Evidence-based medical treatment of peripheral arterial disease: A rapid review

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ABSTRACT

Introduction: Peripheral arterial disease (PAD) treatment guidelines recommend the use of statins and antiplatelets in all PAD patients to reduce adverse cardiovascular and limb-related outcomes. In addition, hypertension and diabetes should be treated to reach recommended targets. The aim of this rapid review was to evaluate the level of adherence to evidence-based medical therapy (EBMT) recommended by PAD treatment guidelines in the real-world setting.

Methods: We searched PubMed and Embase using keywords, MeSH and Emtree terms related to the population, exposure and outcomes from their inception to 22 September 2020. We included randomised controlled trials, non-randomised studies, and observational studies reporting adherence to at least 1 of these 4 drug classes: (1) statins, (2) antiplatelets, (3) antihypertensives and (4) antidiabetic drugs. Non-English articles, abstracts, dissertations, animal studies and case reports or series were excluded. A narrative summary of the results was performed.

Results: A total of 42 articles were included in the review. The adherence to lipid-lowering drugs/statins ranged from 23.5 to 92.0% and antiplatelets from 27.5 to 96.3%. Only 7 and 5 studies reported use of "any anti-hypertensive" and "any anti-diabetic" medications, respectively, and the proportion of the cohort treated were generally close to the proportion with hypertension and/or diabetes. Adherence in studies published in 2016–2020 ranged from 52.4–89.6% for lipid-lowering drugs and 66.2–96.3% for antiplatelets.

Conclusion: EBMT adherence in PAD patients was highly variable and a substantial proportion in many settings were undertreated. There was also a notable lack of studies in Asian populations.

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Keywords: Evidence-practice gap, medication adherence, pharmacoepidemiology

INTRODUCTION

Peripheral artery disease (PAD) is characterised by debilitating atherosclerotic occlusion of arteries in the lower extremities.[1] Globally, it was estimated that more than 230 million individuals suffer from PAD in 2015, including about 50 million in Southeast Asia and 74 million in the Western Pacific Region.[2] The incidence of PAD is increasing significantly across Asia with an advancing age and increasing prevalence of diabetes, which is associated with 2- to 4-fold increase in the incidence of PAD.[3] Given that Asia has more than 50% of the diabetes prevalence worldwide, it is estimated that there are several million patients with PAD in Asia, many asymptomatic and undiagnosed.[4] The severity of PAD ranges from atypical lower-extremity symptoms, intermittent claudication to chronic limb threatening ischaemia (CLTI), which causes rest pain, ulcers or gangrene.[5] A recent systematic review found that CLTI was associated with a 1-year mortality rate of 40% and 1-year amputation rates ranged from 15% to 20%.[6] Moreover, PAD patients are at an increased risk of cardiovascular morbidity and mortality.[1] Although endovascular or surgical revascularisation procedures are important facets of PAD management, medical and lifestyle interventions are also essential elements of evidence-based PAD care, both from a perspective of improving cardiovascular mortality as well as limb-related outcomes.[1,5] Dyslipidaemia

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CLINICAL IMPACT

What is New

- This review provides an update of evidence-based medical therapy (EMBT) used in peripheral arterial disease (PAD) since the last systematic review 12 years ago.

Clinical Implications

- The review highlights existing gaps in the use of EBMT in PAD patients, given the highly variable level of adherence found for all 4 classes of EBMT.
- There was a lack of Asian studies, pointing to a need for more research on EBMT use in Asian PAD patients.

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and hypertension are estimated to nearly double the risk of PAD.[1] Lifestyle changes and control of risk factors increase the short and long-term patency of angioplasties and surgical bypasses, resulting in a reduction of target lesion revascularisation.[1]

The 2016 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Management of Patients with Peripheral Arterial Disease and 2017 European Society of Cardiology (ESC) Guidelines recommend that PAD patients be treated lifelong with a statin and an antiplatelet drug, aspirin alone (range 75–325mg per day) or clopidogrel alone (75mg per day), to reduce the risk of cardiovascular events and death.[1,5] All patients should have their serum low-density lipoprotein cholesterol (LDL-C) reduced to <1.8mmol/L (<70mg/dL) or decreased by >50% if the initial LDL-C level is between 1.8 and 3.5mmol/L (70 and 135mg/dL).[7] Statin therapy has been shown to reduce major extremity amputation by 18%, adverse cardiovascular events by 20%, and all-cause mortality by 19%.[8] Furthermore, the use of antiplatelet agents and statins at the time of intervention for PAD patients without known cardiovascular disease has also been associated with better 5-year survival compared to PAD patients receiving no treatment.[9] In addition, hypertension and diabetes should be treated and controlled. As per guidelines, a target blood pressure <140/90mmHg is recommended except in patients with diabetes, for whom a diastolic blood pressure ≤85 mmHg is considered a safer policy.[10]

Despite these guidelines, there is evidence that PAD patients are undertreated. A systematic review of implementation of recommended secondary prevention in PAD patients found that antiplatelet medication, lipid-lowering agents and antihypertensives were prescribed only in 63%, 45% and 46% of PAD patients, respectively.[11] There is also evidence of variation in perioperative antiplatelet and statin usage by procedure and among centres.[11] This rapid review aims to provide an updated evaluation of the level of adherence to evidence-based medical therapy (EBMT) recommended by PAD treatment guidelines in the real-world setting.

