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Medication adherence to antithrombotic therapy in patients with peripheral arterial disease: a systematic review

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Strengths and limitations of this study

- This review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-statement and contains a comprehensive search compiled by a medical database specialist.
- Studies regarding medication adherence to antithrombotic therapy in peripheral arterial disease patients are scarce, leading to limited data.
- The included trials had rather heterogeneous study designs, making a meta-analysis infeasible and creating a wide dispersion in medication adherence proportions.
- This review provides insight into the extent of the patient's poor medication adherence.

ABSTRACT

Introduction: Patients with peripheral arterial disease (PAD) have a high risk of atherothrombotic events (AE). Antithrombotic therapy (ATT) is an important component in the treatment armamentarium to prevent AE. Poor medication adherence (MA) may compromise the preventive benefit. Most MA studies primarily concentrate on patients without PAD diagnosis and non-ATTs. We reviewed the data regarding poor MA to ATT in PAD patients.

Design: Systematic review

Method: Our protocol was based on the PRISMA statement. PubMed, EMBASE, and Cochrane Library were searched from inception to June 2023. Publications with a (sub)cohort of PAD patients that reported on patients' MA to ATT were included. The main exclusion criteria were reviews, expert opinions, and, case reports. All articles were reviewed on eligibility and methodological quality by 2 independent researchers. Primary objective was the proportion of patients with poor MA following patient-, pharmacy- or laboratory-reported outcome measurements. Poor MA is a combined endpoint of primary nonadherence (inability to initiate a prescription), secondary nonadherence (incorrect daily intake), and nonpersistence (discontinuation of daily intake).

Results: We identified 274 potentially relevant records of which 10 studies (32,628 patients) were included. Six studies were RCTs, 2 prospective-, and 2 retrospective studies. Most studies scored a moderate risk of bias and had heterogeneous study designs. Poor MA rates ranged between 2-45%. Higher rates of poor MA were found

in studies with longer follow-ups, pharmacy-reported outcome measurements, and registry-based cohorts.

Conclusion: Heterogeneous study designs create a wide dispersion in the proportions. However, poor MA to ATT was found in approximately one-third of the PAD patients and seemed to increase with longer therapy duration which highlights the magnitude of this societal challenge.

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INTRODUCTION

Peripheral arterial disease (PAD) is associated with a high risk of atherothrombotic events (AE).(1, 2) The annual cardiovascular mortality risk of patients with intermittent claudication is approximately 5% compared to 11.5% for patients with critical limb-threatening ischemia.(3) In contrast to other atherosclerotic diseases such as coronary artery disease and cerebrovascular diseases, the overall long-term risk of major adverse cardiovascular events (MACE) of PAD patients is 2-fold worse.(4, 5) Last decades, revascularisation techniques have improved which resulted in a 40% reduction in major lower limb amputations. However, the high cardiovascular mortality risk has barely declined.(1, 2, 6, 7)

A cornerstone in PAD management is prevention of MACE through pharmacological therapies through lifelong antihypertensives, statins, and antithrombotic therapy (ATT).(1, 2, 8) Medication adherence (MA), which is the ability to take medication following prescriptions, is believed to be an essential factor for pharmacological therapies to be effective.(9, 10) However, approximately 50% of patients with long-term medication due to chronic diseases in developed countries have a poor MA.(11) More specifically, in patients with cardiovascular protective medicines, poor MA was found in 25-80%.(12-15) Nevertheless, the majority of these studies are outdated and primarily concentrate on patients without PAD diagnosis and non-ATTs. MA is partly influenced by overarching factors such as healthcare systems, but many factors are disease- and patient-related such as clinical symptoms, socioeconomic background, and, medication side effects.(15-17) This underscores the importance of reporting on MA rates in specific patient populations and medication groups.

MA comprises two main elements: 'adherence' (or 'compliance') and 'persistence'.(9, 15). No universally accepted consensus exists, however, adherence is mainly used to describe correct daily intake and persistence represents the continuation of daily intake.(9, 15) Adherence can be subdivided into primary- (or initiation) and secondary adherence to differentiate between the ability to initiate a new prescription and the daily intake after initiating the first prescription. Patients are mostly considered adherent when approximately 80% of the intake is as prescribed.(18, 19) MA is measured through patient- (questionnaires), pharmacy- (counting pills, refill records), or biochemical/laboratory-reported outcome measurements (Table S1).(20)

The optimal ATT in PAD patients is still under debate.(1, 8, 21, 22) MA is generally not discussed in trials although poor MA might lead to substantial bias and thus erroneous outcomes. As far as we are aware, there are no systematic analyses regarding MA to ATT prescriptions in PAD patients. Therefore, we initiated this study to assess medication adherence specifically for ATT in patients with PAD.

