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REVIEW ARTICLE

Management of Intermittent Claudication: the Importance of Secondary Prevention

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Atherosclerotic peripheral arterial disease (PAD) is a common disorder usually associated with silent or symptomatic arterial disease elsewhere in the circulation and a cluster of cardiovascular risk factors inducing atheroma progression and/or thrombotic complications. Because of these strong clinical associations, especially with coronary heart disease, the ankle-brachial pressure index (ABPI) is of prognostic significance. The clinical management of IC should include relief of symptoms combined with prevention of secondary cardiovascular complications, e.g. acute thrombotic events causing limb- or life-threatening ischaemia, which are often due to atherosclerotic plaque rupture leading to thrombotic vessel occlusion. Many patients with PAD do not receive an optimum package of secondary prevention, tailored to include maximum cholesterol reduction, BP and glycaemic control, ACE inhibition and single or combination anti-platelet therapy. This review considers recent information from large secondary prevention trials, e.g. the PAD subgroups within the HOPE, CAPRIE and statin studies. Slowing progression of atherosclerosis, and inducing stabilisation and regression of atheromatous plaques, is now feasible using long-term combination drug therapy. The phrase ''conservative therapy'', popular among vascular surgeons, implies a passive minimal-intervention strategy of surveillance and lifestyle advice; such terminology is perhaps no longer appropriate since considerable improvements in survival are likely to accrue if all patients with PAD, especially those with low ABPI, receive vigorous, titrated medical therapies, tailored to individual patients, as part of an evidence-based secondary prevention regime.

Key Words: Secondary prevention; Intermittent claudication; ACE inhibitors; Atherosclerosis.

Introduction

Medical and surgical therapies for patients with intermittent claudication (IC) have two separate but complementary objectives: (1) symptom relief, i.e. improved walking distance and quality of life, and (2) prevention of secondary vascular complications, especially plaque rupture leading to acute thrombotic events that may be limb-threatening and/or life-threatening. Survival is related to the severity of peripheral arterial disease (Fig. 1),[1] and different treatment strategies for IC (both medical and surgical) have variable effects on each of these therapeutic goals (Fig. 2). For example, lower limb revascularisation in those patients with Fontaine stage II may improve the symptoms of IC, but surgical procedures do not affect overall survival, whereas for the corresponding disorder in the heart (stable angina) coronary artery by-pass grafting may be indicated for relief of angina (e.g. when maximal medical therapy fails) and/or prolongation of life expectancy (e.g. when there is triple vessel disease and impaired left ventricular function).[2] Similarly, medical therapies such as aspirin have no effect on arterial symptoms, either angina or intermittent claudication, but antiplatelet therapy reduces the risk of secondary thrombotic complications in the heart, brain and lower limb, which in turn prolongs survival when used as secondary prevention.

Although the majority of patients with IC do not require surgical intervention, there is good evidence that a package of long-term medical therapies, tailored to the needs of individual patients, provides effective secondary prevention to modify atherosclerotic disease progression in major arteries (i.e. plaque stabilisation and/or regression) and in particular to reduce the risk of acute thrombotic complications such as acute limb

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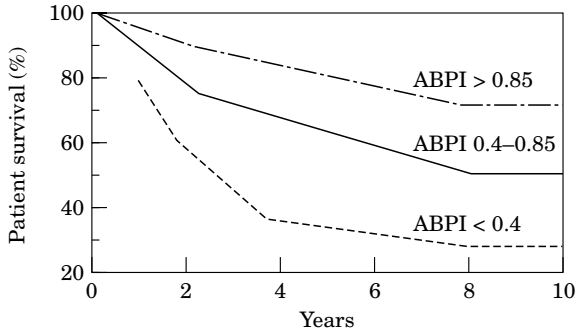

Fig. 1. ABPI is a prognostic marker. Patient survival according to ABPI, reflecting the strong association with silent or symptomatic arterial disease in the heart and brain. Adapted from [1].