METHODS

Study selection

We searched PubMed and Embase using keywords, MeSH and Emtree terms related to the population, exposure and outcomes (Table 1), from their inception to 22 September 2020. Terms in each element were combined using the Boolean operator "OR" and then results from each element combined using "AND". Filters were applied to restrict language to "English". We included randomised controlled trials, non-randomised studies, and observational studies reporting adherence to at least 1 of these 4 drug classes: (1) statins ("any lipid-lowering drugs" were also included as they are likely to represent overall antilipid treatment including when statins were not suitable), (2) antiplatelets, (3) antihypertensives and (4) antidiabetic drugs. The following types of studies were excluded: (1) full text not available in English, (2) conference abstracts, (3) dissertations, (4) animal studies, or (5) case reports. We also screened reviews but included the primary studies instead of the reviews themselves. Two authors screened the studies identified through the search strategy independently, and conflicts were resolved through discussion with a third reviewer.

There were variable definitions of PAD in the studies screened, with some including diseases of the aorta, carotid and/or renal arteries. For the purposes of this review, we restricted the population to lower extremity PAD (disease affecting the aorta-iliac segments and below). Studies that included other populations but reported the results of interest in the PAD subgroup were included. Among duplicate reports of the same study population or database, we selected reports in this order of priority: (1) those that reported more exposures, (2) larger sample size, and (3) most updated results (later study period or publication date). The Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed.[12] This rapid review protocol was also registered in International Prospective Register of Systematic Reviews (PROSPERO) on 12 August 2020.

Data collection

One reviewer extracted key information and results from each study: first author, publication year, country of origin, setting, study design, study period, population inclusion and exclusion criteria, sample size, exposures, outcome measurement method, outcomes, and information needed for risk of bias assessment. A random 10% sample was checked by a second reviewer and the compliance rate was 100%. Risk of bias was assessed using the National Heart, Lung and Blood Institute (NHLBI) standardized Quality Assessment Tool by one reviewer and was randomly checked by the second reviewer.[13]

Data analysis

As the studies were rather diverse in the types of PAD patients included, context and definition of adherence, we performed a narrative summary of the results. For studies that measured adherence trend over several years, we took the value at the latest time period where available. However, for studies that reported adherence at different timepoints relative to a medical encounter for PAD diagnosis, intervention or management (e.g. before admission, after admission and follow-up), the data for each timepoint were retained as this provides a view on the effect of the encounter on quality of treatment. In these cases, the latest time point reported was used for showing the overall trend.

For the main results, we only showed the overall drug classes and the main drug or drug class of choice to simplify data presentation, rather than all specific drug entities or classes. For studies that reported angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blockers (ARBs) separately but not ACEI/ARBs, this was imputed by adding ACEI and ARBs as these drugs were generally not used together. Results for ACEIs alone were also presented in the same category. For antidiabetic medications, only results for "any antidiabetics" and/or metformin (drug of choice) were shown. We also explored the results by continent of origin and publication year to determine if there were regional differences and if adherence has improved over time. Due to the varied

nature of the PAD populations included, it was difficult to accurately group them by severity. Comorbidities were also not consistently reported to allow for subgroup analysis by these characteristics. All analyses were conducted in R version 3.5.1.[14]

RESULTS

Search results

The search strategy yielded a total of 1,843 articles from both PubMed and Embase as of 22 September 2020; 42 articles were finally included in this review (Fig. 1). The details of the included studies are shown in Table 2. The studies were published between 2004 and 2020, with almost two-thirds in the last 5 years. Most of the studies originated from the US or Europe, with only 1 paper from Asia. The median sample size was 588 patients (range 72–175,865). The type of PAD populations in the included studies varied from those patients with mild symptoms (only intermittent claudication) to those with rest pain/tissue loss (CLTI). Thirty-four studies (81%) were rated as "good" quality while the remaining 8 were "fair", according to the NHLBI quality assessment tool.

Overall adherence to EBMT

Of the 42 included studies, 41 (97.6%), 31 (73.8%), 25 (59.5%) and 8 (19.0%) studies reported adherence on lipid-lowering drugs, antiplatelets, antihypertensives and antidiabetic drugs, respectively. However, among the 25 studies that reported antihypertensives, only 7 (28/0%) reported use of "any antihypertensives",[15,16,31,35,44,45,52] and among the 8 studies that reported antidiabetic drugs, only 5 (62.5%) reported use of "any antidiabetics".[15,16,39,44,52] The rest reported specific drugs or classes of antihypertensives/antidiabetics separately, and it was not possible to infer the proportion of the cohort who received pharmacological treatment as patients may be on multiple agents.

There was substantial variability in the level of adherence to all 4 classes of drugs (Fig. 2). The adherence to lipid-lowering drugs or statins ranged from 23.5 to 92.0% and antiplatelets from 27.5 to 96.3%. There was a strong correlation between adherence to lipid-lowering drugs and antiplatelets. Studies that had low adherence to lipid-lowering drugs also tended to have low antiplatelet adherence, and vice versa (Pearson's r=0.81, $P<0.0001$).

