Controversies in Cardiology 1

Controversies in stable coronary artery disease

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Coronary heart disease is still highly prevalent worldwide, and stable angina pectoris is one of its more common presentations. Three major controversies are risk factor management, drug therapy, and intervention. As well as the major risk factors stated by the Framingham study and European guidelines, other factors include abdominal obesity, metabolic syndrome, and psychological stress. How should these additional factors be rated? With respect to drug therapy, apart from aspirin, all patients with stable angina should be assessed for statin treatment. Although statins will reduce coronary events by about one third in patients with vascular disease, the absolute benefit depends on the absolute risk. Non-controversially, all patients should be considered for angiotensin-converting-enzyme inhibitors. The concept that β blockers are protective from future coronary events can be disputed. Percutaneous coronary intervention can relieve symptoms without extending lifespan beyond medical therapy. However, strong mortality data favour coronary-artery bypass grafting in individuals with triple-vessel or even double-vessel disease. Thus, effort angina needs comprehensive assessment, lifestyle changes, and treatment tailored to the individual patient.

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This is the first in a Series of four articles on controversies in cardiology

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Coronary heart disease remains a major worldwide threat.[1] The disease is initiated with the assault of multiple risk factors on the endothelium and progresses to the formation of subintimal foam cells, atheroma, and diffuse coronary disease (figure 1). The coronary arteries are eventually riddled with diffuse atheroma at different stages of progression, including the angiographic stenosis typical of stable angina pectoris with other lesions at different sites and at various stages of evolution (figure 2). We review three major aspects of the management of stable coronary artery disease, namely risk factor assessment, drug therapy including lipid-lowering substances, and medical or surgical intervention. All these aspects have continuing controversies.

Which risk factors matter?

Primary prevention begins with risk factor control. With respect to risk factor calculation, the seven major conventional risk factors in the Framingham study were: age, sex, blood pressure, total and high-density cholesterol, smoking, glucose intolerance, and left-ventricular hypertrophy.[2] European guidelines are even simpler, with only five factors: age, sex, systolic blood pressure, total cholesterol, and smoking.[3] For patients with stable angina, only hypertension therapy and lipid lowering receive level A recommendations from leading US authorities (panel 1)[4,5] and European authorities focus on lifestyle, aspirin, and statins (panel 2).[3]

So which recommendations should doctors confronted by patients with stable angina believe? What is the role of other risk factors excluded from Framingham and European risk calculations, such as obesity, lack of exercise, metabolic syndrome, insulin resistance, psychological stress, markers of inflammation, microalbuminuria, and

Search strategy and selection criteria

We searched MEDLINE with "stable angina" as key words in combination with "guidelines", "risk factors", "diet", "stress", "exercise", "lifestyle modifications", "anti-anginal drugs", "percutaneous coronary intervention", "coronary artery bypass grafting", and "cognitive loss". We searched all major cardiovascular journals, *The Lancet*, *British Medical Journal*, *New England Journal of Medicine*, *Journal of the American Medical Association*, and http://www.theheart.org for similar or related articles. We also searched reference lists in key articles. More than 200 articles were analysed.

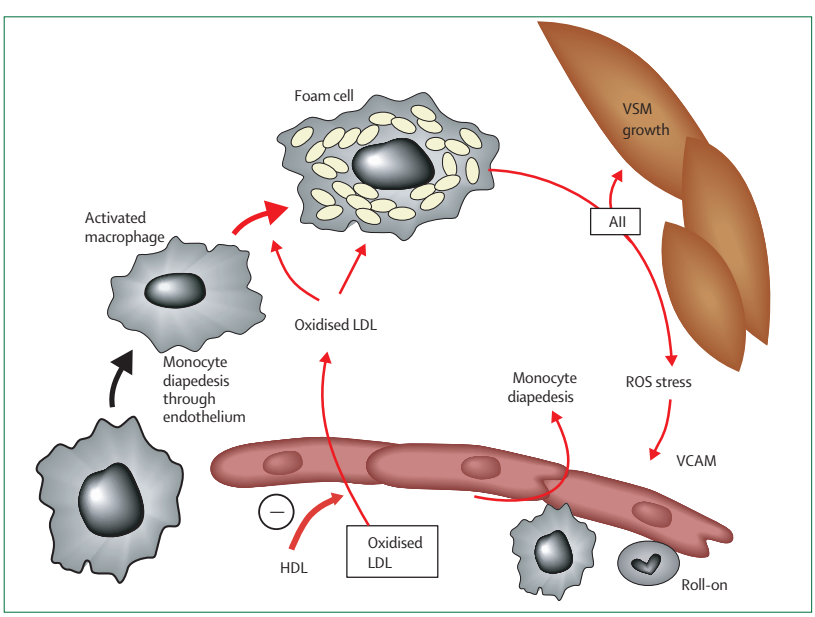

Figure 1: **Proposed role of vascular endothelium in atherogenesis**
Early endothelial damage is prompted by several factors including oxidised LDL, with a protective effect of HDL. Neutrophils roll on and adhere to the damaged endothelium to promote adhesion of macrophages, which then traverse the endothelium by diapedesis. Internally activated macrophages become foam cells by uptake of oxidised LDL, and also synthesise angiotensin II (AII) that promotes oxidative stress caused by reactive oxygen species (ROS) to stimulate the formation of vascular-cell adhesion molecule (VCAM). VCAM promotes the roll-on and binding of macrophages to the endothelium. AII also promotes growth of vascular smooth muscle (VSM) cells, an integral part of atherogenesis.