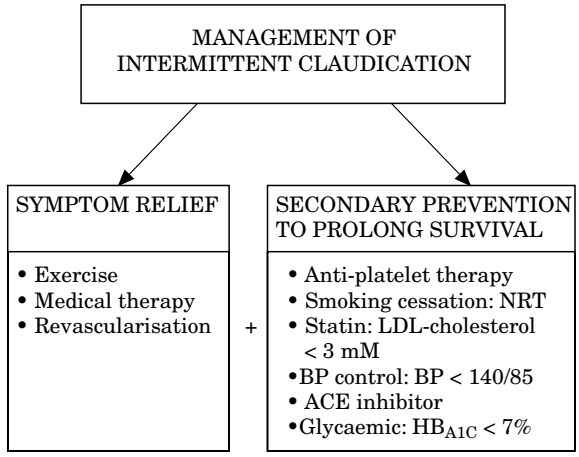

Fig. 2. Medical and surgical therapies that relieve symptoms of IC should be combined with separate treatments that provide secondary prevention, ie evidence-based interventions that reduce the risk of limb-threatening or life-threatening thrombotic complications.

ischaemia, acute myocardial ischaemia or sudden death. The term "conservative therapy", often used by vascular surgeons, is perhaps no longer appropriate for patients with IC because it implies a clinical management based largely on passive surveillance and exercise, without surgical or intensive medical intervention. This is particularly inappropriate now that randomised controlled trials have demonstrated the efficacy and safety of a range of medical therapies for prolongation of survival among patients with atherosclerotic vascular disease, whether or not this disease manifests initially as cardiac, peripheral or cerebral symptoms. The purpose of this review is to provide an update on the evidence behind effective secondary prevention that improves outcome (but not exercise-induced symptoms) in this high-risk patient group.

Clinical Trials of Secondary Prevention

Application to patients with symptomatic PAD

Because the presence of IC signifies an increased risk of mortality, both from lower limb vascular complications (e.g. acute limb ischaemia, ulceration and gangrene) and non-limb vascular complications (e.g. acute myocardial infarction, stroke or sudden death), it is essential that patients with IC are given appropriate secondary prevention. Unfortunately, most of the evidence pertaining to this patient population has been extrapolated from large secondary prevention studies undertaken primarily in patients with symptoms of coronary heart disease (CHD), some of whom also had PAD, but in practice all patients with clinical evidence of atherosclerosis – irrespective of whether the earliest symptoms of arterial stenosis localise to the heart, brain or legs – merit a package of secondary prevention treatments (Fig. 2).

Smoking cessation

Cigarette smoking is the single most powerful risk factor associated with the aetiology and clinical progression of PAD. Among patients with IC, continued smoking is clearly associated with a greater likelihood of developing disabling claudication, limb-threatening ischaemia, amputation and the need for surgical intervention.[3,4] In addition, patency rates and survival are much lower among patients who smoke following a revascularisation procedure.[5]

The increased cancer risk from smoking and the adverse effects on lung function persist for many years after a long-term smoker gives up cigarettes, but the excess risk of cardiovascular disease (i.e. death and nonfatal myocardial infarction) diminishes relatively quickly after smoking cessation, e.g. within 2–4 years.[6] Thus, patients with IC can be reassured that the vascular benefits of smoking cessation accrue almost immediately, even though the carcinogenic risk lingers on for at least another decade. This justifies a more intensive, evidence-based approach to smoking cessation in PAD patients, making use of treatments that have been shown to relieve symptoms of nicotine withdrawal and improve quit rates among motivated but nicotine-dependent smokers.

Strategies to help patients quit smoking should go beyond simple advice and retribution. Because nicotine is a drug of dependence (it is the other constituents of cigarettes that promote atheroma), spontaneous quit rates are low even among patients

