

Symptoms of peripheral arterial disease: ramipril

Evidence summary

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Key points from the evidence

The content of this evidence summary was up-to-date in June 2015. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

The evidence for the efficacy of ramipril in relieving the symptoms of peripheral arterial disease is very limited.

Two small RCTs ([Ahimastos et al. 2006](#), n=40 and [Shahin et al. 2013a](#), n=33) found that, compared with placebo, over 24 weeks, ramipril 10 mg daily improved maximum and pain-free walking times and distances in people with stable intermittent claudication, a symptom of peripheral arterial disease. However, while these differences were statistically significant, the clinical importance of the results is unclear. No adverse effects were reported in 1 study. In the other study, the adverse effect most often reported with ramipril

was cough, which led to discontinuation in some cases.

The studies have many limitations and ramipril has not been compared directly with other treatments for intermittent claudication. Higher quality evidence on the efficacy and safety of ramipril is needed in order to determine its place in therapy.

A [third study](#) (n=212) was originally included in this evidence summary but has now been removed. This follows a [statement](#) published in the Journal of the American Medical Association (JAMA), which advises that the study has been retracted after the lead author admitted to fabricating the results of this and [a related study](#). This author was also the lead author for another study included in this evidence summary ([Ahimastos et al. 2006](#)) and it is unclear whether the integrity of that study is also affected. However, because of the paucity of evidence, the decision has been taken to present the results, with the proviso that the data may not be robust.

Regulatory status: Ramipril is licensed for reducing cardiovascular risk in people with peripheral arterial disease, but its use to treat symptoms of peripheral arterial disease is off-label.

Effectiveness	Safety
<p>Compared with placebo over 24 weeks, ramipril 10 mg daily statistically significantly improved:</p> <ul style="list-style-type: none"> • mean maximum walking time and mean pain-free walking time (Ahimastos et al. 2006, n=40; both p<0.001; clinical importance unclear) • mean maximum walking distance and mean pain-free walking distance (Shahin et al. 2013a, n=33; both p=0.001; clinical importance unclear). 	<ul style="list-style-type: none"> • According to the summary of product characteristics for Tritace, common adverse effects of ramipril (seen in between 1 in 10 and 1 in 100 people) include headache, dizziness, cough, sinusitis, dyspnoea, gastrointestinal disturbances, rash, muscle spasms, myalgia, hyperkalaemia, hypotension, syncope, chest pain and fatigue. • No adverse effects were reported the study by Ahimastos et al. (2006). In Shahin et al. (2013a), the adverse effect most often reported with ramipril was cough, which led to discontinuation in some cases.

Patient factors	Resource implications
<ul style="list-style-type: none">• Renal function should be assessed before and during ramipril treatment, particularly in people with renal impairment.• The results of the studies may not be generalisable to people with certain comorbid conditions (for example, disease limiting mobility or renal impairment).• Most of the participants in the studies were white and it is known that ACE inhibitors are less effective for treating hypertension in people of African or Caribbean family origin; therefore, the studies may not apply to this population.• It is not known how ramipril compares with other treatments for intermittent claudication.	<ul style="list-style-type: none">• The cost of 28 days' treatment with ramipril 10 mg is £1.28 for capsules, £1.32 for tablets and £358.40 for 2.5 mg/5 ml oral solution (Drug Tariff, October 2015).

Introduction and current guidance

Peripheral arterial disease, also known as peripheral vascular disease, is a condition in which arteries that carry blood to the legs (or less commonly the arms) are narrowed or blocked. Peripheral arterial disease is generally caused by atherosclerosis and it is associated with an increased risk of cardiovascular events even when it is asymptomatic. The most common initial symptom of peripheral arterial disease is pain in the legs while walking, which is relieved by rest, known as intermittent claudication.

Treatment options for intermittent claudication include management of cardiovascular risk

factors (for example, smoking, obesity, diabetes, hypertension, using antiplatelet drugs and statins), supervised exercise and vasoactive drug treatment (naftidrofuryl oxalate). See the NICE guideline on [lower limb peripheral arterial disease: diagnosis and management](#) for more information.

Full text of [introduction and current guidance](#).