The adherence to antihypertensives and antidiabetics were also highly variable (Figure 2). These values reflect the proportion of the entire PAD cohort treated

Table 1. Search terms

| Element	Plain text	MeSH terms (PubMed)	Emtree terms (EMBASE)
Population	"peripheral arterial disease" OR "peripheral artery disease" OR "chronic limb ischemia" OR "chronic limb threatening ischemia" OR (limb AND ischemia) OR (limb AND atherosclerosis)	"peripheral arterial disease"	"peripheral occlusive artery disease"
Exposure	"medical therapy" OR "medical treatment" OR guideline* OR medication* OR drug* OR aspirin OR clopidogrel OR antiplatelet* OR anticoagulant* OR statin* OR antihypertensive OR antidiabetic OR antihyperglycemic OR hypoglycemic OR "antithrombotic agent"	"evidence-based practice" OR aspirin OR clopidogrel OR "platelet aggregation inhibitors" OR anticoagulants OR "hydroxymethylglutaryl-CoA reductase inhibitors" OR "antihypertensive agents" OR "hypoglycemic agents"	"drug therapy" OR "evidence-based practice" OR "acetylsalicylic acid" OR clopidogrel OR "antithrombocytic agent" OR "anticoagulant agent" OR "hydroxymethylglutaryl coenzyme A reductase inhibitor" OR "antihypertensive agent" OR "antidiabetic agent"
Outcome	adherence OR compliance	"medication adherence" OR "guideline adherence" OR "treatment adherence and compliance"	"medication compliance"

*: wildcard search symbol
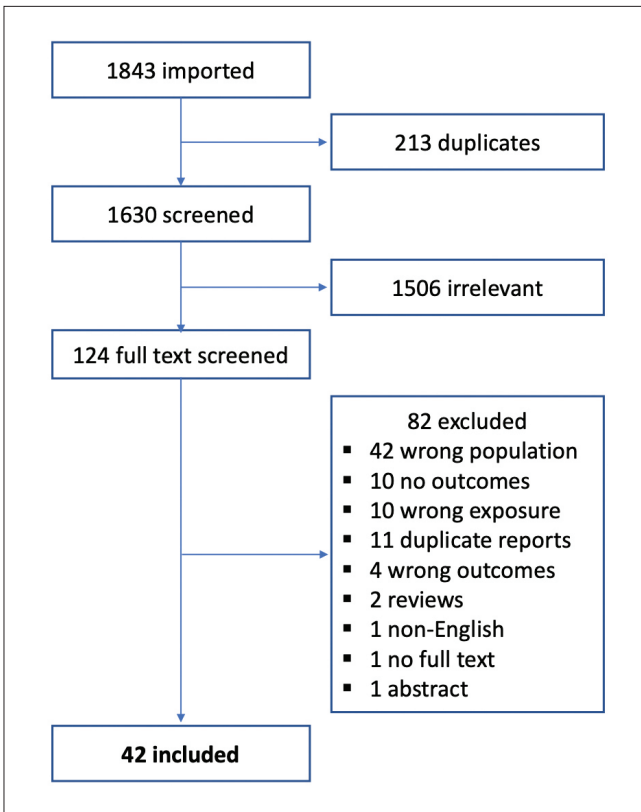
Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

with these drugs, so the proportion of those with hypertension and diabetes were also indicated where available to provide more context for the results (Fig. 2, light grey squares). Several studies have very

high or 100% adherence relative to the proportion of the cohort who had the corresponding comorbidities (hypertension or diabetes).[15,16,31,45,46,52,54] For the other studies with seemingly suboptimal antihypertensive adherence, only ACEI/ARBs were represented and/or the proportion of the cohort with hypertension was unknown. Similarly, for antidiabetics, either only metformin was represented or the proportion of diabetics was unknown.[31,39]

Adherence to EBMT by continent and publication year

European and North American studies had similarly wide distributions in adherence to both lipid-lowering drugs (31.3–92.0% and 23.5–85.3%, respectively) and antiplatelets (27.5–92.9% and 44.5–91.3%, respectively). International studies tended to have higher adherence (range 64.2–89.6% for lipid-lowering drugs and 81.7–89.6% for antiplatelets) (Fig. 3 panel A).

When grouped by publication year, there was a trend of increasing adherence with newer studies. Adherence in studies published in 2016–2020 ranged from 52.4–89.6% for lipid-lowering drugs and 66.2–96.3% for antiplatelets (Fig. 3 panel B).

Adherence at different timepoints around a medical encounter

In general, adherence to all classes of medications improved immediately after discharge from an admission or consultation for peripheral arterial disease diagnosis, intervention or management, when compared to before the encounter (Fig. 4). However, in studies that continue to follow up further, adherence tends to drop slightly

Table 2. Characteristics of included studies

Study	Country	Setting/context	Study design	Study period	n	Short description of PAD population	Time point of outcome measurement	Adherence measurement method
Bhatt,[15] 2006	International	Outpatients (REACH registry)	Prospective cohort	Dec 2003–Jun 2004	8273	IC or hx of related interventions	Baseline	Manual extraction (definition unclear)
Bianchi,[16] 2007	US	Vascular surgery clinic	Retrospective cohort	Not stated; 1-year period	167	IC and CLI	At presentation to vascular clinic	Manual extraction (definition unclear)
Brown,[17] 2004	Canada	Population-based (Saskatchewan Health)	Retrospective cohort	1991–2000	281	DM with symptomatic PAD	Not stated	Dispensing records
Cambou,[18] 2010	France	Academic hospital (COPART registry)	Prospective cohort	Jun 2004–Oct 2008	903	LE-PAD	At discharge	Manual extraction (definition unclear)
Chaudhry,[19] 2018	US	Community primary care practice	Retrospective cohort	May–Jul 2015	73	Symptomatic PAD, previous revasc/ amp, or evidence of occlusion	Within 6 months from PAD diagnosis	Manual extraction (definition unclear)
Chen,[20] 2017	US	Vascular centre	Retrospective cohort	Jun 2006–May 2013	879	IC or CLI	Pre-procedure and during follow-up	Prescription records
Chung,[21] 2013	US	Vascular surgery clinic	Prospective cohort	Aug 2010–Jan 2012	98	CLI	Baseline	Manual extraction (definition unclear)
Cimminiello,[22] 2017	Italy	Specialised vascular outpatient clinics (IDOMENEO study)	Prospective cohort	Jun 2011–Dec 2013	213	Symptomatic PAD excluding candidates for revasc and CLI	Not stated	Prescription records
de Grijs,[23] 2018	US	Vascular surgery clinic	Retrospective cohort	Jul 2004–Jul 2014	250	Patients undergoing SFA/PA stenting	At time of procedure	Largely self-report
de Liefde,[24] 2008	Netherlands	Tertiary hospital	Prospective cohort	Jul 1993–Dec 2005	2022	Hx of IC, leg pain or other symptoms	Baseline	Prescription records
Dopheide,[25] 2018	Switzerland	University hospital	Cross-sectional	Jan 2010–Sep 2017	1109	Chronic symptomatic PAD (Fontaine II, III, IV) referred for LL revasc	At referral to vascular surgery outpatient clinic	Prescription records
Federman,[26] 2005	US	Hospital	Retrospective cohort	Sep 2001–Apr 2003	143	ABI<0.9 or had LEB	12–18 months after non-invasive testing	Prescription records