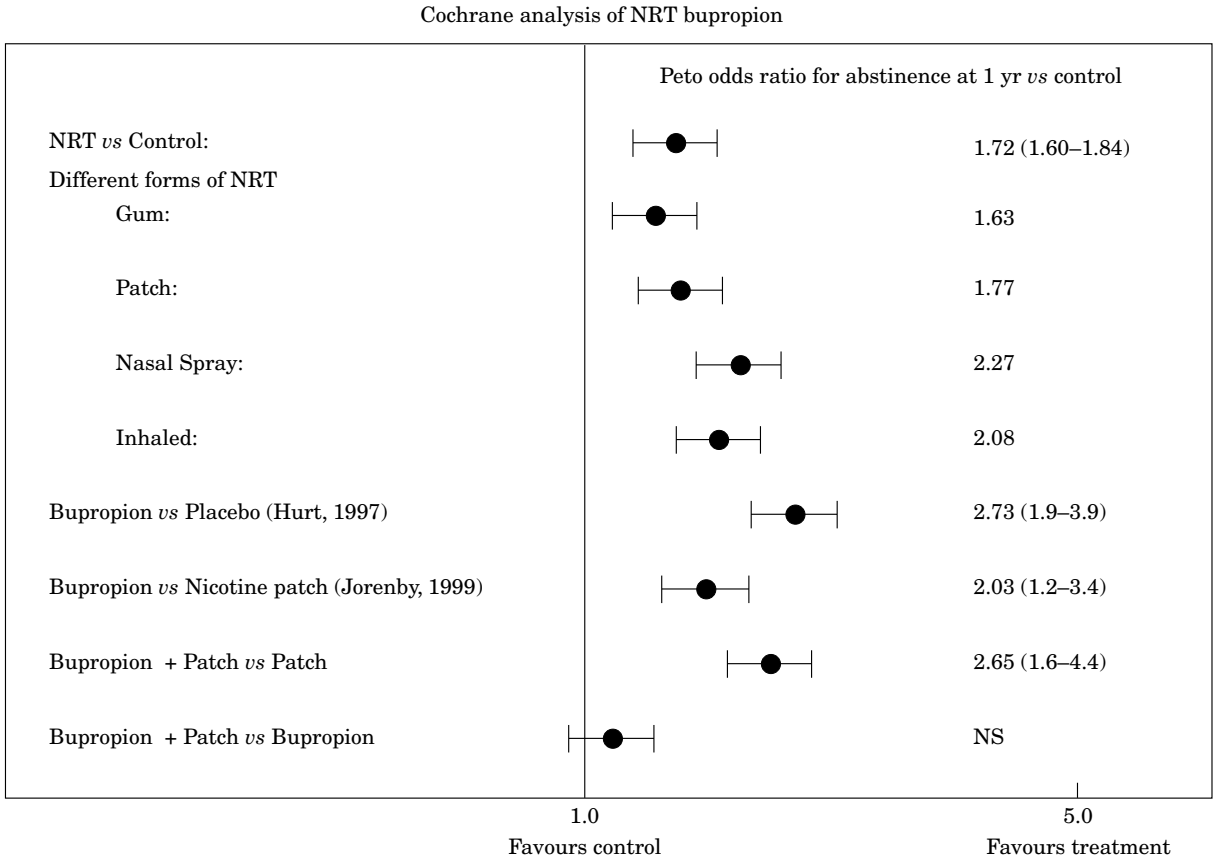

Fig. 3. The Cochrane review group has undertaken a meta-analysis of over 50 randomised controlled trials of nicotine replacement therapy (NRT)[7] and 3 studies with bupropion.[8] Both treatments in motivated patients effectively double the quit rate at 1 year, relative to placebo.

who want to give-up (<5% per year). Psychological counselling and support improves cessation rates modestly, but there have been over 50 randomised, placebo-controlled trials (RCTs) using various forms of nicotine replacement therapy (NRT) showing that quit rates after 1 year are doubled among motivated patients given active NRT and educational support. The Cochrane database has undertaken a meta-analysis of RCTs of NRT and shown beyond doubt that this approach is safe and effective (Fig. 3).[7] There has also been a Cochrane meta-analysis of a smaller number of RCTs using an oral agent, the antidepressant bupropion, as a 2-month course of therapy to relieve nicotine withdrawal symptoms (Fig. 3).[8] It too is effective but the weight of evidence favours NRT as the preferred first-line option.