Product overview

Ramipril is an angiotensin-converting enzyme inhibitor (ACE inhibitor) that is licensed for treating hypertension, renal disease and symptomatic heart failure. It is also licensed for the secondary prevention of acute myocardial infarction, and the reduction of cardiovascular morbidity and mortality in people with manifest atherothrombotic cardiovascular disease (including peripheral arterial disease) or diabetes with at least one cardiovascular risk factor. See the [summary of product characteristics for Tritace](#) for more information.

This evidence summary considers the evidence for using ramipril to treat the symptoms of peripheral arterial disease (intermittent claudication), rather than for reducing cardiovascular risk in people with peripheral arterial disease. The use of ramipril to treat symptoms of peripheral arterial disease is off-label.

Full text of [product overview](#).

Evidence review

- This evidence summary discusses 2 randomised controlled trials (RCTs: [Ahimastos et al. 2006](#) and [Shahin et al. 2013a](#) [n=40 and n=33 respectively]) that evaluated ramipril for treating people with stable intermittent claudication and concurrent medical treatment, and no comorbid conditions limiting walking ability or renal impairment. Participants were randomised to receive ramipril 10 mg daily or placebo for 24 weeks (including a 2-week dose titration period using ramipril 5 mg daily in [Shahin et al. 2013a](#)).

- [Ahimastos et al. \(2006\)](#) found that ramipril 10 mg daily statistically significantly increased mean maximum walking time (451 seconds, $p < 0.001$) and mean pain-free walking time (227 seconds, $p < 0.001$) compared with placebo over 24 weeks. [Shahin et al. \(2013a\)](#) reported walking distance rather than time and found that, compared with placebo, ramipril 10 mg daily statistically significantly improved mean maximum walking distance (131 m, $p = 0.001$) and mean pain-free walking distance (122 m, $p = 0.001$) over 24 weeks. Although unclear from the data reported, improvements from baseline in the studies may be [clinically important](#) (see the [evidence review](#) section of this evidence summary for more details).
- [Ahimastos et al. \(2006\)](#) found that ramipril 10 mg daily improved Walking Impairment Questionnaire distance, speed and stair-climbing scores at 24 weeks compared with baseline (all $p < 0.001$) but no comparisons with placebo are reported.
- [Shahin et al. \(2013a\)](#) found no statistically significant differences between the groups in the 3 quality of life measures used in the study (scores ([EQ-5D](#), [Short-Form 36 Health Survey \[SF-36\]](#) and [King's College Hospital's vascular quality of life questionnaire \[VascuQoL\]](#))).
- According to the [summary of product characteristics for Tritace](#), common adverse effects of ramipril (seen in between 1 in 10 and 1 in 100 people) include headache, dizziness, cough, sinusitis, dyspnoea, gastrointestinal disturbances, rash, muscle spasms, myalgia, hyperkalaemia, hypotension, syncope, chest pain and fatigue. Renal function should be assessed before and during ramipril treatment, particularly in people with renal impairment.
- No adverse effects were reported the study by [Ahimastos et al. \(2006\)](#). In [Shahin et al. \(2013a\)](#), the adverse effect most often reported with ramipril was cough, which led to discontinuation in some cases.

- The 2 studies were small (n=33 and n=40), affecting their statistical power to detect differences between the groups. Participants had stable intermittent claudication that limited their mobility and exercise tolerance, and stable concurrent medical therapies. The results may not be generalisable to people with less severe intermittent claudication or comorbid conditions (for example, concomitant disease limiting walking, including coronary artery disease, or renal impairment). Most of the participants in the studies were white and it is known that ACE inhibitors are less effective for treating hypertension in people of African or Caribbean family origin; therefore, the studies of intermittent claudication may not apply to this population. The treatment period was 24 weeks and it is not known whether benefits will be maintained in the longer term. It is also not known how ramipril compares with other treatments for intermittent claudication because the studies were placebo controlled.

Full text of [evidence review](#).

Context and estimated impact for the NHS

The cost of 28 days' treatment with ramipril 10 mg is £1.28 for capsules, £1.32 for tablets and £358.40 for 2.5 mg/5 ml oral solution ([Drug Tariff](#), October 2015).

Full text of [context and estimated impact for the NHS](#).

