Can We Use β-Blocking Agents in Patients With Peripheral Artery Disease?

Denis L. Clement

Peripheral artery disease (PAD) has been for many years a chapter in cardiovascular diseases that did not attract the interest of clinicians. Intermittent claudication, the most common clinical manifestation of PAD, was considered a rather unimportant symptom. Several new findings published during the last decade have profoundly changed our views on PAD. First, intermittent claudication significantly impacts on the quality of life and on the activities of the patients experiencing it. Moreover, and at least as important, a number of large-scale studies and registries unraveled severely increased risk for coronary and cerebrovascular morbidity and mortality in PAD patients. In fact, this should not surprise us, because the most frequent cause of PAD is, by far, atherosclerosis. The increased risk is of particular importance, because many patients with proven PAD are completely asymptomatic. In such cases, PAD is only detected by clinical examination (absent peripheral pulses) or by measuring ankle brachial pressure index. Whichever way they are detected, the increased risk is present whether the disease is symptomatic or not. Therefore, with all of this in mind, physicians and scientists alike start to realize that PAD should be seen not only as a local problem but also as a marker of atherosclerosis elsewhere in the body.

As a consequence, treatment of PAD patients should be oriented at symptoms, if present, but above all, at controlling total CV risk (Table). Symptoms of intermittent claudication are best treated with regular training and smoking cessation; pharmacological approach by drugs like cilostazol or nafidrofuryl can further improve claudication distance. Total risk is controlled by adaptation of lifestyle and antiplatelet therapy. Hypertension often is associated with PAD; systolic hypertension is especially highly prevalent in PAD patients, most likely because of stiffening of the large arteries. Thus, antihypertensive drugs will be necessary in many PAD patients.

There is no convincing evidence of superiority of one antihypertensive drug over another with respect to controlling hypertension in PAD patients or affecting their claudication distance. Slightly better results are obtained by ACE inhibitors, and in some studies an increase in muscle blood flow has been shown; this was accompanied by a limited increase in walking distance (for literature review, see Reference 5).

There has been a long-standing controversy about using β-blocking agents in hypertensive PAD patients. It was postulated that, by blocking the β2-dependent vasodilating effect, the peripheral α-1 effect may predominate, leading to vasoconstriction and increase in limb ischemia. However, except in patients with critical limb ischemia, such a negative finding has never convincingly been documented. On the contrary, several studies, including a meta-analysis on patients with intermittent claudication, were unable to show a negative effect of β-blocking agents in these patients.

This question has been reopened in the study of Espinola-Klein et al because of the availability of β-blockers with vasodilating capacities, such as nebivolol. Such vasodilator properties could be helpful in case of decreased muscle blood flow as exists in many PAD patients, especially while walking.

A total of 128 patients with intermittent claudication and essential hypertension were included. Treatment with nebivolol or metoprolol was administered double blind and in randomized order during 48 weeks. Absolute claudication distance improved significantly in both patient groups (P<0.05 for both), with no difference across treatments at the end of the study. However, the initial claudication distance was higher in the nebivolol group (increased by 33.9% compared with baseline) than in the metoprolol group (increased by 16.6%). Both drugs were equally effective in lowering blood pressure.

These results should stop all further speculations on a possible negative effect of β-blockers in the treatment of hypertension in stable PAD patients; the data did clearly show that there is no decrease in walking distance but rather an increase during the 48-week follow-up of this large cohort of patients. Such an increase has often been observed in long-term follow-up studies of intermittent claudication, as such patients tend to be well compliant with all advice on lifestyle adaptation and training given at the time of the regular controls. For those clinicians who still have doubts on the effects of β-blockade in these patients, the results of the ankle brachial pressure index during β-blockade should convince them: this was done in the present study and again showed no decrease but even a significant albeit small increase of ankle brachial pressure index. It should be noted that recording an ankle brachial pressure index is a useful tool in these patients both for diagnosis and follow-up; it provides valuable information on the degree of stenosis and, moreover, it is an excellent technique to estimate prognosis.
Table. Management of Hypertension in Patients With Peripheral Artery Disease

<table>
<thead>
<tr>
<th>Intermittent Claudication*</th>
<th>Management of</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Total Cardiovascular Risk</td>
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<tr>
<td>Lifestyle adaptation</td>
<td>Lifestyle adaptation</td>
</tr>
<tr>
<td>Regular training</td>
<td>Antiplaet therapy</td>
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<tr>
<td>Stop smoking</td>
<td></td>
</tr>
<tr>
<td>Drug treatment (cilostazol, nafidrofuryl, etc)</td>
<td>Drug treatment</td>
</tr>
</tbody>
</table>

*Many patients are asymptomatic.

Nebivolol did significantly better than metoprolol with respect to initial claudication, that is, first pain when walking on the treadmill. Absolute claudication distance was similar for both drugs. In general, initial claudication pain responds better to any drug therapy than the absolute distance where maximal ischemia is urging the patient to stop walking. The greater improvement with nebivolol than with metoprolol on initial pain may well be relevant in daily life, because patients most often stop when claudication pain starts; they rarely pursue walking until maximal pain in contrast to what is done on the treadmill in the clinic. It would be interesting to confirm such findings using tools like claudimeters, which are able to measure the number of steps or the distances walked by the patient in their normal environment. The treadmill is considered a reliable and objective tool to measure walking distance, but it still is, to some extent, artificial and not always similar to what patients experience in normal life.

β-Blockade could even be indicated to treat hypertension in PAD patients. As mentioned above, PAD patients have a clearly increased risk to develop cardiovascular morbidity and mortality should be highlighted; to this extent, lifestyle adaptation and platelet inhibition play essential roles. All of the clinicians taking care of PAD patients with hypertension should devote their best efforts to the management of this special category of patients.

In any case, the results of the present study bring another piece of evidence that β-blocking agents can indeed be used in patients with stable PAD. Moreover, because first claudication pain was postponed in the patients randomized to nebivolol, β-blockers with vasodilating capacity may be preferred.

Disclosures

None.

References

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