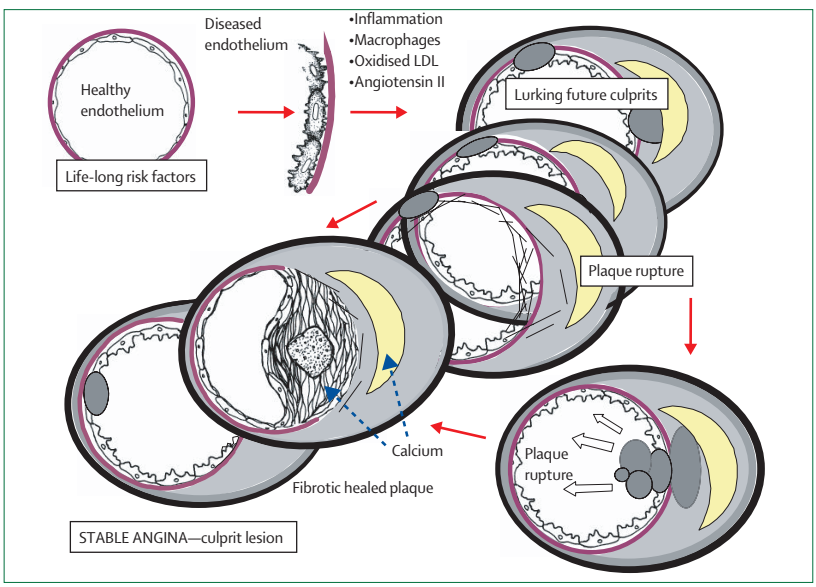

Figure 2: **Role of culprit lesion in stable effort angina**
The multiplicity of potential future culprit lesions is striking; multiple plaques and mature and dynamic evolving lesions can greatly change the clinical outlook. The major aspect of this model (compared with previous theories) is the potentially high number of vulnerable early plaques that could become unstable, some at the stage when the coronary arteries have been eccentrically deformed (lurking future plaques) so that the lumen diameter is virtually unchanged. Thus, there may be no angiographic traces. Once the lumen diameter is much narrowed (culprit lesion), the plaque is relatively stable. Therefore, severe coronary disease seen on a coronary angiogram might paradoxically be safer than an apparently healthy lumen.

markers of altered thrombosis such as homocysteine and fibrinogen?

Opinion

In reality, both the Framingham[6] and the vast international INTERHEART[7] studies show that a restricted number of potentially modifiable risk factors can account for the vast majority of myocardial infarction, which relegates other factors to second place. In INTERHEART, nine risk factors accounted for 90% or more of the population attributable risk.[7] The following five factors accounted for 80% of the population attributable risk: blood apolipoprotein B-to-A ratio abnormalities (an estimate of LDL-to-HDL ratios; odds ratio 3·25), smoking (2·87), diabetes (2·37), hypertension history (1·91), and abdominal obesity measured as the waist-hip ratio (1·12). The waist-hip ratio showed a stronger relation with myocardial infarction than the conventionally used body-mass index.[8] Indeed, the body-mass index was not significant when the waist-hip ratio was included in analysis. In INTERHEART, the relative risks of abdominal obesity and stress[9] were exactly related to myocardial infarction, for the first time in a large international study.

Protective factors were daily consumption of fruit and vegetables (odds ratio 0·70), regular physical activity (0·86), and moderate alcohol (0·91), all with $p<0·0001$ (apart from alcohol with $p=0·03$) in comparisons of the highest to lowest tertiles. Logically, risk factors for stable angina and myocardial infarction should be the same, but this view is assumed rather than strictly proven. In practice, there are still patients with coronary disease with few known risk factors, which could indicate genetic changes in enzymes regulating inflammation and oxidative stress.[10]

Metabolic syndrome

Although diabetes is a recognised risk factor, the metabolic syndrome is a controversial one and its existence is questioned by US and European diabetes societies.[11] Shifting definitions have been a problem.[12] The International Diabetes Federation and the American Heart Association[13,14] affirm that this syndrome exists and is important. Both agree that three or more of the following five features are required for diagnosis: enlarged waist-line, low HDL-cholesterol, hypertension, increased plasma triglycerides, and fasting plasma glucose at 5·6 mmol/L or more.[13] The International Diabetes Federation regards abdominal obesity as essential, which is not far removed from the US view that abnormal adipose tissue metabolism could be the crucial factor uniting the syndrome.[14] Both groups agree that reduced waist restrictions should be set for Asians.