Information for the public

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with peripheral arterial disease who are thinking about trying ramipril.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Full evidence summary

Introduction and current guidance

Peripheral arterial disease, also known as peripheral vascular disease, is a condition in which arteries that carry blood to the legs (or less commonly the arms) are narrowed or blocked. The usual cause of peripheral arterial disease is atherosclerosis ([Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease](#) NICE technology appraisal 223).

The NICE guideline on [lower limb peripheral arterial disease: diagnosis and management](#) highlights that the condition is a marker for increased risk of cardiovascular events even when it is asymptomatic. The most common initial symptom of peripheral arterial disease is pain in the legs while walking, which is relieved by rest, known as intermittent claudication. When circulation is severely reduced, critical limb ischaemia occurs, characterised by ischaemic pain at rest, ulceration, tissue loss and gangrene.

The incidence of peripheral arterial disease increases with age. Population studies have found that about 20% of people aged over 60 years have some degree of peripheral arterial disease. Incidence is high in people who smoke, people with diabetes and people with coronary artery disease. In most people with intermittent claudication the symptoms remain stable, but approximately 20% will develop increasingly severe symptoms, of whom some will develop critical limb ischaemia.

Mild intermittent claudication is generally managed in primary care: referral to secondary care is usually reserved for people whose symptoms do not resolve or deteriorate, or are disabling. Treatment options for intermittent claudication include management of cardiovascular risk factors (for example, smoking, obesity, diabetes, hypertension, using antiplatelet drugs and statins), supervised exercise and vasoactive drug treatment (naftidrofuryl oxalate).

People with severe and disabling intermittent claudication that is inadequately controlled by the above treatments are often referred to secondary care for consideration of endovascular treatment (such as angioplasty and stenting) and bypass surgery.

NICE technology appraisal guidance on [cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease](#) recommends naftidrofuryl oxalate as an option for treating intermittent claudication in people for whom vasodilator therapy is considered appropriate after taking into account other treatment options. Cilostazol, pentoxifylline and inositol nicotinate are not recommended. The NICE guideline on [lower limb peripheral arterial disease: diagnosis and management](#) advises that naftidrofuryl oxalate should be considered only when supervised exercise has not led to satisfactory improvement and the person prefers not to be referred for consideration of angioplasty or bypass surgery. Progress should be reviewed after 3 to 6 months and treatment discontinued if there has been no symptomatic benefit.

For more information on the management of peripheral arterial disease, see the NICE clinical knowledge summary on [peripheral arterial disease](#) and the NICE pathway on [lower limb peripheral arterial disease](#).

This evidence summary considers the evidence for using ramipril to treat the symptoms of peripheral arterial disease (intermittent claudication), rather than for reducing cardiovascular risk in people with peripheral arterial disease.

Product overview

Drug action

Ramipril is an angiotensin-converting enzyme inhibitor (ACE inhibitor), which causes vasodilation by inhibiting the conversion of angiotensin I to the vasoconstrictor

angiotensin II, and preventing the breakdown of the vasodilator bradykinin (see the [summary of product characteristics for Tritace](#)).

Regulatory status

Ramipril is licensed for treating hypertension, renal disease and symptomatic heart failure. It is also licensed for the secondary prevention of acute myocardial infarction, and the reduction of cardiovascular morbidity and mortality in people with manifest atherothrombotic cardiovascular disease (including peripheral arterial disease) or diabetes with at least one cardiovascular risk factor. See the [summary of product characteristics for Tritace](#) for more information.

The use of ramipril to treat symptoms of peripheral arterial disease is off-label.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using ramipril outside its authorised indications.

Cost

The usual dose of ramipril for licensed indications is 1.25 mg daily to 10 mg daily. For this dose range, the cost of ramipril tablets and capsules is between £1.07 and £1.33 for 28. Ramipril 2.5 mg/5 ml oral solution costs £96.00 for 150 ml ([Drug Tariff](#), October 2015).

Evidence review

This evidence summary discusses 2 [randomised controlled trials](#) (RCTs) that evaluated ramipril for treating intermittent claudication in people with peripheral arterial disease.