Anti-platelet therapy and warfarin

Aspirin therapy, while having no effect on walking distance or symptom status, does seem to modify the clinical course of PAD. Large randomised trials have shown that aspirin, either as monotherapy or in combination with dipyridamole, delays the progression of established PAD, as assessed by serial angiography, and decreases the need for surgical revascularisation.[9,10] Aspirin also improves patency rates following revascularisation.[11] The standard dose of aspirin for secondary prevention is usually 75–150 mg daily; higher doses of aspirin provide no clear therapeutic advantage but the incidence of gastrointestinal side-effects is much higher. For example, in the secondary prevention of transient ischaemic attacks, aspirin 30 mg was no less effective than aspirin 283 mg, but had fewer complications.[12]

The CAPRIRE study[13] showed that, overall, the advantages of clopidogrel over aspirin are modest (<9%), but in the subgroup with PAD clopidogrel had a more impressive effect (Fig. 4). Thus, in patients with IC newer antiplatelet agents may be preferred instead of aspirin for secondary prevention, especially among those patients who are intolerant or allergic to aspirin. More recent studies in patients with unstable angina suggest that the benefits of clopidogrel and aspirin are additive,[14] implying that combination anti-platelet therapy will become more widely established. Pre-

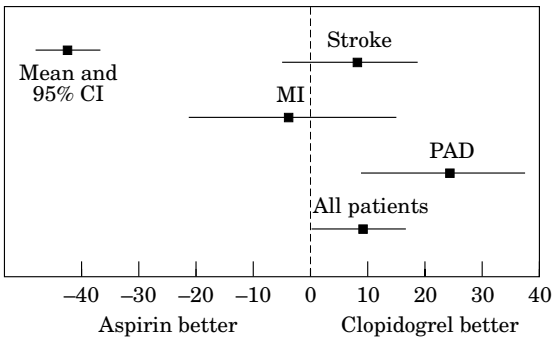

Fig. 4. In the CAPRIE study,[13] patients with PAD seem to obtain an even greater benefit with clopidogrel (relative to aspirin) compared with overall results for the entire study population.

vious combination strategies found only a marginal advantage in adding dipyridamole to aspirin following TIA, but clopidogrel + aspirin seems to be significantly more effective, at least following an episode of unstable angina (relative risk reduction was 20% vs aspirin alone for the composite primary endpoint of cardiovascular death, myocardial infarction and stroke at 1 year[14]).

Among patients with non-valvular atrial fibrillation (AF) and IC, in whom there is a particular risk of acute embolic lower limb ischaemia and stroke, RCTs and meta-analyses have clearly indicated that anticoagulation with warfarin (target INR 2.5–3.5) is superior to aspirin,[15] although in elderly patients the benefits of warfarin need to be carefully balanced on an individual patient basis against the risk of life-threatening bleeding complications, e.g. following a simple fall or via gastrointestinal blood loss. AF affects 3–5% of the entire population over 60 years old, and physicians routinely consider anticoagulation in patients with AF under the age of 85 years, even in the absence of thromboembolic symptoms, assuming the individual patient is otherwise mobile, reasonably well and able to comply with warfarin therapy and monitoring. There is no evidence to support the routine use of warfarin (instead of aspirin or in addition to aspirin) for secondary prevention in IC patients in sinus rhythm, although in some patients short-term anticoagulation may be considered surgically beneficial to avoid lower-limb complications post-operatively.

Lipid lowering therapy

Large randomised, placebo-controlled clinical trials in patients with established CHD have clearly demonstrated major reductions in cardiac (and non-cardiac) morbidity and mortality with statin therapy, e.g. the 4S study with simvastatin[16] and the CARE study with pravastatin.[17] These drugs block the rate-limiting enzyme in endogenous cholesterol biosynthesis in the liver (HMG-CoA reductase); less than 20% of circulating cholesterol (as opposed to fat, i.e. triglycerides) is derived from the diet. Therapy with simvastatin 20–40 mg or pravastatin 40 mg at night (most endogenous cholesterol biosynthesis occurs overnight), among patients with symptomatic CHD, reduced circulating cholesterol levels, on average, by 32%, with 30–40% reductions in fatal and non-fatal CHD events.[16,17] Stroke risk was also reduced in both the 4S and CARE trials (20% reduction), suggesting that the statin had extra-cardiac effects on the progression of atherosclerotic disease elsewhere in the circulation.