Panel 1: **Recommendations for risk factor management in patients with stable angina, from the American College of Cardiology and American Heart Association**

Class 1 (general agreement)[4]
Hypertension therapy (level A)
Lipid-lowering target to less than 2·6 mmol/L (level A)
Smoking cessation (level B)
Exercise training (level B)
Diabetes management (level C)
Weight reduction in obese patients in the presence of hypertension, hyperlipidaemia, or diabetes (level C)

Class 2 (conflicting evidence)[5]
Weight reduction and increased physical activity in metabolic syndrome (level B)
Weight reduction in obese patients without class 1 conditions (level C)

Level A=multiple randomised trial data. Level B=data from one randomised trial or non-randomised studies. Level C=expert opinion.

Panel 2: **Key recommendations from European guidelines on cardiovascular disease management for patients with established coronary heart disease**[3]

- **Lifestyle changes**
  Stop smoking
  Healthy food choices
  Increase physical activity
- **Prescription of aspirin and a statin**
- **Consider drug therapy**
  Antihypertensive compounds
  β blockers
  Angiotensin-converting-enzyme (ACE) inhibitors

Although the LDL concentration could apparently be healthy, the small dense particles are atherogenic.[12] This syndrome increases cardiovascular risk by 1·5–3-fold and the diabetes risk by 3–5-fold. In the calculation of cardiovascular risk, waistline, hypertension, and HDL concentration (via the apolipoprotein B-to-A ratio) were assessed in INTERHEART. A continuum of glycaemic risk exists, as has been shown in 13 163 apparently healthy young men followed for a mean of 5·7 years.[15] In this study, the hazard ratios for new diabetes were 2·33–3·05 for glucose amounts of 5·0–5·6 mmol/L;[15] the ratios rose to above 8 for individuals with such glucose values associated with high triglyceride concentrations or obesity. Men with hypercholesterolaemia who showed three of the five metabolic syndrome features were recorded to have a hazard ratio of 3·19 for cardiovascular disease.[16] When four or more features are present, the hazard ratio for new diabetes rose to a surprising 24·4 times.

Opinion

The diagnosis of metabolic syndrome should be considered in every patient with angina. The more components of the syndrome present, the greater the risk of coronary disease. What can be done to protect individuals with the metabolic syndrome from new diabetes? Weight loss and exercise are more effective than metformin treatment.[17] For hypertension, ACE (angiotension-converting-enzyme) inhibitors or angiotensin-receptor blockers have the general property of lessening new diabetes.[18] The clinical relation of the metabolic syndrome and diabetes with coronary disease lies in the progressive vascular injury that occurs while insulin resistance deteriorates to overt diabetes.[19]

Diabetes and vascular damage

Type 2 diabetes is now regarded as a cardiovascular disease equivalent, largely acting via atherogenic dyslipidaemia. Additionally, control of glycaemia is a standard recommendation for individuals who have diabetes with typical angina. In the large prospective European study, DECODE,[20] the 2-h postglucose sugar concentration (a less practical measure) was more clearly related to cardiovascular mortality than was the fasting blood glucose. The reason could be due to microvascular dysfunction related to high values of postprandial glucose (figure 3).[21,22] Microvascular disease in general could be a cause of typical anginal chest pain with healthy coronary arteries on the basis of endothelial dysfunction.[23] Microvascular dysfunction and remodelling could also be the result of macrovascular disease, in which case percutaneous coronary intervention would improve this dysfunction.[24] Therefore, in individuals with diabetes, both macrovascular and microvascular dysfunction could contribute to anginal symptomatology.

Hyperglycaemia produces cardiovascular damage by multiple mechanisms (panel 3).[25] Microcirculatory damage could indicate endothelial dysfunction that, in turn, could deteriorate into macrovascular damage.[22] Glycaemic control should improve the cardiovascular outcome in type 2 diabetes.[26] In patients with extensive macrovascular disease, pioglitazone—an agonist for peroxisome-proliferator-activated receptor γ—was tested in the PROactive study.[27] Most patients were already treated by metformin, sulphonylureas, or both. The composite secondary endpoint of all-cause mortality, non-fatal myocardial infarction, and stroke was reduced by 16% at the risk of a modest 3% increase in heart failure (not defined). Apart from improved glycaemic control, mechanisms of benefit included increased HDL amounts and reduced triglycerides.