METHODS

The protocol of this systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-statement (PROSPERO: CRD42023431803).(23, 24)

Search strategy and study selection

The systematic literature search was performed from inception to June 7th, 2023. The bibliographic databases PubMed, Embase.com, and Wiley/Cochrane Library were used. The index terms "Peripheral Arterial Disease", ''Antithrombotic Drugs'', "Treatment Adherence and Compliance" along with their synonyms and/or closely related words, were included. The search was compiled by a medical database specialist (see Figures S1, S2, and S3).

The search results were first deduplicated to which all obtained articles were screened on title and abstract by two independent researchers (EW and BM). Subsequently, the remaining articles were fully reviewed for eligibility and the references were screened for relevant publications (Figure S4). In case of disagreement, the study was reviewed by a third reviewer (CU).

Eligible publications contained a (sub)population of adult PAD patients and reported on patients' (non)adherence and/or (non)persistence to ATT. Publications before the year 2000, review articles, expert opinions, case reports, use of polypills, only nurse-led intensified follow-up, and non-English articles were excluded (Figure S4).

Outcome definitions and measurements

The primary objective was the proportion of PAD patients with poor MA following patient-, pharmacy-, or biochemical/laboratory-reported outcome measurements (Table S1). Poor MA includes; primary nonadherence (the inability to initiate a new prescription), secondary nonadherence (incorrect daily dosage/timing/frequency after initiating a new prescription), and nonpersistence (discontinuation of the medication intake).(9, 15, 20)

Secondary objectives were the proportion of PAD patients with (1) poor MA following pharmacy-reported outcome measurements, (2) primary nonadherence following pharmacy-reported- and (3) all outcome measurements, (4) secondary (short- and long-term) nonadherence following pharmacy-reported- and (5) all outcome measurements, and (6) nonpersistence following pharmacy-reported- and (7) all outcome measurements. Short-term was defined as a maximum follow-up of 6 months and long-term follow-up was defined as more than 6 months.

Data extraction and data analysis

The extracted data included; first author, year of publication, study design, country, number of PAD subjects, disease stage, mean age, male-female ratio, type of ATT, type of MA subgroup(s), the proportions of the MA, follow-up length, the MA outcome measurement.

The data were retrieved and collected in Review Manager Web (RevMan Web), version 4.14.0., The Cochrane Collaboration, Londen, UK. The number of patients who were adherent/persistent and nonadherent/nonpersistent were extracted from the articles. Subsequently, the proportions of adherence/persistence and nonadherence/nonpersistence were calculated and processed in tables. Clinical homogeneity was assessed based on the study designs and definitions of nonadherence and/or non-persistence.

Quality assessment

The Cochrane Risk-of-Bias (ROB) tool was applied to assess the quality of the included randomised controlled trials (RCTs) that reported MA as primary outcome. The Cochrane ROB tool identifies different domains of bias and classifies risk into high-, low-, or unclear risk.(25) The overall quality was deemed high if all domains had a low ROB or 1 domain was unclear. Unclear ROB was considered if 2≥ domains were unclear and high ROB was assigned if 1≥ domain had a high ROB.

For the non-RCTs and RCTs that report MA as a subanalysis, the methodological index for non-randomised studies (MINORS) score was used.(26) This method provides a 12-item list for comparative studies and an 8-item list for noncomparative studies. This score contains 3 classes; 0 (not reported), 1 (reported inadequate), and 2 (reported adequate). The overall quality for non-comparative trials was considered poor if the score was ≤8, moderate between 9-14, and good if ≥15. For the comparative trials, the score ranges were ≤15, 16-22, and ≥23.

RESULTS

Screening process

The search identified 274 potentially relevant records after deduplicating. No articles were added by cross-linking. After reviewing the title and abstract, 227 articles were excluded and 4 articles could not be retrieved. The remaining 45 records were fully screened of which 10 records could be included; 6 RCTs, 2 prospective-, and 2 retrospective studies (Figure S1). In case of conflicting screening decisions, consensus was found between EW and BM.

Risk-of-bias assessment

Three articles were RCTs with MA as the main analysis of the trial and, therefore, the Cochrane ROB tool was used (Table S2). The MINOR-score was used for the other 7 articles (Table S3). Overall, most studies had a moderate ROB. Concerns regarding the ROB arise mostly due to patient-reported outcomes and non-adjudicated endpoints that could be easily influenced by knowledge of the intervention. Moreover, most articles did not calculate a sample size based on the MA outcome.