ABI: ankle brachial index; amp: amputation; CLI: critical limb ischaemia; DM: diabetes mellitus, hx: history; IC: intermittent claudication; LE: lower limb; LEB: lower extremity bypass; LL: lower limb; PAD: peripheral arterial disease; PVD: peripheral vascular disease; PVI: peripheral vascular intervention; revasc: revascularisation; SFA/PA: superficial femoral artery/ popliteal artery
Superscript numbers: Refer to REFERENCES

Table 2. Characteristics of included studies (Cont'd)

Study	Country	Setting/context	Study design	Study period	n	Short description of PAD population	Time point of outcome measurement	Adherence measurement method
Gebauer,[27] 2016	Germany	University hospital	Prospective cohort	Jan 2005–Jan 2010	572	Symptomatic PAD undergoing angiography/angioplasty	At discharge and 3-year follow-up	Prescription records
Hageman,[28] 2018	Netherlands	General practitioners in primary care	Cross-sectional	Jan–Dec 2015	123	New patients with abnormal ABI	At referral to vascular surgery outpatient clinic	Mention of drug in medication list in referral
Halle,[29] 2018	US	Outpatient vascular clinic	Retrospective cohort	May–Aug 2016	96	IC, rest pain or tissue loss	At follow-up at outpatient vascular clinic	Having prescription and patient knowing it and taking it with not more than 1 missed dose in preceding 7 days
Høgh,[30] 2013	Denmark	Population-based	Retrospective cohort	Jan 1996–Dec 2006	9866	Primary vascular reconstruction for IC, ischaemic rest pain, ulceration or gangrene	After discharge from primary vascular reconstruction	Filling at least 1 prescription within 6 months after primary vascular surgery reconstruction
Iacopi,[31] 2019	Italy	Tertiary hospital	Retrospective cohort	Jan 2011–Dec 2015	603	CLI	At admission	Manual extraction (definition unclear)
Khan,[32] 2007	UK	Vascular clinics (PREPARED-UK registry)	Prospective cohort	Jun 2002–Sep 2003	478	IC and new referral only	Baseline	Manual extraction (definition unclear)
Ko,[33] 2017	South Korea	Hospital (K-VIS ELLA registry)	Retrospective cohort	Jan 2006–Jul 2015	3073	LE-PAD treated with endovascular therapy	At discharge	Prescription records
Komajda,[34] 2016	International	Hospitals (CICD-PILOT registry)	Prospective cohort	Apr 2013–Dec 2014	201	Patients undergoing PVI	Before hospital admission/consultation and at discharge	Manual extraction (definition unclear)
Lafeber,[35] 2013	The Netherlands	Academic medical centre (SMART study)	Prospective cohort	Jan 1996–Dec 2009	936	IC, angioplasty or amp	On diagnostic screening day	Self-reported

ABI: ankle brachial index; amp: amputation; CLI: critical limb ischaemia; DM: diabetes mellitus; hx: history; IC: intermittent claudication; LE: lower limb; LEB: lower extremity bypass; LL: lower limb; PAD: peripheral arterial disease; PVD: peripheral vascular disease; PVI: peripheral vascular intervention; revasc: revascularisation; SFA/PA: superficial femoral artery/ popliteal artery
Superscript numbers: Refer to REFERENCES

Table 2. Characteristics of included studies (Cont'd)

Study	Country	Setting/context	Study design	Study period	n	Short description of PAD population	Time point of outcome measurement	Adherence measurement method
Maggioni,[36] 2017	Italy	Community (ARNO Observatory)	Retrospective cohort	Jan 2011–Dec 2014	1038	PVD with IC or rest pain	First month and first year after discharge	Prescription continuity (≥300 treated days/year)
Martin,[37] 2020	US	Vascular clinics	Time series (Plan-Do-Study-Act)	Feb–Apr 2018	120	LE-PAD	After clinic visit	Prescription records
Meltzer,[38] 2018	US	Vascular clinics (VQI database)	Retrospective cohort	2011–2013	1030	PVI or LEB for symptomatic PAD	Preoperative	Prescription records
Müller-Bühl,[39] 2011	Germany	Primary care (CONTENT database)	Case-control	Apr 2007–Mar 2010	479	IC	Not stated	Prescription records
Neumann,[40] 2009	Germany	Primary care (PACE-PAD study)	Prospective cohort	Dec 2004–Jun 2005	6129	Fontaine I-IV	Baseline	Indicator on questionnaire
O'Donnell,[41] 2017	US	Academic medical centre (Vascular Study Group of New England)	Retrospective cohort	Jan 2005–Dec 2014	931	Chronic limb-threatening ischaemia undergoing first-time revasc	Postoperative	Discharge medication list
Páquet,[42] 2010	Canada	Tertiary hospital (RAMQ database)	Retrospective cohort	Jan 1997–Dec 2006	5962	LE-PAD	At discharge	Prescribed medications in pharmaceutical file
Pepió Vilaubí,[43] 2018	Spain	Primary care (PREseAP study)	Prospective cohort	Jan 2004–2009	72	PAD confirmed by Echo Doppler or positive ABI test	Baseline	Prescription records
Perren,[44] 2009	Switzerland	Tertiary hospital	Prospective cohort	Mar–May 2007	88	PAD based on symptoms or testing	At discharge	Prescription records
Poussa,[45] 2007	Finland	Vascular clinics	Cross-sectional	Jan 2002–Dec 2003	214	Patients admitted for diagnostic angioplasty or revasc	At referral and after consultation	Prescription records
Qvist,[46] 2019	Denmark	Population-based (VIVA substudy)	Retrospective cohort	Oct 2008–Jan 2011	2051	Diagnosed based on ABI	Initiators 120 days after screening	Prescription records