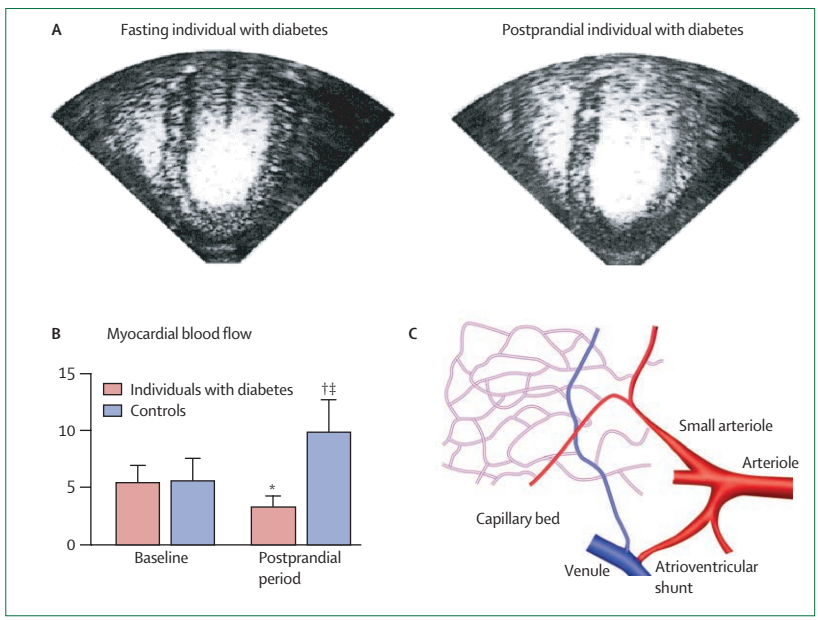

Figure 3: **Hyperglycaemic impairment of myocardial perfusion in patients with type 2 diabetes**
(A) Myocardial perfusion pattern delineated by microbubble contrast echocardiography. In postprandial individuals, reduction of myocardial blood volume can be seen, with fewer translucent areas (especially at apex of heart near the bottom). (B) Reduction in myocardial blood flow after meal. Mean values are shown; errors bar indicate SDs. Blood flow expressed in arbitrary units. *p<0·01 between postprandial and fasting individuals. †p<0·01 between control and diabetic postprandial values. ‡p<0·01 between baseline fasting and postprandial in controls. (C) Presumed site of damage in the microcirculation. Microcirculation diagram reproduced from reference 21, with permission. Other panels reproduced from reference 19, with permission, Scognamiglio R, Negut C, De Kreutzenberg SV, Tiengo A, Avogaro A. Postprandial myocardial perfusion in healthy subjects and in type 2 diabetic patients. *Circulation* 2005; **112:** 179–84.

Opinion

Hyperglycaemia exerts several harmful effects on the coronary circulation. Good glycaemic control remains the standard advice without clear trial support. The

Panel 3: **Proposed biochemical mechanisms of hyperglycaemia and cardiovascular damage[25]**

- Activation of polyol and glucosamine pathways
- Increased advanced glycation endproducts (AGE)
- Activation of growth-promoting protein kinase C
- Increased amounts of free radicals

Panel 4: **Dietary recommendations for patients**

- Mediterranean diet including high fruit and vegetables, whole grain cereals and bread, low-fat dairy products, fish, and lean meat[3,37]
- Oily fish and omega-3 fatty acids[3]
- Total fat intake no more than 30% of calories, saturated fats less than 30% of total fat, and cholesterol less than 300 mg/day[3]
- Replace saturated fat by complex carbohydrates, and monounsaturated and polyunsaturated vegetable and marine fats[3]
- Nuts, especially almonds[38] and walnuts[39]
- Cranberry[40] or purple grape juice[41] or similar
- Moderate regular alcohol intake[42]

PROactive study[27] could increase the use of glitazones to prevent macrovascular complications. However, vigorous reduction of LDL-cholesterol[28] and blood pressure[29] should remain prime goals.

How important are biomarkers in risk assessment?

C-reactive protein (CRP) is a newly proposed independent marker of cardiovascular risk that predicts future cardiovascular events. Coronary heart disease is increasingly seen as an inflammatory process, as indicated by ultrasensitive CRP. Ultrasensitive CRP is especially high if the plaque is unstable.[30] The severity and extent of angiographic coronary artery disease and the ultrasensitive CRP value are independent and additive predictors of risk.[30,31]

Another biomarker, brain natriuretic peptide, gave estimates for 5-year mortality in chronic stable angina of 5% in the first quartile, rising to 33% in the highest quartile.[32] Overall, the hazard ratio for plasma pro-brain natriuretic peptide was 5·83 versus only 1·32 for CRP. Since the left ventricle produces and releases brain natriuretic peptide in response to biomechanical stress, these data indicate that the peptide amount is an early marker of left-ventricular dysfunction.

Opinion

Although the links between ultrasensitive CRP and active coronary heart disease are strong, separation of ultrasensitive CRP from traditional cardiovascular risk factors is difficult.[33] In otherwise borderline cases, an ultrasensitive-CRP value of more than 3·0 mg/L[34] could affect therapeutic decisions. Patients with relatively normal LDL concentrations and increased ultrasensitive-CRP values have a case for statin therapy.[35,36] Prospective proof awaits a current statin trial. Different and possibly more sensitive biomarker information can be given by amounts of brain natriuretic peptide.

Which are the best lifestyle choices?