Study sample/study characteristics

The characteristics of the included studies are shown in Table 1. In total 32628 PAD patients were analysed. Most studies were executed in Europe, however, the two largest trials (EUCLID and VOYAGER PAD) that accounted for 63% of the included patients were executed in various countries and continents.(27, 28) MA was mostly reported as a sub-analysis. The included trials had rather heterogeneous study designs, making a meta-analysis infeasible.

	1st Author	Country	YOP	PAD cohort	Severity disease	ATT	Age	Female (%)	FU (M)
Randomised controlled trials									
1	Cassar (42)	United Kingdom	2006	67	R1-3 w EVR	A w C or PLB	Mn 66 (R: 43-80)	15 (22)	1
2	Haile (30)	Sweden	2022	105	R1-3 w EVR/SVR	Any ATT	Md 72 (IQR: 69-77)	54 (52)	12
3	Hess (28)	Multiple	2022	6564	R1-6 w EVR/SVR	ASA w PLB or DOAC	Mn 68 (IQR: 60-76)	1704 (26)	Md 28 (IQR: 22-34)
4	Jivegard (46)	Sweden	2005	281	R4-6	ASA w PLB or LMWH	Mn 74 (SD:9)	126 (45)	3
5	Qvist (29)	Denmark	2019	2051	R 0-6 w/o EVR/SVR	Any ATT	Mn 70 (SD: 2.9)	0 (0)	60
6	Weissler (27)	Multiple	2022	13842	R1-6 w/o EVR/SVR	C or T	Mn 67 (IQR: 59-75)	3884 (28)	30 (up to 42)
Prospective trials									
7	Ferreira (43)	Spain	2010	194	NR	Any APT	Mn 64 (SD: 11.2)	43 (22)	12
8	Kremers (47)	Netherlands	2023	246	R1-4	Any APT	Mn 69 (SD: 9.2)	105 (43)	12
Retrospective studies									
9	Halle (32)	United States	2017	100	R1-6 w/o EVR/SVR	Any APT	Mn 64 (SD: 9.5)	42 (42)	NR
10	Wawruch (31)	Slovak Republic	2021	9178	R 0-6 w/o EVR/SVR	Any APT	Mn 75	5285 (58)	60
Total				32628				11258 (35)	

YOP = year of publication; w = with; w/o = with or without; A = acetylsalicylic acid; ATT = antithrombotic therapy; DOAC = direct-acting oral anticoagulant; PLB = placebo; LMWH = low molecule weight heparin; C = clopidogrel; APT = antiplatelet therapy; NR = not reported; EVR = endovascular revascularisation; SVR = surgical/open revascularisation; Mn = mean; Md = median; R = range; SD=standard deviation; M = Months.

Table 1: Articles eligible for this systematic review

Medication adherence

Poor MA following all outcome measurements ranged between 2-45% and following pharmacy-reported measurements between 9-45% (Table 2). One study, however, reported on all 3 subcategories of poor MA (i.e. primary-, secondary adherence, and persistence) and reported a total risk of 33%.(29) Overall, higher proportions of poor MA were found in studies with longer follow-ups, pharmacy-reported outcomes, and registry-based methods.(29-31)

One study reported on primary nonadherence and was based on a pharmacy-reported outcome measurement which occurred in 31% of the study population (Table 3). Short-term secondary nonadherence was reported in 3 articles and ranged between 9-26% (Table 4). Two of the 3 articles applied pharmacy-reported outcome measurement and found rates between 9-21%. Long-term secondary nonadherence, described in 5 articles, showed rates ranging between 5-26% which are comparable rates to the short-term secondary nonadherence (Table 4). Following the pharmacy-reported outcome measurement long-term secondary nonadherence occurred in 14-20% of the patients. Lastly, nonpersistence was found between 2-33% (Table 5). Nonpersistence within the pharmacy-reported group ranged between 27-33%. Higher rates of nonpersistence were found in studies with longer follow-ups and registry-based methods.

Nr.	Ref.	Measurement (Table S1)	Good MA	Poor MA	FU period (M)
Pharmacy ROM					
1	Cassar (42)	B	91%	9%	6
2	Haile (30)	B, C	70%	30%	18
3	Qvist (29)	C	55%	45%*	60
4	Wawruch (31)	C	57%	43%	60
Pharmacy- and patient-ROM					
5	Hess (28)	Patient-reported (NR) and pharmacy-reported (B)	68%	8%	Md 28 (IQR: 22-34)
Patient-ROM					
6	Ferreira (43)	NVQ	82%	2%	12
7	Halle (32)	G	74%	26%	NR
8	Jivegard (46)	NVQ	74%	26%	3
9	Kremers (47)	D	95%	5%	12
10	Weissler (27)	NR	72%	10%	30 (up to 42)

- MA = medication adherence; NVQ = non-validated questionnaire; NR = not reported; Md = median; M = months; IQR = interquartile range; ROM = reported outcome measurements

* Nonpersistence is excluded since the proportion of the patient who were nonadherent and nonpersistent is lacking.