ABI: ankle brachial index; amp: amputation; CLI: critical limb ischaemia; DM: diabetes mellitus; hx: history; IC: intermittent claudication; LE: lower limb; LEB: lower extremity bypass; LL: lower limb; PAD: peripheral arterial disease; PVD: peripheral vascular disease; PVI: peripheral vascular intervention; revasc: revascularisation; SFA/PA: superficial femoral artery/ popliteal artery
Superscript numbers: Refer to REFERENCES

Table 2. Characteristics of included studies (Cont'd)

Study	Country	Setting/context	Study design	Study period	n	Short description of PAD population	Time point of outcome measurement	Adherence measurement method
Rehring,[47] 2006	US	Managed care system	Cluster randomised controlled trial	May 2003–Sep 2004	90	IC or hx of peripheral revasc	Within 4 months of baseline	Prescription records
Renard,[48] 2015	US	Hospitals	Prospective cohort	Jan 2008–Dec 2011	10,169	Patients undergoing LE PVI for symptomatic PAD	Prior to PVI, after procedure and at 6 months	Discharge prescription and self-report at 6 months
Reynolds,[49] 2020	US	Integrated healthcare delivery system	Retrospective cohort	Oct 2002–Sep 2015	11,059	Severe PAD	At diagnosis (12 months before and within 1 month after diagnosis)	Dispensing records
Saxon,[50] 2020	International	PAD speciality clinics (PORTRAIT registry)	Prospective cohort	Jun 2011–Dec 2015	1275	Patients with new or worsening PAD symptoms, excluding Rutherford II–III	After PAD workup at subspecialty clinic	Prescription records
Sillesen,[51] 2007	Denmark	Nurse-led rehabilitation clinic	Prospective cohort	Apr 2000–May 2004	693	Symptomatic PAD	At entry and over 12 months	Prescription records
Skórkowska-Telichowska,[52] 2018	Poland	Angiology outpatient unit	Prospective cohort	2011–2013	126	IC (Fontaine II)	At entry	Self-report
Slovut,[53] 2014	US	Hospital	Prospective cohort	Jan 2007–Dec 2010	734	Patients undergoing revasc for LE-PAD	At admission and discharge	Medication listing
Steenhof,[54] 2014	Canada	Tertiary hospital	Retrospective cohort	Jan 2010 until 150 patients	150	LE-PAD patients admitted to vascular surgery	Before and after admission	Listing of medications in discharge summary
Thiney,[55] 2018	France	University hospital	Retrospective cohort	Jan 2013–Jul 2017	140	Patients hospitalised for LE-PAD revasc	At discharge and end of follow-up (4 years)	Prescription records
Willey,[56] 2018	US	Population-based	Retrospective cohort	2009–2011	175,865	LE-PAD	Filling of prescription within 90 days of initial PAD diagnosis	Prescription records

