

## Medical management of PAD: Expand or consolidate?

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In this issue of the *Annals*, a rapid review of adherence to evidence-based medical treatment<sup>1</sup> highlights an important and underappreciated aspect of the management of patients with peripheral arterial disease (PAD). It is easy, upon meeting a patient, to prescribe appropriate medication in an outpatient setting and believe that one's job is done; that the patient's risk has been optimised. It is clear from this review, and from previous work,<sup>2</sup> that this is not the case.

The authors conclude that adherence to evidence-based medical treatment is extremely variable, and that undertreatment is common. The variability in adherence is probably less surprising than how low adherence rates are in most of the studies compiled. For lipid-lowering medications, some of the larger and more recent included studies show encouraging adherence rates; however, only 10 of the 41 studies on lipid-lowering drugs report over 75% adherence. Over half (24/42) of the included studies, including the majority of the larger studies, showed between 50 and 75% adherence, while over 1 in 6 studies (7/41) reported adherence below 50%. The adherence to antiplatelet medication is more encouraging. While the majority of larger reports again fall between 50 and 75%, a much greater proportion (17/31) report adherence above 75%, and far fewer (3/31) below 50%.

There are often legitimate reasons for non-adherence with or non-prescribing of all of these medications, such as muscle cramps or liver function derangement with statins, or bleeding complications and gastrointestinal (GI) upset with antiplatelets. The use of "any antiplatelet" is more appropriate than singling out aspirin, as this reflects current guidelines and some patients may take clopidogrel given its more favourable side-effect profile regarding GI bleeding.<sup>3</sup> The lowest adherence rate in the entire review was in a study recording only aspirin use, which is perhaps instructive. This study is an outlier, and had other antiplatelets been included, the result may have been markedly different or at least more in line with the other studies.

Interpretation is more difficult in the case of antidiabetic and antihypertensive medication. The authors are of course limited in the inferences that can be drawn from each study, given the heterogeneity in reporting of both hypertensive patients and hypertensive medication use in individual publications. It is clear however that there is extreme variability in adherence to medication. It is encouraging to see that adherence rates have generally improved over time but it is clear as the authors suggest that improved adherence strategies are needed along with implementation studies to gauge the effect of this. The impact of nurse-led clinics to maximise adherence reported by Sillesen et al.<sup>4</sup> suggests a way forward in this regard. Anecdotally, in our practice, it is common to find patients have stopped, or their primary care doctor has stopped, a medication outright when dose alteration or a change to another medication in a similar class may have been more appropriate—such as using a different statin or changing antiplatelet.

Numerous recent studies have shown that a variety of medications can help either with symptom control or in reducing adverse cardiovascular events in patients with PAD. When viewed in the context of this ever-expanding repertoire of medications, this latest review forces a separate question to be confronted: in the attempt to medically manage PAD, should the focus be to introduce new and improved treatments into practice? Or should we first aim to maximise adherence to existing guidelines?

Large multicentre randomised trials have shown a modest but significant benefit in patients with PAD, both primarily and after revascularisation, to taking a combination of aspirin and low-dose rivaroxaban.<sup>5,6</sup> Pentoxifylline and cilostazol are sometimes prescribed to help in the management of PAD symptoms. A Cochrane review showed uncertain benefit with pentoxifylline due to poor-quality heterogeneous evidence;<sup>7</sup> in another review, cilostazol was considered beneficial in improving walking distance, but with an increase in adverse side effects that were generally mild and treatable.<sup>8</sup> Neither of these medications are

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recommended in the European guidelines, although cilostazol is recommended by the American College of Cardiology/American Heart Association (ACC/AHA).<sup>9</sup> Both are frequently prescribed.

These medications all show promise in the management of PAD. One must wonder however what negative effects their addition may have. A previously well claudicant could in a single outpatient visit be commenced on aspirin and a statin, cilostazol and low-dose rivaroxaban. This patient could go from no daily medications to 4, with more than once daily dosing. A similar patient with diabetes or hypertension, or both, could soon be on 6 or more separate medications with complex dosing schedules. That is to say nothing of the comorbid patient who may already be on multiple medications.

This presents 3 significant challenges. First, more than once daily dosing is a significant risk factor for non-adherence.<sup>10,11</sup> In both the COMPASS and VOYAGER PAD trials, non-adherence to trial medications was high, with a 16.5% overall non-adherence<sup>6</sup> and annualised discontinuation rate of 14% per year,<sup>5</sup> respectively. It is reasonable to expect that, outside the more controlled conditions of a randomised trial, real-world adherence rates could be lower still. A large part of this may have been due to the association between multiple daily dosing and non-adherence.

Second, as the authors of this review have correctly identified, polypharmacy is one of a number of patient and physician factors that can contribute to non-adherence. Multiple medications can be a necessary evil in the appropriate management of many conditions, and in younger patients many medications may be manageable. However, in older adults who often have multiple comorbidities, more medications and altered physiology, polypharmacy increases the risk of adverse drug events.<sup>12</sup> These patients may be prone to prescribing cascades where additional medications are prescribed for new symptoms or ailments without first considering that existing medications may be the cause of those symptoms. This can lead to increasingly complex medication regimens, with each additional medication increasing the risk of side effects,<sup>13</sup> rates of medication errors<sup>13</sup> and non-adherence.<sup>11</sup>

Finally, the additional medications that can be used in PAD outside those highlighted in the review, such as cilostazol and rivaroxaban, are not benign. Cilostazol poses a risk of polypharmacy in treating its multiple “easily managed” side effects. The combination of aspirin and rivaroxaban will lead to an increased bleeding risk compared to aspirin alone. While the

benefits may outweigh the risks in COMPASS<sup>6</sup> and VOYAGER PAD,<sup>5</sup> it is not certain how this plays out in the real world with concurrent use of hypoglycaemic medications and antihypertensives by frail patients who tend to be underrepresented in trials.

As newer treatments emerge and their evidence base grows, their adoption into guidelines and clinical practice must take into account the population in which PAD predominates. Our patients tend to be older, frequently have comorbidities and are all at high risk of polypharmacy. Younger and fitter patients may benefit from an aggressive, multimodal approach to medical management of their PAD. For others, that approach means increased risk of errors, non-adherence, and side effects. It is important that the treatments we prescribe for older adults in particular, align themselves with “what matters most” to that particular person. Current Emergency Cardiac Care (ECC) and ACC/AHA guidelines recommend lifelong aspirin and a statin, as well as management of hypertension and diabetes where indicated, in patients with PAD. Adherence to these medications is already lower than what we would hope, so an important step before considering addition of further medications is to focus on ensuring patients are appropriately prescribed, and compliant with core evidence-based best medical therapy.

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