The purpose of treatment is to extend life and to improve symptoms. Much lifestyle advice (panels 1, 2, and 4)[3–5,37–42] and the use of statins and other preventive drugs are aimed at slowing coronary disease long-term, whereas symptom relief is best accomplished by the use of antianginal drugs and by revascularisation.

(1) Which diet?

Many choices of diet exist. Weight-loss diets, although seldom adhered to, do reduce risk factors.[43] The traditional Mediterranean diet is rich in fruit, vegetable legumes, whole grains, fish, nuts, and low-fat dairy products; the major source of fat is olive oil, with a substantial contribution from omega-3 fatty acids.[44] The greater the adherence to this diet, the greater the benefits such as reduction of blood pressure and weight,[45] with attenuation of inflammatory and coagulation processes.[46] Therefore, this diet can be expected to reduce the rate of progression of coronary disease, although angina relief has not been studied. Increasing evidence also shows the protective effects of omega-3 fatty acids, derived from oily fish or from plant extracts such as flax seed oil, which are high in the Mediterranean diet.[44,47–49] Much the same diet is recommended by the American Heart Association, the American Diabetes Association, and the American Cancer Society.[50] However, it should be noted that low-fat, low-salt, high-vegetable diets could bring down cholesterol or blood pressure (or both) without inducing any weight loss.[51] Panel 4[3,37–42] includes practical advice for patients. Moderate alcohol intake, also a part of the Mediterranean diet, gives an estimated mortality risk reduction of about 20%.[52] Combined dietary change could achieve a 15–45% mortality risk reduction,[52] but with some quoted studies being retrospectively suspect.

(2) Stress

Stress relief, meditation, and psychotherapy remain controversial methods for management of coronary disease, but need further investigation now that psychosocial stress has emerged as a major risk factor for myocardial infarction.[9]

(3) Exercise

Although increased exercise remains a standard recommendation for effort angina, no clear evidence-based programme for exercise training has been established. As reviewed by Thompson,[53] some programmes recommend aerobic exercise training be done at least three times a week for at least 20 min, at 70–85% of the heart rate at the onset of electrocardiographic ischaemia, whereas others exercise patients to the point of early angina and then cut back on the workload or give nitroglycerin. Proof that such training benefits stable angina is scarce. In one controversial study[54] on highly selected patients, exercise training gave better results than stenting over 1 year. Pooled data suggest that exercise could reduce mortality by 25% in patients with coronary disease.[52]

(4) Antioxidants and vitamins

Despite extensive testing, no evidence has shown that vitamin or antioxidant supplementation (other than dietary modification as mentioned previously) has any effect on outcome in the prevention or treatment of stable coronary disease.[5]

(5) Passive smoking

How harmful is it? Repetitive brief passive smoking is disastrous with effects as severe as 80–90% of chronic active smokers.[55] In US adolescents (aged 12–19 years) passive and active smoking had respective odds ratios of 4·7 and 6·1 for an association with metabolic syndrome.[56]

When and how should statins be used?

Although patients with stable angina are given aspirin and strict control of their blood pressure, they should also be assessed for statin treatment. The benefits of statins are proportional to LDL reduction (ie, low concentrations of LDL-cholesterol result in few cardiac events and increased benefits; figure 4),[28,57–59] especially in secondary prevention and in patients with diabetes. Therefore, all individuals with vascular disease should be considered for statin treatment. Three possible policies have been proposed: (1) treat to a target concentration of LDL, as indicated in many guideline recommendations;[3] (2) standard low doses, as in some atorvastatin trials;[28,60] and (3) treat to achieve a 5-year reduction of LDL-cholesterol by 1·0–1·5 mmol/L.[61] The third aim will reduce the incidence of major events by about 20–33%, irrespective of their initial cholesterol concentrations, with the absolute expected event reduction dependent on the amount of pre-therapy risk.[61]

All individuals with existing coronary disease are defined as being potentially high risk.[12] For those judged to be at very high risk, the new ultra-low goals of LDL concentration are 1·8 mmol/L.[62,63] How strong are the arguments for the routine use of high-dose statins? In the TNT (Treating to New Targets) trial,[58] top doses of atorvastatin (80 mg daily) reduced mean LDL from about 2·6 mmol/L to 2·0 mmol/L, and major cardiovascular events fell by 22% versus a low dose (10 mg daily). In the IDEAL study (Incremental Decrease in Endpoints through Aggressive Lipid lowering) on 8888 patients with a previous myocardial infarction,[64] atorvastatin (at 80 mg per day) reduced the secondary endpoint (any coronary event) when compared with simvastatin (mostly given at 20 mg per day). However, the primary endpoint was not different nor did the mortality rate fall. The final LDL concentrations were 2·1 mmol/L in the atorvastatin group versus 2·6 mmol/L in the simvastatin group, which modestly supported the hypothesis stating that "the lower the LDL concentration, the better", as well as having about twice the cost of drug-discontinuing adverse events (9·6% for atorvastatin *vs* 4·2% for simvastatin). These results do not strongly favour a fixed high dose of statins. Statin side-effects, apart from liver damage, include myalgia and the newly described peripheral neuropathy.[65] In the Heart Protection Study,[66] 40 mg of simvastatin led to non-significant increases of liver enzymes, and about 6% of individuals had myalgia, although rhabdomyolysis was rare (0·05% of treated individuals *vs* 0·03% of controls). Rhabdomyolysis was not significantly increased in the large meta-analysis.[61] Increased insulin resistance[67] needs consideration in those with metabolic syndrome. Combination of the Mediterranean diet with a statin regulates the insulin resistance.[67]