ABI: ankle brachial index; amp: amputation; CLI: critical limb ischaemia; DM: diabetes mellitus; hx: history; IC: intermittent claudication; LE: lower limb; LEB: lower extremity bypass; LL: lower limb; PAD: peripheral arterial disease; PVD: peripheral vascular disease; PVI: peripheral vascular intervention; revasc: revascularisation; SFA/PA: superficial femoral artery/ popliteal artery
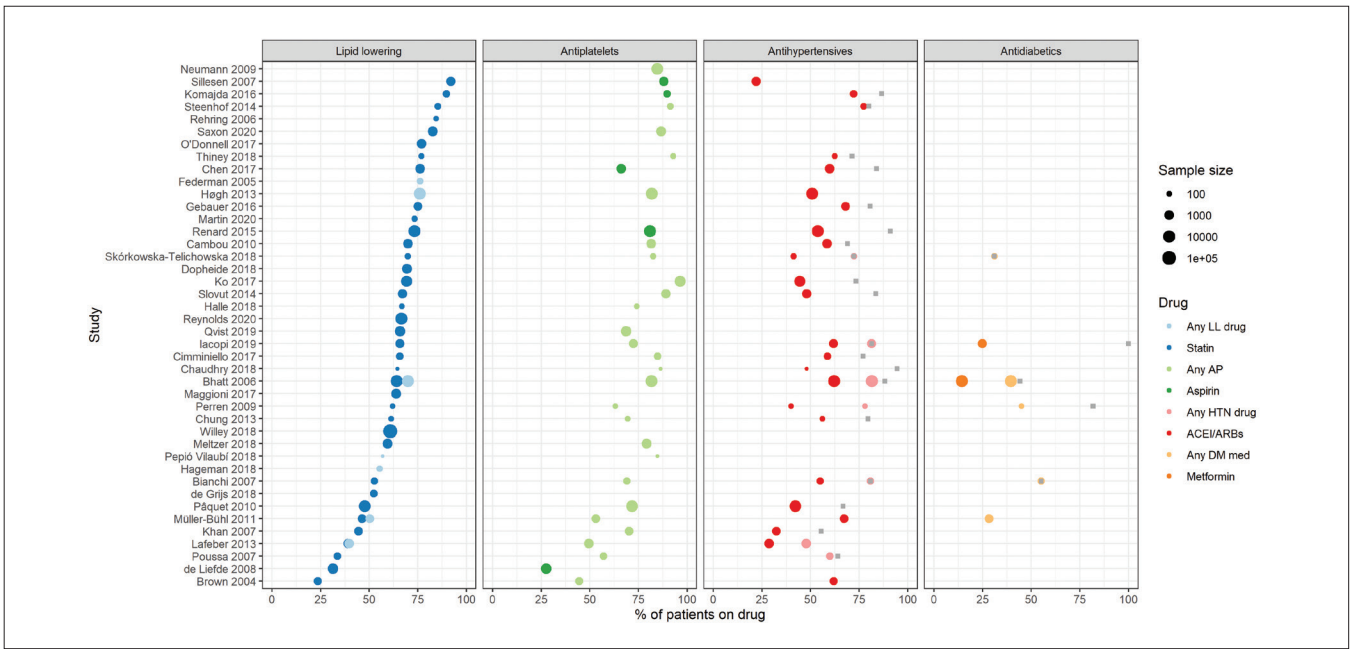Superscript numbers: Refer to REFERENCES

Fig. 2. Adherence to lipid-lowering drugs, antiplatelets, antihypertensives and antidiabetic medications.
For studies that reported adherence at different time points, the latest one is presented here. For antihypertensives and antidiabetic medications, the results reflect the percentage of the entire peripheral artery disease cohort taking those drugs. The light grey squares in the antihypertensives and diabetes mellitus medications panels represent the percentage of the cohort that have hypertension and diabetes, respectively.
LL: lipid lowering; AP: antiplatelets; HTN: hypertension; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; DM: diabetes mellitus
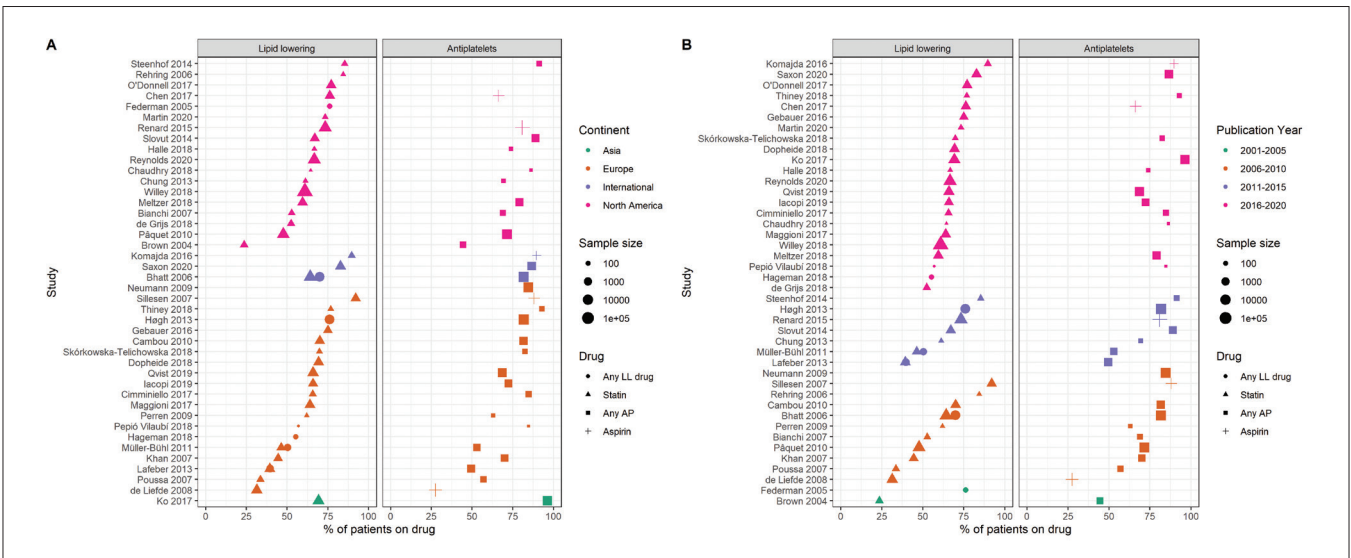

Fig. 3. Adherence to lipid-lowering drugs and antiplatelets by continent and publication year.
For studies that reported adherence at different time-points, the latest one is presented here. Panel A shows similarly wide distributions in adherence to both drug classes in Europe and North America, whereas international studies tended to have higher adherence. Panel B shows a general increasing trend in adherence to both drug classes over time.
LL: lipid lowering; AP: antiplatelets