A third RCT ([Ahimastos et al. 2013](#), n=212) was originally included in this evidence summary but has now been removed. This follows a [statement](#) published in the Journal of the American Medical Association (JAMA), which advised that the RCT has been retracted after the lead author, Anna Ahimastos, admitted to fabricating the results of this and [a related study](#). This author was also the lead author for another RCT included in this evidence summary and it is unclear whether the integrity of that study is also affected. However, because of the paucity of evidence, the decision has been taken to present the results, with the proviso that the data may not be robust.

The results of a meta-analysis by [Shahin et al. \(2013b\)](#) have also been removed from the evidence summary because they were primarily based on the RCT by [Ahimastos et al. \(2013\)](#). However, some background data on the studies that are still included was obtained from the meta-analysis and is still referenced within the document.

[Ahimastos et al. \(2006\)](#) **and** [Shahin et al. \(2013a\)](#)

- **Design:** Both studies were randomised, placebo-controlled, double-blind trials.
- **Patients:** The study by [Ahimastos et al. \(2006\)](#) was undertaken in Australia and included 40 people. [Shahin et al. \(2013a\)](#) was undertaken in the UK and included 33 people. Participants in both studies had stable intermittent claudication for 6 months (which limited their mobility and exercise tolerance), an ankle brachial pressure index (ABPI, a measure of the severity of peripheral arterial disease) of less than 0.9 at rest, blood pressure of 160/100 mmHg or less, and no concomitant disease limiting walking (including coronary artery disease), renal impairment or ACE inhibitor or angiotensin receptor blocker treatment. Participants in [Ahimastos et al. \(2006\)](#) had no history of diabetes or hypertension. See table 1 for more information on baseline characteristics.
- **Intervention and comparison:** In the study by [Ahimastos et al. \(2006\)](#), participants were randomised to receive ramipril 10 mg daily or placebo for 24 weeks, and were asked to maintain their lifestyle throughout the trial. Baseline characteristics were reported to be similar between the groups. In [Shahin et al. \(2013a\)](#), participants were randomised to receive ramipril 5 mg daily or placebo for 2 weeks, followed by 10 mg daily or placebo for 22 weeks. In this study, the majority of baseline characteristics were similar between the groups. The methods of randomisation used suggest allocation was concealed in both studies.

- Outcomes:** In [Ahimastos et al. \(2006\)](#), outcomes were assessed before and after treatment and included maximum and pain-free walking times (treadmill speed 3.2 km/hour, incline 12%), [Walking Impairment Questionnaire](#) scores (WIQ, an assessment of walking distance, speed and stair-climbing ability in peripheral arterial disease, scored from 0–100 with higher scores indicating fewer symptoms and greater functional capacity) and adverse events. From the information on [statistical powering](#) of the study, the primary outcome is assumed to be change in maximum walking time, although this is not specified in the paper. Participants in [Shahin et al. \(2013a\)](#) were followed up at weeks 2, 6 and 24. Outcomes included treadmill maximum and pain-free walking distances (treadmill speed 2.5 km/hour, incline 10%), quality of life scores ([EQ-5D](#), [Short-Form 36 Health Survey \[SF-36\]](#), [King's College Hospital's vascular quality of life questionnaire \[VascuQoL\]](#)) and adverse events. From the information on powering of this study, the primary outcome is assumed to be change in maximum walking distance, although this is not specified in the paper. ABPI was also assessed in the studies but is not discussed in this evidence summary because it is a disease orientated outcome and has limited applicability to practice.

Table 1 Baseline characteristics of study participants

	Ahimastos et al. (2006)	Shahin et al. (2013a)
Mean age	66 years	64 years
Male	38/40 (95%)	25/33 (76%)
Mean ABPI	0.56	0.63 ^a
Mean BMI	24 kg/m ²	28 kg/m ²
Mean blood pressure	139/85 mmHg ^a	143/80 mmHg ^a
Mean maximum walking time	239 seconds	Not reported
Median maximum walking distance	Not reported	140 metres
Current smokers	17/40 (42.5%)	16/33 (48.5%)
Diabetes mellitus	Excluded	11/33 (33%)
Hypertension	Excluded	20/33 (61%)

Medications	Aspirin 9/40 (22.5%) Lipid-lowering drugs 11/40 (27.5%)	Antiplatelet drugs 31/33 (94%) Lipid-modifying drugs 28/33 (85%)
Abbreviations: ABPI, ankle brachial pressure index; BMI, body mass index ^a Information obtained from Shahin et al. (2013b)		