There seems to be a curvi–linear relationship between cholesterol reduction and improved survival in the 4S and CARE trials, i.e. a relationship of diminishing return with ever-lower levels of cholesterol. Simvastatin and pravastatin are the only statins licensed for secondary prevention; newer statins, without mortality evidence, are licensed only for "cholersterol reduction", and the recent withdrawal of cerivastatin highlights the incomplete safety database for newer statin drugs.

Relatively little is published about the subgroups of patients in these trials with PAD; only 4% of participants in the 4S study had IC at baseline.[16] Nevertheless, statin therapy is associated with plaque stabilisation and useful anti-inflammatory effects in the vessel wall, and there is nothing to suggest that this pharmacological effect is confined to disease in the coronary arteries.

A Cochrane meta-analysis of lipid-lowering therapy in patients with PAD concluded that cholesterol reduction probably reduces mortality,[18] and there is evidence that statins may alter the clinical course of PAD. For example, an analysis of the 4S study showed that the incidence of "new or worsening" IC was significantly lower in CHD patients treated with simvastatin (Fig. 5).[19] Thus, patients with symptomatic PAD and hypercholesterolaemia (total cholesterol >5 mmol/L), as well as those with overt CHD, should be treated with a statin to achieve target LDL-cholesterol levels <3 mmol/L. The benefits apply equally to men and women; those above and below 65 years of age; and especially patients with diabetes.

Blood pressure reduction

The Framingham epidemiological study provides observational evidence that patients with high blood

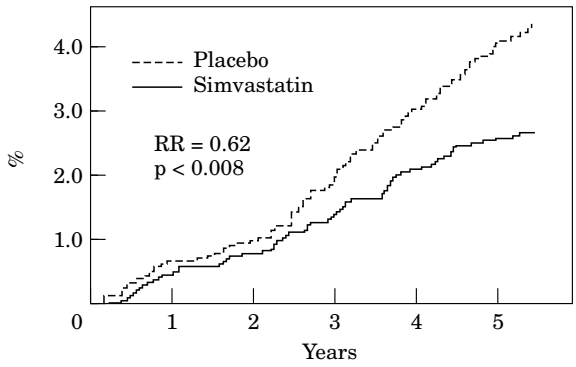

Fig. 5. Simvastatin-treated patients in the 4S study had a lower incidence of "new or worsening" IC, consistent with an effect of the statin on plaque stabilisation and regression in the legs.[19]

pressure (BP) are at greater risk of developing IC (Fig. 6).[20] Isolated systolic hypertension (ISH), in particular, is very common in the elderly and closely associated pathophysiologically with increased arterial stiffness, pressure-wave reflection and an increased systolic BP load on the heart causing LV hypertrophy. Large placebo-controlled intervention studies over the last 20 years, randomising patients at ever-lower levels of BP, have shown conclusively that even modest reductions in BP (eg 10/5 mmHg with monotherapy) translate into significant reductions in stroke (40%) and CHD (16%) mortality, and total cardiovascular mortality (30%).[21] More recently, the Hypertension Optimal Treatment (HOT) trial showed that, among treated hypertensives, aiming for lower target BP levels (<80 mmHg diastolic) achieves maximum cardiovascular protection.[22] Even non-hypertensive patients treated with BP-lowering therapy, e.g. following a stroke, also benefit from added secondary prevention.[23]

Thus, the modern definition of hypertension ("that level of BP above which treatment does more good than harm") is steadily reaching lower thresholds of BP that were previously regarded as within the "normal" range. The intervention trials in hypertension have generally not included lower-limb endpoints, but it is clear that high BP is a risk factor for IC and that ISH in particular (commonly associated with PAD) predisposes to arterial stiffness, cardiac hypertrophy and progression of the atherosclerotic process. Tight BP control (target BP <140/85 mmHg) is therefore an essential aspect of management in elderly patients with IC, and this will inevitably require combination drug therapy. Diuretics are ideal first-line treatments for elderly patients with ISH. The risk of underlying renovascular disease should always be considered in patients with PAD, treatment-resistant hypertension and mild renal impairment, especially smokers.