Other modes of LDL-cholesterol lowering

These approaches might be preferred to very high-dose statins, or needed in addition to statin treatment to achieve a target concentration of LDL in high-risk patients. Ezetimibe is an inhibitor of intestinal absorption of dietary cholesterol that can help to reach LDL-cholesterol goals.[68]

Low concentrations of HDL-cholesterol

A low concentration of HDL-cholesterol is a well-recognised risk factor in the Framingham calculations and an integral part of the metabolic syndrome. HDL-cholesterol is not in the European score chart.[3] Nicotinic acid and fibrates increase HDL by 16% and 10%, respectively, with fibrates being better than nicotinic acid at reducing triglycerides.[69] Bezafibrate reduced myocardial infarction in the metabolic syndrome and reduced cardiac death in individuals with four or five syndrome features.[70] Lifestyle measures that modestly raise HDL are exercise, moderate alcohol intake, and almonds.[38,71] Large increases in HDL by 50–100% can be achieved by the new inhibitors of cholesterol ester transfer protein (CETP), now being tested in combination with a statin.[72] Until outcome results are published, the focus of drug treatment will remain on LDL-cholesterol lowering.

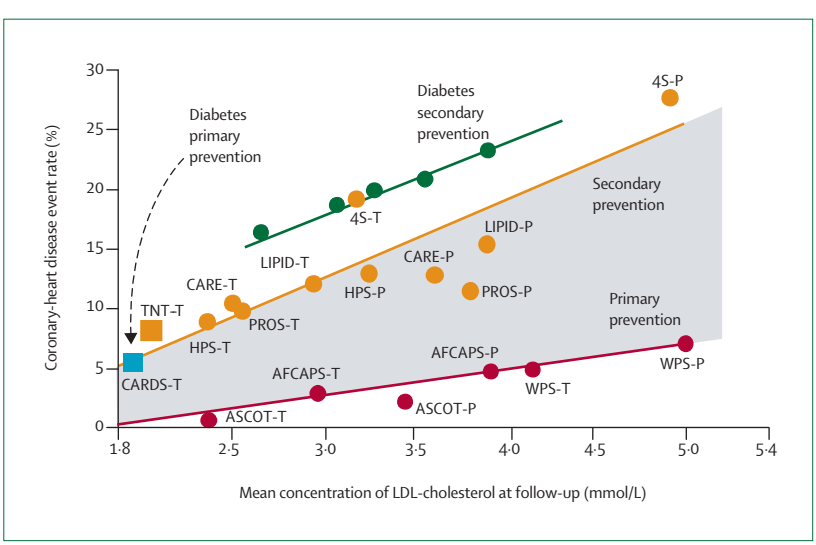

Figure 4: **Effects of reduction of LDL-cholesterol on coronary heart disease event rate**
Relation between LDL-C lowering and coronary heart disease events in major trials for primary and secondary prevention. P=placebo group. T=treatment group. Figure modified from reference 57 (which also includes definitions of trials), with permission. Added trials are CARDS[28] and TNT.[58] For individual references to Diabetes Secondary Prevention, see Fisher, 2004.[59]

Opinion

The extent of risk should determine the vigour of the attack. The best policy is to follow that of the largest and most recent meta-analysis,[61] aiming at a 1·0–1·5 mmol/L reduction of LDL over 5 years, irrespective of the initial value. Once achieved, a further reduction of a similar amount of LDL would again be expected. However, how low should concentrations goals go? In this respect, the treat-to-target approach is useful. We prefer to use statins, which are well validated by many large trials. If resources are scarce, any LDL reduction is better than none (figure 4). With respect to low HDL-cholesterol, fibrates are the preferred choice in the metabolic syndrome.

Should all patients with stable coronary artery disease receive ACE inhibitors?

The benefits of ACE inhibition depend on the risk profile. The greatest protection was given by ramipril in the HOPE study,[73] in which more than half the participants had stable angina. Less protection by perindopril was recorded in the EUROPA study,[74] in which all individuals had stable angina and a raised rate of statin use. In low-risk but otherwise well-treated patients, trandolapril gave some protection, including reducing new diabetes.[75,76]

Opinion

All patients should be considered for ACE inhibitors, which have many indications in coronary and associated diseases, including: previous myocardial infarction, left-ventricular dysfunction, diabetic nephropathy, or raised insulin resistance from statins in individuals with type 2 diabetes;[77] or prevention of new diabetes.[18] For stable angina in high-risk groups, ramipril and perindopril have the best trial data. The trials in which ACE inhibitors improved outcomes were HOPE[73] and EUROPA,[74] in which the patients were at increased risks, again stressing the importance of risk stratification.