Table 2 Summary of results for [Ahimastos et al. \(2006\)](#) and [Shahin et al. \(2013a\)](#)

		Placebo	Ramipril 10 mg	Analysis
Randomised	Ahimastos et al. (2006)	n=20	n=20	
	Shahin et al. (2013a)	n=19	n=14	
Efficacy	Ahimastos et al. (2006)	n=20	n=20	
	Shahin et al. (2013a) ^a	n=17	n=12	
Primary outcome 1: change in mean maximum walking time at 24 weeks	Ahimastos et al. (2006)	-10 seconds	441 seconds	Difference 451 seconds 95% CI 367 seconds to 536 seconds p<0.001

Primary outcome 2: change in mean maximum walking distance at 24 weeks ^b	Shahin et al. (2013a)	Not reported	Not reported	Difference 131 m 95% CI 62 m to 199 m p=0.001
Selected secondary outcomes:				
Change in mean pain-free walking time at 24 weeks	Ahimastos et al. (2006)	Not reported	Not reported	Difference 227 seconds 95% CI 175 seconds to 278 seconds p<0.001
Change in mean pain-free walking distance at 24 weeks ^b	Shahin et al. (2013a)	Not reported	Not reported	Difference 122 m 95% CI 56 m to 188 m p=0.001
Change in median WIQ distance score at 24 weeks	Ahimastos et al. (2006)	Not reported	16% p<0.001 ^c	Comparison with placebo not reported
Change in median WIQ speed score at 24 weeks	Ahimastos et al. (2006)	Not reported	15% p<0.001 ^c	Comparison with placebo not reported
Change in median WIQ stair climbing score at 24 weeks	Ahimastos et al. (2006)	Not reported	50% p<0.001 ^c	Comparison with placebo not reported
Quality of life at 24 weeks ^b	Shahin et al. (2013a)			No significant differences between the groups in SF-36, EQ-5D or VascuQoL scores
Safety	Ahimastos et al. (2006)	n=20	n=20	

	Shahin et al. (2013a)	n=17	n=12	
Patients reporting adverse events	Ahimastos et al. (2006)	None	None	
	Shahin et al. (2013a)	2/19 (10.5%) withdrew giving no reason	4/14 (28.6%) reported cough 1/14 (7.1%) reported dizziness 2/14 (14.3%) withdrew with cough or dizziness	No statistical analyses reported

Abbreviations: ABPI, ankle brachial pressure index; CI, confidence interval; p, p value; SF-36, Short-Form 36 Health Survey; VascuQoL, King's College Hospital's vascular quality of life questionnaire; WIQ, Walking Impairment Questionnaire

^a 2 people were lost to follow-up in each group and were not included in analyses

^b Comparisons in Shahin et al. (2013a) are from 2 weeks to 24 weeks, not baseline to 24 weeks, because participants received a lower dose of ramipril (or placebo) for a 2-week run-in period

^c p value is for change from baseline

Clinical effectiveness

Ahimastos et al. (2006) (n=40) found that, in people with intermittent claudication, ramipril 10 mg daily statistically significantly increased mean maximum walking time (451 seconds, p<0.001) and mean pain-free walking time (227 seconds, p<0.001) compared with placebo over 24 weeks. It is unclear whether these improvements are clinically important. However, in the ramipril groups, the mean maximum walking time approximately tripled in Ahimastos et al. (2006) (from 234 seconds to 675 seconds) compared with baseline, which may be considered a relevant improvement by patients.

Shahin et al. (2013a) (n=33) reported walking distance rather than time and found that, compared with placebo, ramipril 10 mg daily statistically significantly improved mean maximum walking distance (131 m, p=0.001) and mean pain-free walking distance (122 m, p=0.001) over 24 weeks. According to the full NICE guideline on peripheral arterial disease, the minimum clinically important difference is a doubling in baseline values for mean maximum walking distance and pain-free walking distance. Although the complete data are not reported by Shahin et al. (2013a), at baseline median maximum walking distance was 137 m and pain-free walking distance was 81 m, and improvements in these outcomes at 24 weeks are reported to be statistically significant compared with 2 weeks and 6 weeks (p=0.006 and p=0.010 respectively for maximum walking distance and p=0.020 and p=0.042 respectively for pain-free walking distance).

