) extracorporeal circulation in 64 patients undergoing CABG has been more promising. MECC was associated with improved cerebral oxygen delivery during surgery, and neurocognitive performance at 3 months was better when compared with CECC.

REMOTE ISCHAEMIC PRECONDITIONING FOR TREATMENT OF STABLE CORONARY DISEASE

Its proponents see remote ischaemic preconditioning (RIPC) as a useful and inexpensive means of improving outcomes across a range of cardiovascular disorders. They must be frustrated, therefore, by the technique's failure to penetrate clinical practice, conflicting reports of its efficacy and mechanistic uncertainty combining to undermine clinical confidence in the utility of RIPC. Some recent randomised trials have been favorable, reporting protection against contrast-induced nephropathy during cardiac catheterization and reduction in myocardial injury during heart valve surgery. Perhaps the most favorable has been a randomized trial of prehospital RIPC in 333 patients with STEMI who underwent primary PCI. The group with RIPC showed a significant improvement in myocardial salvage index compared with the group without (0.75 vs 0.55) although the trial was not powered for coronary events. Against this must be set a negative trial of RIPC in a group of patients undergoing CABG, but this is unlikely to be the last word, and already a meta-analysis of nine studies including 704 patients has concluded that RIPC significantly reduces troponin release during CABG. Mechanistic studies of interest include one crossover study in patients with stable coronary artery disease in which RIPC reduced platelet activation during exercise testing without protecting against ischaemic ECG changes. In another study of forearm blood flow using venous plethysmography in healthy volunteers, RIPC protected against impaired endothelium-dependent vasomotor function induced by ischaemia. However, this protection was unaffected by infusion of a bradykinin B2 receptor antagonist, leading the authors to conclude that bradykinin is not a mediator of RIPC.

PROGNOSTIC BIOMARKERS IN STABLE CAD

Circulating biomarkers. Interest in circulating cardiovascular biomarkers has never been higher, and methodological papers have been developed to alert researchers to the standards necessary for proper evaluation of their prognostic utility. However, a systematic review of 83 CRP studies was critical of their general quality and concluded that the magnitudes of association between CRP and prognosis among patients with stable coronary disease are insufficiently uncertain that no clinical practice recommendations can be made. The same authors were equally critical of 19 BNP studies in patients with stable coronary disease, reporting that clinically useful measures of prediction and discrimination were generally unavailable, and concluding that the unbiased strength of association of BNP with prognosis in stable coronary disease is unclear. The availability of high-sensitivity assays has seen renewed interest in troponins as markers of risk in stable coronary disease, a US study of 984 patients in the Heart and Soul Study reporting that each doubling in hs-cTnT level is associated with a 37% higher rate of cardiovascular events. Meanwhile the PEACE investigators have reported that among 3623 patients with stable coronary artery disease, hs-cTNI is independently associated with cardiovascular death or heart failure (HR 1.88 (1.33 to 2.66; p<0.001)), the association with non-fatal myocardial infarction being weaker (1.03 to 2.01; p=0.031). Evidence from CTCA suggests that clinically silent rupture of non-calcified plaque with subsequent microembolisation is a likely pathophysiological mechanism of troponin elevation but it is too soon to know whether it will have a clini-
cal role in the prognostic assessment of stable coronary artery disease. The same applies to the mid-regional portion of proadrenomedullin and other biomarkers currently under investigation.

**Vascular biomarkers.** Carotid intima-media thickness (cIMT) is well established as a predictor of cardiovascular events in the general population and, more weakly, in patients with stable coronary artery disease. Its predictive value may be enhanced by additional consideration of the extent of carotid plaque allowing derivation of the ‘total burden score’ which was shown by Chinese investigators to improve the prediction of the 5-year risk of cardiovascular endpoints compared with cIMT alone. Certainly, the value of cIMT alone for cardiovascular risk prediction in the general population is under question following a large meta-analysis of participant-level data in 45 828 individuals in which cIMT added almost nothing to the Framingham Risk Score. Further questions have been raised by another meta-analysis of participant-level data which included 36 984 individuals followed-up for an average of 7 years. The investigators showed no association between progression of cIMT and risk of cardiovascular events, questioning the validity of using changes in cIMT as a surrogate endpoint in trials of cardiovascular risk.

**Calcium and parathyroid hormone.** Studies suggesting that people who take calcium supplements may be increasing their risk of myocardial infarction have stimulated interest in serum calcium and its relation to cardiovascular events in patients with CHD. A recent study has confirmed that vitamin D, parathyroid hormone and calcium show association with cardiovascular risk factors in US adolescents, and now we have data in 1017 patients with stable coronary artery disease followed-up for a median of 8.1 years, suggesting that high calcium levels, but not high phosphate levels, might be asso- ciated with all-cause and cardiovascular mortality (HR 2.39 to 4.66). The mechanism of this association is unclear, but the demonstration in the same cohort of a similar association between high parathyroid hormone and cardiovascular mortality may implicate calcium mobilisation from bone on the causal pathway.

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## References