Success rates in achieving the current targets for BP control (BP <140/85 mmHg) among treated hypertensive patients are relatively low (<30%), even in specialist centres. This partly reflects the difficulty in lowering systolic BP, especially in the elderly, and it also reflects issues of tolerability and compliance with multiple antihypertensive therapies. Many patients develop postural symptoms or other drug-related side effects which limit the capacity to up-titrate medication in pursuit of target BP levels. Nevertheless, even modest BP reductions confer large clinical benefits and clinicians should strive for lower levels of treated BP within the context of what is acceptable and tolerable therapy for individual patients.

Angiotensin converting enzyme (ACE) inhibitors – effects beyond BP reduction

It has been well established for a number of years that ACE inhibitors prolong survival and reduce symptoms and hospitalisation rates among patients with all grades of heart failure, but the recent HOPE study showed that long-term treatment with ramipril (compared to placebo) as add-on to other cardiovascular therapies confers significant reductions in morbidity and mortality among patients with CHD (and asymptomatic patients with diabetes plus one other risk factor) who do not have left ventricular (LV) dysfunction.[24] Some 9541 patients were randomised to ramipril 10 mg or matching placebo in 19 countries for a mean follow-up period of 4–6 years. The primary endpoint of combined cardiovascular death, MI and stroke was reduced by 22% ($p<0.000002$); and all-cause mortality was 17% lower ($p<0.0035$). Secondary endpoints included significantly fewer ramipril-treated patients needing a revascularisation procedure (cardiac or peripheral) (relative risk reduction 12%, $p<0.0015$). Vitamin E, which was also evaluated in the HOPE trial (vs placebo) using a 2×2 factorial design, had no significant effects.

A subgroup analysis of 4046 subjects with PAD in the HOPE trial suggests that this particular subgroup gains even more benefit from ramipril compared with those without PAD (Fig. 7).

This very large and well conducted clinical trial provides persuasive evidence that effectively any patient with symptomatic atherosclerotic disease (or asymptomatic diabetics with one other risk factor), including those with IC, should be treated with an ACE inhibitor as part of secondary prevention, irrespective of other background medical therapies and even if they are normotensive with normal LV function.