Ahimastos et al. (2006) found that ramipril 10 mg daily improved WIQ distance, speed and stair-climbing scores at 24 weeks compared with baseline (all p<0.001) but no comparisons with placebo are reported.

Shahin et al. (2013a) found no significant differences between the groups in the 3 quality of life measures used in the study (EQ-5D, SF-36 and VascuQoL).

Safety and tolerability

No adverse events were reported in participants in Ahimastos et al. (2006) (n=40) and follow-up was complete.

In the run-in phase of the study by Shahin et al. (2013a), 4/38 people withdrew because of cough and 1/38 withdrew because of headache. Of the 14 people randomised to receive ramipril, 1 experienced hyperkalaemia (which resolved without complications), 4 experienced cough and 1 experienced dizziness. The person with dizziness and 1 person with cough withdrew from the study. Of the 19 people randomised to receive placebo, 2 withdrew without giving a reason.

According to the summary of product characteristics for Tritace, common adverse effects of ramipril (seen in between 1 in 10 and 1 in 100 people) include headache, dizziness, cough, sinusitis, dyspnoea, gastrointestinal disturbances, rash, muscle spasms, myalgia, hyperkalaemia, hypotension, syncope, chest pain and fatigue. Serious adverse effects include angioedema, hyperkalaemia, renal or hepatic impairment, pancreatitis, severe skin reactions and neutropenia/agranulocytosis. Renal function should be assessed before and during ramipril treatment, particularly in people with renal impairment.

Evidence strengths and limitations

The [Heart Outcomes Prevention Evaluation study](#) showed that ramipril has beneficial effects on morbidity and mortality and it is licensed for the reduction of cardiovascular morbidity and mortality in patients with manifest atherothrombotic cardiovascular disease (including peripheral arterial disease). The 2 small RCTs by [Ahimastos et al. \(2006\)](#) and [Shahin et al. \(2013a\)](#) suggest that ramipril 10 mg daily also improves treadmill walking ability (maximum walking and pain free walking) in people with intermittent claudication over 24 weeks and the improvements appear to be clinically important. This is supported by improvements in WIQ distance, speed and stair-climbing scores in [Ahimastos et al. \(2006\)](#), which may be more representative of activities of daily living than treadmill tests. However, the WIQ is a measure of walking impairment generally, not just that due to intermittent claudication, and [Ahimastos et al. \(2006\)](#) state that the WIQ has restricted capacity to discriminate between people with poor exercise tolerance. In addition, the studies have other limitations.

Clinical specialists involved in the development of the NICE technology appraisal considered that neither ABPI or pain-free walking distance were clinically relevant outcome measures because ABPI is used in clinical practice only as a diagnostic tool for peripheral arterial disease, and pain-free walking distance can be difficult to assess without using a fixed-speed treadmill because patients usually adjust the speed of their walking to avoid pain and to maximise walking distance. Treadmill testing is unlikely to be offered in the course of routine clinical practice. In addition, the clinical specialists agreed that maximum walking distance was the most suitable outcome measure. One of the specialists involved in the production of this evidence summary considered that walking times (used in [Ahimastos et al. 2006](#)) are of little value in assessing clinical impact of treatments for intermittent claudication. In addition, walking distance should be supported by a quality of life measure because a small increase in walking distance may not affect a person's quality of life. [Shahin et al. \(2013a\)](#) found no differences between the groups in 3 quality of life measures.

The 2 studies were small (n=33 and n=40), affecting their power to detect differences between the groups. Participants had stable intermittent claudication that limited their mobility and exercise tolerance, and stable concurrent medical therapies. The results may not be generalisable to people with less severe intermittent claudication or comorbid conditions (for example, concomitant disease limiting walking, including coronary artery disease, or renal impairment). Participants in [Ahimastos et al. \(2006\)](#) had no history of diabetes or hypertension. A higher proportion of participants in [Shahin et al. \(2013a\)](#) had

hypertension or diabetes mellitus and took antiplatelet and lipid-lowering drugs than in the other study.