(absolute decrease ranging from 0.4 to 11.0%),[27,48,55] with an exception in Maggioni et al., where an absolute increase of 26.5% might have been contributed by the high rate of readmissions within the first year. However, over a longer follow-up of 3 years, adherence to statins (in the entire cohort including patients with acute coronary syndrome and cardiovascular disease) did drop from 59.9 to 48.4%.[36]
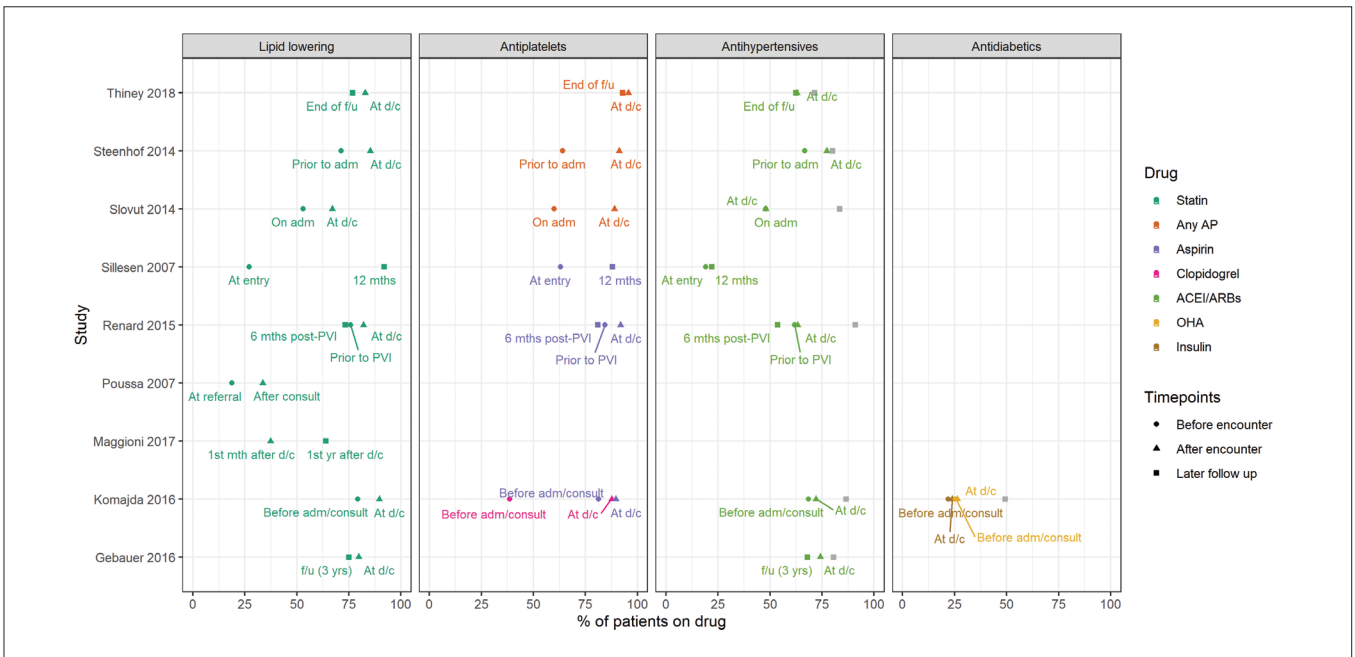
Fig. 4. Effect of healthcare encounter for peripheral artery disease (PAD) on drug adherence.
The adherence at different time-points relative to a medical encounter for PAD is shown. The medical encounter is usually a consultation or an admission for a PAD-related intervention. Generally, adherence is improved after the encounter and falls slightly upon further follow-up. For antihypertensives and antidiabetic medications, the results reflect the percentage of the entire PAD cohort taking those drugs. The light grey squares in the antihypertensives and diabetes mellitus medications panels represent the percentage of the cohort that have hypertension and diabetes, respectively.
f/u: follow-up; d/c: discharge; adm: admission; PVI: peripheral vascular intervention; AP: antiplatelets; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; OHA: oral hypoglycaemic agent

DISCUSSION

Twelve years after the last systematic review on the use of EBMT in PAD patients, the situation remains sadly the same.[11] The main findings of this review showed that medical therapy adherence was highly variable, and undertreatment with EBMT in PAD patients was common. Another striking finding was the lack of Asian studies. We found only one Korean study,[33] highlighting a gap in the literature for Asian PAD patients in general. This was also the same as the previous systematic review, which had one study from China.[11] The Korean study included 3,434 patients treated for intermittent claudication or CLTI from 2006 to 2015 at 31 hospitals across Korea, and found prescription rates at discharge to be relatively high for any antiplatelet drug (96.3%) but moderate for statins (69.2%).[33] However, in the Chinese study from the previous systematic review, PAD patients with another cardiovascular risk factor had much lower prescription rates for antiplatelets (72.4%) and statins (41.9%).[57] The variation mirrors that seen in North America and Europe, suggesting that there may be local contextual factors affecting the implementation of PAD guidelines.

We used the 2016 ACC/AHA and 2017 ESC guidelines for management of PAD patients as the reference for best medical therapy.[1] Both guidelines, which originated from different continents, as well as the global vascular guidelines for CLTI patients,[58] agree on the universal treatment of PAD patients with statins and antiplatelets, and control of hypertension and diabetes in those who have them. The ESC guidelines recommend ACEI/ARBs as first line therapy for hypertension in PAD patients, while metformin was recommended as the hypoglycaemic agent of choice in the global vascular guidelines for CLTI patients.[5,58] Unlike the previous systematic review by Flu et al., we did not focus on heart rate lowering medications because this was not a class of drug specifically recommended in the guidelines.[1,5,11] In fact, beta blockers had been thought to worsen PAD symptoms but this has been revised and beta blockers are now considered acceptable treatments in recent guidelines.[1] We also excluded exercise therapy and smoking cessation to focus on EBMT.