Because patients in the HOPE study were already

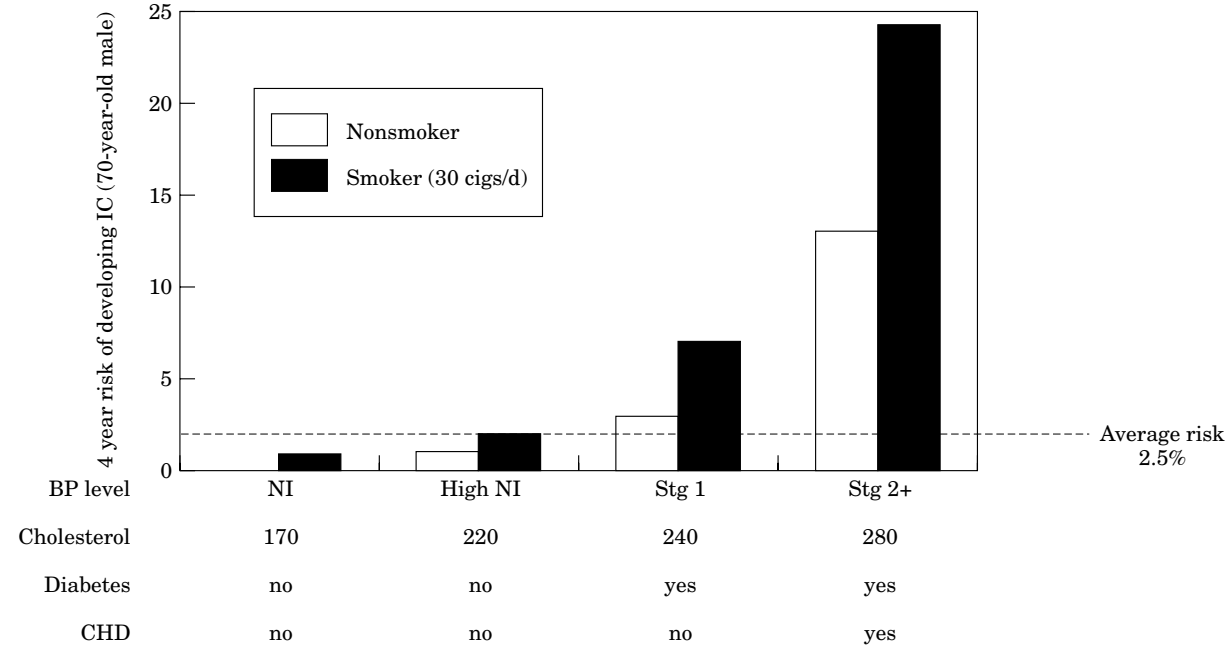

Fig. 6. The relationship between BP and IC. Eastimated 4-year probability of intermittent claudication in 70-year old men in the Framingham Heart study according to category of normal (NI), high-normal (high NI), stage 1 and stage 2 hypertension. The multiplicative interaction between BP and other risk factors is also illustrated. Reproduced from [20].

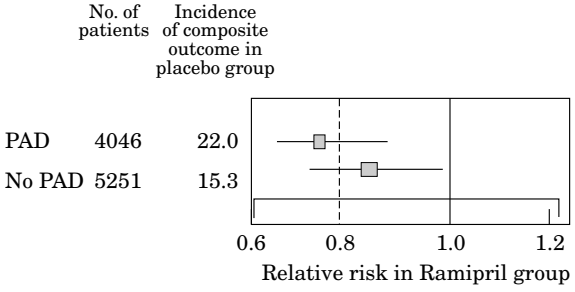

Fig. 7. The results of the HOPE study[24] according to whether patients had PAD or not at baseline. The benefits of ramipril 10 mg/d were at least as good (if not better) in the PAD subgroup.

treated with various BP-lowering and other cardiovascular therapies, e.g. anti-anginals, baseline BP prior to the addition of ramipril or placebo was relatively good (139/79 mmHg). Only 46% of study participants had a prior diagnosis of hypertension. The net antihypertensive effect of ramipril was only 2/3 mmHg, which seems unlikely to explain the considerable benefits in terms of prolonged survival. Thus, it seems likely that ACE inhibitors confer protective effects on the atherosclerotic process that are clinically important, e.g. improved endothelial function, over and above the benefits attributable to BP reduction.

The notion of non-BP-mediated benefits of ACE inhibitors in secondary prevention is also supported by the recent PROGRESS study,[23] in which non-hypertensive patients received considerable benefits from secondary prevention using ACE inhibitor based therapy (perindopril) which could not be solely attributable to the antihypertensive effect. For example, perindopril-based therapy reduced the risk of recurrent stroke by 32% and 27% in hypertensive and non-hypertensive patients, respectively, and the corresponding reductions in all major vascular events were 29% and 24% ($p<0.001$).[23]

Thus, the significance of the HOPE study (a single but very large, well conducted trial) would suggest that all patients with symptomatic PAD, where possible, should receive an ACE inhibitor in addition to their other cardiovascular therapies. ACE inhibitors are contra-indicated in patients with bilateral renal artery stenosis (RAS), or unilateral RAS in a single functioning kidney. They should otherwise be used with caution in the presence of renal impairment and if there is a suspicion of possible RAS. Because the incidence of RAS is quite high in the PAD population, it is therefore essential to use a low starting dose and to check the serum electrolytes 1 week and 1 month after starting or increasing ACE inhibitor therapy. In the HOPE trial (and other pragmatic ACE inhibitor studies), where patients were not screened in detail to exclude RAS, the actual incidence of complications (e.g. renal failure) was surprisingly low.