Should β blockers be the antianginal drugs of choice?

β blockers effectively prevent angina, but no data show any protection against the life-threatening complications of coronary artery disease, except in post-infarct patients and in those with heart failure. A contentious statement is: "All patients with coronary artery disease should now be treated with an ACE-inhibitor in addition to aspirin, a β blocker, a statin, and aggressive risk factor modification".[78] In Europe, 67% of newly diagnosed patients with stable angina are treated with a β blocker and 27% with a calcium-channel blocker.[79] However, no decisive evidence proves that all patients with stable angina need β blockers or calcium-channel blockers except for symptomatic relief and blood-pressure reduction.[80,81] In support for primary β-blocker use in angina, it is often incorrectly stated that "in hypertension β blockers reduce morbidity and mortality",[82] which is now known not to be the case.[80] Combination antianginal therapy with β blockers and dihydropyridine calcium-channel blockers is safe.[81] Scarce data suggest outcome equivalence of β blockers and long-acting calcium-channel blockers.[83] β blockers but not calcium-channel blockers have consistently reduced insulin sensitivity,[84,85] and are more likely to precipitate overt diabetes,[86] which is an anticipated risk especially in individuals with the metabolic syndrome. β blockers could lessen sexual performance, reduce exercise capacity, and increase weight as well as causing fatigue. Calcium-channel blockers have none of these defects. Which class of drug should be used first?

Opinion

Calcium-channel blockers are preferred when maintenance of the quality of life and exercise capacity is the main need—eg, a middle-aged, sexually active man with modest angina. β blockade is essential in patients with previous myocardial infarction, low ejection fractions, or multivessel coronary artery disease with risk of incipient heart failure. No definitive outcome data exist; hence, when the quality of life is not the prime concern, a β blocker is often chosen unless contraindicated (as in the metabolic syndrome). When combined, these drugs give added efficacy.[87]

When is intervention needed? Which type of stent should be used?

The traditional controversy of medical treatment versus interventional therapy has mellowed since optimum management of stable angina patients has become multidimensional.[88] Thus, similar 1-year survival rates have been recorded after medical therapy, percutaneous coronary intervention, and coronary-artery bypass grafting, with the highest incidence of Q-wave myocardial infarction and need for additional procedures in patients receiving percutaneous coronary intervention.[89] Medical therapy gave excellent survival but resulted in much more residual angina than the intervention groups. Coronary-artery bypass surgery was the best choice for multivessel coronary artery disease. However, even such comparisons are indecisive because of the continuing improvement in all three treatments. For example, new antianginal substances could supplement existing drugs (table).[90]

	Action	Advantage
Trimetazadine, ranolazine, perhexilene	Metabolically active; could act by inhibiting oxygen-wasting fatty-acid metabolism	Haemodynamically inert
Ivabradine	Sinus node slowing, inhibits pacemaker current (I_f)	No effect on contractility or blood presure, no bronchospasm
Nicorandil	Vasodilator, potassium-channel activator, and has nitrate-like effect	Improves outcome[90]

Table: **Metabolic and other new antianginal drugs**

Currently, there is an increasing trend towards the use of percutaneous coronary intervention, even in individuals with no or few symptoms.[91] Yet the only benefit of the procedure is to reduce angina and to improve the quality of life,[91] mostly in patients with angina at least once a day.[92] A current meta-analysis of 2950 patients with stable coronary disease in 11 trials shows that the procedure offers no benefit over medical therapy.[93] Patients' expectations often exceed real improvements in a procedure that carries small but real risks of life-threatening complications.[91,94,95] Recurrent events (after about 6 months) are almost always due to progressive disease rather than restenosis.[96] Compared with bare metal stents,[97] drug-eluting stents reduced cardiac death, infarction, or revascularsation, but were less cost effective. Thus drug-eluting stents may be used if the cost is not important or if recommended for high-risk groups.

Left-main coronary artery intervention

Since early unsatisfactory results with percutaneous transluminal coronary angioplasty, this condition has been the domain of the surgeon. Again, risk prediction is important with excellent outcomes in people at low risk, by contrast with 25% mortality in those at high risk.[98] Increased biomarkers such as CRP help to predict death or myocardial infarction in this condition. In patients with high CRP, indirect evidence suggests that aggressive statin therapy could reduce CRP and risk.[98]

Opinion

Percutaneous coronary intervention for stable angina is not indicated as an urgent procedure but is often precipitated if the pattern of angina worsens or if anti-anginal drugs have side-effects. With intensive medical therapy in stable patients, intervention can be delayed with few adverse events.[99] Patients who opt for a quality-of-life-improving intervention should have the procedure, accepting the very low but real risk of peri-procedural myocardial infarction, but they should fully understand that percutaneous coronary intervention provides symptomatic relief and that only improved quality of life can be offered. No decisive evidence exists to support that all patients with stable angina need a percutaneous coronary intervention, except for symptomatic relief.