The evidence supporting these recommendations have been present for a long time and the same recommendations have been made as early as in 1999.[59] However, there are gaps in knowledge and action on the recommended treatment targets for vascular surgeons.[60] One of several potential reasons is low provider comfort levels in treating PAD patients.[45] The

previous systematic review by Flu et al. also summarises possible factors for suboptimal implementation of recommended secondary prevention in PAD patients. The authors grouped them into patient-related factors (understanding of disease, compliance, polypharmacy), physician-related factors (underdiagnosis of PAD, lack of knowledge of risk factor modification, lack of time and reimbursement) and healthcare-related factors (responsibility is spread out).[11] A systematic meta-review of the barriers and facilitators to implementation of clinical practice guidelines echoed many of these factors but included factors in the guideline, and political and social contexts.[61] In particular, consistent leadership, which provides clear objectives of care and rallies together care providers from difference disciplines, is a key facilitator.[61]

The large variation we saw in the level of adherence to EBMT is likely due to varying efforts in the implementation. We observed a trend of increasing adherence with time, possibly due to the increasing recognition that focused efforts are needed for understanding the implementation factors and designing strategies to overcome the barriers to implementing clinical practice guidelines in recent years.[61] In particular, collaborative care between vascular surgeons, primary physicians and internists, is important and effective in bringing about better EBMT adherence and thus long-term outcomes, given that the responsibility of instituting EBMT is unclear otherwise.[60] Suboptimal adherence to EBMT is associated with higher risk of major amputation and death.[21] Statin use is associated with lower major adverse cardiovascular events and mortality.[56] It is therefore important that more research efforts are directed towards understanding and improving implementation of the PAD guidelines into practice.

It was difficult to ascertain the quality of hypertension and diabetes treatment due to the variability in the type of drugs or drug classes that were reported. For hypertension, ACEI/ARBs are the drugs of choice according to the ESC guidelines, but treatment with any antihypertensive would have been considered adherent.[5] Among the 6 studies that reported use of "any antihypertensive", the level of use was quite close to the proportion with hypertension, suggesting that majority of hypertensive patients were being treated.[15,16,31,35,44,45] Comparing the level of ACEI/ARBs use with "any antihypertensive", it appears that ACEI/ARBs were not always the drug of choice.[15,31,35] In one study though, ACEI/ARBs use was very close to the hypertensive proportion.[54] For diabetes, treatment was 100% in 2 studies[16,52] but less than ideal in the study by Perren et al.[44] For these 2 conditions, we reported the level of

use in the entire cohort and the proportion with the conditions for context, instead of assuming that antihypertensives and antidiabetic drugs are only used in patients with hypertension and diabetes, respectively, as it may not be necessarily the case.

Our protocol initially included anticoagulants as an exposure, as guidelines recommend that they should not be used for prevention of atherosclerosis.[1,5,58] However, in the course of the review it was difficult to establish if there were other indications for anticoagulants, so we decided to exclude this exposure. Some studies reported use of "antiplatelets and/or anticoagulants" but again it was not possible to establish if patients had good justifications to be given anticoagulants instead of antiplatelets. The recent COMPASS and VOYAGER trials showed that the combination of low-dose rivaroxaban and aspirin significantly reduced the incidence of acute or chronic limb ischaemia and its related complications (amputations and death) compared to aspirin alone, suggesting a potential role for rivaroxaban in the management of PAD patients. However, the risk of major bleeding is higher with the combination of an antiplatelet and anticoagulant, and the decision to use requires an individualised assessment of the risks and benefits.[62]

The 9 studies that reported adherence at multiple timepoints relative to a medical encounter for PAD diagnosis or treatment suggested that these encounters were opportunities to review and institute EBMT in patients who have not been receiving them (Fig. 4). In one setting where CLTI patients were managed in a nurse-led PAD rehabilitation clinic, the statin adherence rate increased dramatically from 27 to 92% after a year with 5 visits.[51] This was a successful example of active implementation of EBMT in practice, through collaborative management of the patients, regular monitoring and feedback to patients and their family and/or family practitioners on their performance on risk factor targets using printouts.[51] Other care settings for PAD patients will need to understand their context, barriers and facilitators to find a strategy that works for improving EBMT adherence rates.

There are several limitations in our study. Firstly, there was some variability in the outcome definitions in the studies. Most of the studies measure adherence by whether patients were prescribed the drugs, and this was ascertained by dispensing records, documentation in various sources, and even self-reporting. This therefore represents a mixture of physician's and patient's adherence. Secondly, the results may have been an underestimate of physicians' adherence to

EBMT prescription. There could be legitimate reasons for withholding certain treatments or drug substitution (e.g. other lipid-lowering agents instead of a statin), but the reasons were not captured in most studies. Also, if dispensing records were used, the non-adherence could be on the patients' part. Despite these issues, the results still provided useful indications of EBMT exposure in PAD patients. Thirdly, the reported adherence levels do not reflect actual patient adherence. Having a prescription or dispensing record does not necessarily mean drug administration. However, this is an inherent limitation of large scale pharmaco-epidemiological studies. Fourthly, by including only articles published in English, we might have missed some studies. Lastly, our review did not include most of the primary studies in the previous systematic review by Flu et al. likely due to the slightly different search terms used.[11] However, we found very similar results so this was unlikely to have affected our conclusions.

CONCLUSION

In conclusion, EBMT adherence in PAD patients is highly variable and a substantial proportion in many settings are undertreated. Our results also point to research gaps in 2 areas. Firstly, more Asian studies of EBMT adherence are needed. Secondly, for settings with less-than-ideal EBMT adherence, implementation studies on strategies to improve adherence to EBMT are the logical next steps.

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