Glycaemic control in diabetes

Patients with diabetes tend to have more severe, often distal and diffuse, multivessel PAD that is less amenable to revascularisation, and restenosis in diabetics is a particular problem following angioplasty.[25] The risk of lower limb ulceration is exacerbated by microvessel disease and neuropathy, as well as PAD, and amputation rates among diabetics (mainly distal amputations) are 40-fold higher than in age-matched nondiabetic controls.[26]

Type 2 diabetes is very much a clinical syndrome in which hyperglycaemia is only one facet; other features include insulin resistance, hypertension, obesity and dyslipidaemia. The major benefit of tight glycaemic control is in the prevention of microangiopathy (retinopathy, nephropathy, neuropathy), whereas tight BP control has a much greater impact on macrovascular complications and death rates. For example, in the UK Prospective Diabetes Study (UKPDS), every 10 mmHg reduction in systolic BP was associated with a 12% reduction in any diabetes-related complication; 15% reduction in death related to diabetes; 11% reduction in MI; and 13% reduction in microvascular complications.[27] Thus, BP reduction ameliorates microvessel complications and (unlike tight glycaemic control) reduces diabetes-related deaths.

Increasing Hb_{A1c} is still a risk factor for large vessel complications,[28] but the principal benefits of glucose reduction are in microvessel protection and, for the lower limb, prevention of neuropathy and secondary complications such as ulceration and infection. For every 1% increase in Hb_{A1c} there is a 28% increased risk of death, independent of age, BP, serum cholesterol and smoking status.[28] More importantly, however, over 80% of the population excess mortality risk associated with HbA1c occurs in men with HbA1c concentrations of 5–6.9% (which is the majority of the population and includes people who, by definition, are not diabetic).[28]

Multiplicative interaction of risk factors

Most patients with IC have more than one modifiable risk factor, and it is important to remember that risk factors have greater-than-additive effects on overall risk (Fig. 6).[20] Thus, a clinical strategy of multiple risk factor intervention is likely to yield significantly greater benefits than incomplete treatment with targeted secondary prevention of single risk factors.

Table 1.

Experimental studies of potential new secondary prevention therapies are focusing on:

- reversing endothelial dysfunction (an early hallmark of arterial disease) by restoring normal vasorelaxation, antithrombotic mechanisms and inter-cellular adhesion;
- plaque stabilisation and regression via blocking inflammatory processes;
- prevention of neointimal hyperplasia and restenosis following balloon injury during angioplasty;
- changes in intima-media thickness to reflect slowing of the atherosclerotic progression;
- use of crosslink breakers to inhibit advanced glycosylation (AGE) processes in the mediation of vascular ageing and vascular stiffness.

Therapeutic Targets for New Vascular Disease-modifying Agents: the Future of Secondary Prevention

RCTs of sufficient size and duration to assess treatment effects on morbidity and mortality are the ultimate benchmark standard for establishing the role of a new drug in long-term secondary prevention. But advances in the understanding of how atherosclerotic disease develops and progresses has identified several target mechanisms for new agents aimed at achieving delayed progression, plaque stabilisation and even regression of arterial disease (Table 1).

For example, recent evidence has shown using ultrasound that ramipril treatment in the HOPE study retards the progression of atherosclerosis, as demonstrated by the annual increase in carotid intima-media thickness;[29] adjuvant anti-platelet therapy (clopidogrel + aspirin) provides improved outcomes following percutaneous angioplasty;[30] and statins improve endothelial function, independent of their lipid-lowering effects.[31] In addition, there is recent evidence that cilostazol (a symptom relieving drug in IC) inhibits neointimal hyperplasia and restores endothelial function following balloon injury,[32] and increases vascular endothelial growth factor (VEGF) mediated collateral vessel formation.[33]

Conclusions

IC is a common and disabling symptom associated with increased cardiovascular mortality due to acute thrombotic complications superimposed on a ruptured plaque causing limb-threatening or life-threatening ischaemia. The overall management of patients with IC should include treatments (medical, surgical and

lifestyle) that improve symptoms and functional performance, but this should be combined with evidence-based therapies to prevent secondary vascular complications. Large randomised clinical trials have shown that statin therapy, tight BP and glycaemic control, anti-platelet agents and ACE inhibitors slow the progression of arterial disease, promote plaque stabilisation and regression, with fewer thrombotic events. In addition, evidence-based therapies, especially NRT, double smoking quit rates at 1 year, which in turn accrues an early and worthwhile reduction in overall vascular risk. New therapies in the future may provide added secondary prevention by directly improving endothelial function, reducing neointimal hyperplasia (especially post-angioplasty), and preventing crosslink formation in age-related glycoxidation processes in the vascular wall.

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