When should surgery take place?

Coronary-artery bypass grafting versus percutaneous coronary intervention

Both procedures are very effective in relieving symptoms in patients with stable coronary artery disease. In individuals with coronary stenosis of more than 50%, percutaneous coronary intervention was undertaken in 58% (mostly in younger patients with a low risk profile), and coronary-artery bypass grafting in 21%.[100] By contrast with percutaneous coronary intervention[93] and controversy surrounding its performance in asymptomatic or mildly symptomatic patients, excellent evidence shows that bypass surgery offers long-term survival benefit.[101] Benefit is greatest in patients with severe disease. Several systematic analyses of revascularisation strategies in chronic stable angina[102,103] conclude that compared with percutaneous coronary intervention, coronary-artery bypass grafting was associated with a reduced 5-year mortality, less angina, and fewer revascularisation procedures. An observational analysis in a very large database showed that patients with triple-vessel or double-vessel disease obtain survival advantage with coronary bypass surgery.[104] The major reason is that percutaneous coronary intervention is directed to current culprit lesions, whereas bypass surgery also bypasses future culprits (figure 5).[105]

Cognitive loss: how real?

One important factor is the physician's and patient's perception of the risks of cardiopulmonary bypass, especially those associated with cognitive decline.[106] From a logical viewpoint, the risks of neurological harm would be highest in the most invasive procedure. This notion is not borne out in the small studies available. Neuropsychological outcomes are identical after both interventions[107,108] Cross-clamping the aorta entails risk of atheromatous macroembolisation with risk of neurological complications and cognitive loss.[109] Despite expectations, no evidence shows that off-pump surgery is better than on-pump coronary bypass surgery in this respect.[110] Any real benefits of off-pump surgery remain debatable in view of the paucity of adequately designed trials.[111] Most patients with coronary disease have diffuse vascular disease that affects outcome, irrespective of the treatment strategy chosen.[112,113]

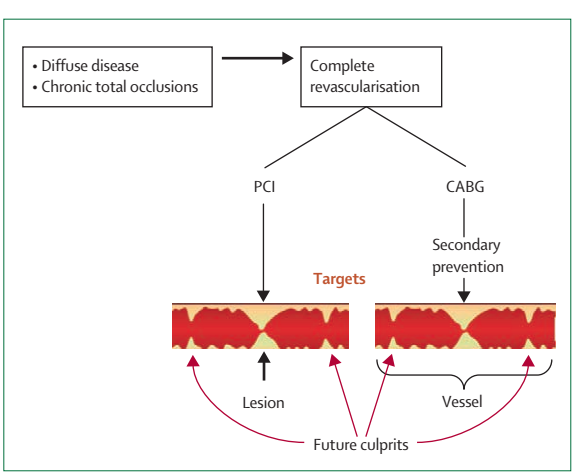

Figure 5: **Factors favouring coronary-artery bypass grafting (CABG) over percutaneous coronary intervention (PCI) in patients with multivessel disease**
Medical therapy is secondary prevention for future coronary events. Percutaneous coronary intervention is directed against culprit lesions, whereas bypass surgery bypasses most of the epicardial coronary vessel, including culprit lesions and future culprit lesions. Secondary prevention addresses not just future culprits and perhaps plaque vulnerability, but could improve endothelial function thereby protecting vessels from future symptom-producing lesions.

Continuing technological advances in percutaneous coronary intervention, including the success of drug-eluting stents in the reduction of restenosis, have resulted in percutaneous approaches being advocated in increasingly complex coronary anatomy,[114] when only a few years ago surgery would have been recommended. The long-term outcome of such strategies is untested. These decisions are complex choices, needing careful consideration by physicians and patients.[105]

Opinion

In view of the survival benefit shown for coronary-artery bypass grafting, the real controversy is why patients with symptoms and anatomy known to benefit from the procedure are still submitted to percutaneous coronary intervention. Multiple factors affect the selection of treatment strategy. Important factors are the physician's and patient's assessments of the risks of cardiopulmonary bypass and associated cognitive decline,[106] largely related to associated widespread vascular disease.[112]

Conflict of interest statement

LHO has given lectures on behalf of Abbott, Aventis, Bayer, Cardiovascular Therapeutics and Servier, and received travel funds. These lectures have been approved for Continuing Medical Educational programmes in South Africa or by the American Heart Association for satellite events. PJC has been an investigator in several pharmaceutical trials in heart disease, and has received honoraria from Bristol-Myers Squibb and Aventis. BJG serves on the Scientific Advisory Board of Cardiovascular Therapeutics, has received honoraria and educational grants from Genentech and Astra Zeneca, and has served on the data safety monitoring boards of trials funded by Abbott Laboratories, Boston Scientific, and Guidant Corporations. We declare that we have no conflict of interest with respect to the contents of the paper.

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