Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, which may shed indirect light on the merit of use of amiodarone on the grounds of its superior efficacy. On the other hand, a longer duration of follow-up would allow sufficient time for development of amiodarone organ toxicity with its attendant significant costs. The major adverse effects of sotalol and propafenone are predominantly seen early in the treatment course, a time frame that the current study would have captured. The long-term toxicity of amiodarone may result in irreversible organ damage with significant chronic care cost implications. Although surveillance testing for amiodarone toxicity was accounted for in the current analysis, this cost may escalate over time as the cumulative dose increases, accompanied by a progressive increase in lung, thyroid and ocular abnormalities.

Finally, the low cost estimates in this study for certain procedures may actually underestimate the beneficial effect of amiodarone. Thirty Canadian dollars for a Cardiology consultation ($19 US, 22 Euros) or $63 for a cardioversion ($39 US, 44 Euros) represents a significant undervaluation of physician and hospital services in most areas. For example, the US Medicare fee schedule lists $118 US dollars as the charge for a typical clinical consultation. The resultant cost difference between the two treatment strategies in most practice settings is likely significantly higher than the estimate from this trial.

Most clinicians are not surprised by these data, with superior efficacy of amiodarone suggested by other trials and clinical experience showing efficacy in refractory patients. Many will still choose to use propafenone or sotalol as first line agents, notwith-standing these data, especially in patients that are not considered at high risk for proarrhythmia, to minimize longstanding exposure to amiodarone. Despite the aforementioned limitations, the authors are to be commended for a strong study that has convincingly demonstrated the superior antiarrhythmic efficacy and short-term cost efficacy of amiodarone in management of atrial fibrillation compared to sotalol and propafenone. Long term follow-up of this patient population may verify the ongoing cost benefit of amiodarone in reducing the cost of atrial fibrillation management, or it may confirm the downside of prolonged exposure to amiodarone.

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which medication(s) to select from the therapeutic arsenal?

Before addressing these questions, three important facts should be recalled. First, peripheral arterial disease is associated with a high risk of fatal and non-fatal cardiovascular ischaemic events, in direct proportion to the severity of the disease evaluated by the ankle–brachial pressure index\(^1,2\). Indeed, one fourth of claudicants will die within 5 years following diagnosis, mostly as a consequence of myocardial infarction, stroke or aortic aneurysm rupture, and another 25% will experience a non-fatal cardiovascular event during that period. Second, in spite of this poor prognosis, peripheral arterial disease appears to be the orphan cardiovascular disease, half of claudicants being not recognized as such. Moreover, once diagnosed, they have significantly less chance of receiving appropriate antithrombotic prophylaxis than patients with coronary or cerebrovascular disease\(^3\). Thus, awareness of the disease should be promoted, as should simple diagnostic tools, in order to identify a larger population of high risk patients who should be given appropriate cardiovascular counselling to aid prevention\(^3\). Third, the poor general prognosis of claudicants contrasts sharply with the relatively benign course of the local disease: only one fourth of claudicants experience symptomatic deterioration, and 2% eventually lose the affected leg\(^4\), which legitimizes a nihilistic therapeutic attitude among some practitioners.

Nevertheless, patients complain of a reduction of walking distance that impairs the quality of daily life. Three options are theoretically available to relieve symptoms: (1) revascularization (either surgically or by interventional radiology), (2) walking exercise, and/or (3) specific medication. All but walking exercise can produce side effects or complications. They should therefore be proposed only to patients in whom the potential benefits outweigh the risks of treatment. Thus, revascularization procedures can be discussed when the walking distance is so short that it is unlikely to be increased substantially by walking exercise and/or when the lesion is localized on the iliac artery with unlikely collateral vessel development. On the other hand, walking exercise is often a true practical alternative to revascularization, especially if the lesions are located on the femoropopliteal segment. In such patients, a substantial increase in the walking distance can be achieved by supervised walking exercise\(^5\). Few randomized trials, however, have compared directly supervised and unsupervised walking training, but advice alone is often considered insufficient\(^4\). The greatest likelihood of success, with at least a doubling of the initial walking distance, is thought to be obtainable by walking to near maximum pain in a supervised programme lasting at least 6 months\(^5\).

Besides physical training, dozens of medications have been proposed over the last three decades to improve the symptoms of claudication, including sulodexid, pentoxifylline, buflomedil, naftidrofuryl, ketanserin, ticlopidine, cilostazol, and, as highlighted in the present issue, sulodexide\(^6\). Initial studies on the effects of oral medication on claudication were methodologically poor\(^7\), and their results did not convince clinicians to prescribe the drugs on a large scale except in a few countries. Nevertheless, larger, methodologically sound studies have shown that pentoxifylline\(^8\), and cilostazol\(^9\) are able to increase walking distance in a statistically and clinically meaningful manner, while the potential benefit of ketanserin was unequivocally refuted\(^10\). Interestingly, ticlopidine was shown both to increase walking distance and reduce cardiovascular risk, but this was the result of a pooled analysis of small studies\(^11\). However, this agent causes rare but serious haematological side effects, and is also cumbersome to use because it requires monitoring the white blood cell count every 2 weeks.

On the other hand, because claudicants must be considered at high risk of cardiovascular events, they should be prescribed antiplatelet agents such as aspirin — as evidenced indirectly by a meta-analysis\(^12\) — or clopidogrel, which was found to be slightly superior to aspirin in a large scale trial\(^13\). These agents markedly reduce the risk of coronary events and stroke, an effect that might be enhanced by the use of statins. None of them, however, has a proven effect on claudication symptoms.

In this context, what are the lessons of the Italian study with sulodexide\(^6\) for the clinician? First, it implies that no currently available medication can meaningfully improve claudication symptoms because the trial design used a placebo as a comparison. One might, however, question why aspirin was only ‘allowed’ in these study patients and not given to all of them, as recommended by the American College of Chest Physicians (ACCP) Consensus Conferences on Antithrombotic Therapy\(^14\). Second, it demonstrates in a well designed, double-blind study that the new agent is associated with a doubling of the pain-free walking distance three times more often than placebo. This end-point was achieved in one fourth of the patients, diabetics and non-diabetics, who received the active drug. Third, sulodexide induced a significant decrease of fibrinogen, the main component of plasma viscosity, thereby offering a plausible, and at least partial, explanation for the mechanism of action of the compound. Fourth, the objective increase in walking distance was accompanied by a subjective improvement reported...
by the patients. Such a finding is absolutely valid in a double-blind study, and is of great importance because treatment of symptoms should primarily improve quality of life. However, the value of doubling the walking distance may not necessarily represent a true improvement of the patient’s daily life. Fifth, perhaps the most remarkable study result was the more than 50% decrease in adverse cardiovascular events compared to placebo (four events against 11 in each group of 143 patients). Although marginally not significant at the conventional $P$-level of 0.05, due to a sample size that was derived without the a priori hypothesis of studying adverse cardiovascular end-points, this finding supports the hypothesis of a protective cardiovascular effect of the drug as suggested in a previous trial\[15\]. Of course, this hypothesis assumes that aspirin users were equally distributed between the two study groups.

In conclusion, patients with intermittent claudication due to peripheral arterial disease need (1) strict control of risk factors, especially smoking, along with antiplatelet medication; (2) walking training, preferably in a formal, supervised programme; (3) in a minority of selected cases, surgical or radiological revascularization; and (4) if the latter is not applicable or if walking training is not sufficient, a drug such as sulodexide that increases walking distance. Future trials should test this drug against a supervised exercise programme plus aspirin for everyone and focus on claudication symptoms and adverse cardiovascular events.

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