Most of the participants in the studies were white and male (average age about 65 years) and around 40% were smokers. It is known that ACE inhibitors are less effective for treating some hypertension in people of African or Caribbean family origin; therefore, the studies on intermittent claudication may not apply to this population.

Ramipril has not been compared directly with other treatments for intermittent claudication. Also, the dose of ramipril used in the 2 RCTs was the maximum licensed dose (10 mg) and it is not known whether lower doses would also improve intermittent claudication. The treatment period was 24 weeks and it is unclear whether benefits will be maintained in the longer term.

Overall, specialists involved in the production of this evidence summary consider that the improvements in walking seen with ramipril in the studies may be clinically relevant. However, they stress that higher quality evidence is needed before recommendations can be made about when it should be used. In line with the NICE technology appraisal guidance on [cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease](#), vasoactive drugs are now used infrequently for intermittent claudication. Off-label drugs should only be considered when there are good clinical reasons to do so, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual. Therefore, the place in therapy of ramipril is likely to be very limited. One of the specialists considered that, if a trial of ramipril treatment is considered appropriate, it should be discontinued after 3 months if there is no benefit.

Context and estimated impact for the NHS

Cost effectiveness

No cost-effectiveness studies were identified that compared ramipril with other treatments or placebo for managing symptoms of peripheral arterial disease.

Costs of 28 days' treatment with ramipril 10 mg daily, the dose used in the studies, are shown in table 3.

Table 3 Costs of ramipril treatment

	Cost (excluding VAT; Drug Tariff , October 2015)	Cost (excluding VAT) of 28 days' treatment at 10 mg daily
10 mg capsules	£1.28 for 28	£1.28
10 mg tablets	£1.33 for 28	£1.33
2.5 mg/5 ml oral solution sugar free	£96.00 for 150 ml	£358.40

Current drug usage

No information on the use of ramipril for treating symptoms of peripheral arterial disease in UK clinical practice was identified.

The [NHS prescription cost analysis for England 2014](#) reports that 26 million community prescriptions for ramipril were dispensed in 2014, costing £40 million (net ingredient cost). The indications for these prescriptions are not provided but it is likely that most will have been for licensed indications. In addition, these data do not include hospital prescriptions.

Information for the public

A [plain English summary](#) is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with symptoms of peripheral arterial disease who are thinking about trying ramipril.

Relevance to NICE guidance programmes

The use of ramipril for treating symptoms of peripheral arterial disease is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

A NICE guideline on [lower limb peripheral arterial disease: diagnosis and management \(CG147\)](#) was published in 2012. It incorporates recommendations from the 2011 NICE technology appraisal on [cilostazol](#), [naftidrofuryl oxalate](#), [pentoxifylline](#) and [inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial](#)

disease (TA233). A NICE pathway on [lower limb peripheral arterial disease](#) brings the guidance and supporting information together in a set of interactive topic-based diagrams.

References

Ahimastos AA, Lawler A, Reid CM et al. (2006) [Brief communication: ramipril markedly improves walking ability in patients with peripheral arterial disease: a randomized trial](#). *Annals of Internal Medicine* 144: 660–4

Ahimastos AA, Walker PJ, Askew C et al. (2013) [Effect of ramipril on walking times and quality of life among patients with peripheral artery disease and intermittent claudication: a randomized controlled trial](#). *JAMA* 309: 453–60

National Institute for Health and Clinical Excellence (2012) [Lower limb peripheral arterial disease: diagnosis and management](#) NICE guideline CG147

National Institute for Health and Clinical Excellence (2011) [Cilostazol, naftidrofuryl oxalate, pentoxifylline and inositol nicotinate for the treatment of intermittent claudication in people with peripheral arterial disease](#) NICE technology appraisal 223

Shahin Y, Cockcroft JR, Chetter IC (2013a) [Randomized clinical trial of angiotensin-converting enzyme inhibitor, ramipril, in patients with intermittent claudication](#). *British Journal of Surgery* 100: 1154–63

Shahin Y, Barnes R, Barakat H et al. (2013b) [Meta-analysis of angiotensin converting enzyme inhibitors effect on walking ability and ankle brachial pressure index in patients with intermittent claudication](#). *Atherosclerosis* 231: 283–90

Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests were declared by any of the expert advisers.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

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