Table 2: Medication adherence

Nr	Ref.	Measurement (Table S1)	Adherence	Nonadherence	FU period (M)
Pharmacy-ROM					

1	Qvist (29)	C	69%	31%	60

ROM = reported outcome measurements

Table 3: Primary nonadherence

Nr.	Ref.	Measurement (Table S1)	Adherence	Nonadherence	FU period (M)
Short-term secondary nonadherence					
Pharmacy-ROM					
1	Cassar (42)	B	91%	9%	6
2	Haile (30)	B, C	79%	21%	6
Patient-ROM					
3	Jivegard (46)	NVQ	74%	26%	3
Long-term secondary nonadherence					
Pharmacy-ROM					
1	Haile (30)	B, C	86%	14%	18
2	Qvist (29)	C	80%	20%	60
3	Wawruch (31)	C	80%	20%	60
Patient-ROM					
4	Halle (32)	G	74%	26%	NR
5	Kremers (47)	D	95%	5%	12

NVQ = non-validated questionnaire; ROM = reported outcome measurements

Table 4: Secondary nonadherence

Nr.	Ref.	Measurement (Table 1)	Persistence	Nonpersistence*	FU period (M)
Pharmacy-ROM					
1	Qvist (29)	C	73%	27%	60
2	Wawruch (31)	C	67%	33%	60
Pharmacy- and patient-ROM					
3	Hess (28)	Patient-reported (NR) and pharmacy-reported (B)	68%	8%	Md 28 (IQR: 22-34)
Patient-ROM					
4	Ferreira (43)	NVQ	82%	2%	12
5	Weissler (27)	NR	72%	10%	30 (up to 42)

- * Non-persistent due to patients' decisions. The proportion of persistence and nonpersistence might not be 100% due to other trial-related reasons such as major bleeding.
- NVQ = non-validated questionnaire; NR = not reported; Md = median; M = months; IQR = interquartile range; ROM = reported outcome measurements

Table 5: Nonpersistence

DISCUSSION

This systematic review provides an overview of the literature about MA to ATT in patients with PAD. The results demonstrate a poor MA rate of approximately one-third. Despite the dispersion of poor MA rates, it shows an insight into the extent of the issue. Higher rates of poor MA were found in studies with longer follow-ups, pharmacy-reported outcomes, and registry-based methods. The secondary objectives show that all subcategories seem to have a nearly equal share in the overall risk of nonadherence.

The trial designs, such as the study type and length of follow-up, might explain partly the dispersion in MA. In this review, 3 articles required minimum effort from participants because of the registry-based or retrospective design and the other articles included extensive follow-up, additional injections, and/or blood samples. Designs that required minimum effort, showed the highest rate of poor MA, nonadherence, and/or nonpersistence.(29, 31, 32) It is plausible that the likelihood of creating a more representative sample rises as the required effort for patients decreases. Literature shows that PAD patients are more precarious compared to patients with other chronic diseases including other atherosclerotic diseases.(33, 34) Precariousness is related to a lower socioeconomic status and patients with low socioeconomic status are less likely to participate in trials.(12, 33, 35, 36)

Regarding the length of follow-up, the literature shows trends that poor MA increases over time.(37-39) This review shows similar results (Tables 2, 4, and 5). One study showed that the highest proportion of nonadherence predominantly occurred between 13 and 24 months with 44% and 35.5% respectively compared to 17% within the first 12 months. This pattern corresponds with the dispersion in our long-term nonadherence results (Table 4).(31)

Additionally, the heterogeneity of the reporting methods, such as the definition of MA and outcome measurements, might be contributing to the variety in proportions between studies. MA includes 3 subcategories; primary nonadherence, secondary nonadherence, and nonpersistence. Most articles, except one, researched only nonpersistence and/or secondary nonadherence. This might underestimate the proportion of poor MA by not identifying all categories of MA. The study that distinguished all 3 subcategories reported the highest proportion of poor MA.(29)

The included studies used patient- or pharmacy-reported measurements to identify poor MA. Patient-reported outcome measurements, i.e. questionnaires and interviews, are at risk for multiple biases such as recall bias compared to pharmacy-reported outcome measurements, i.e. counting returned pills or refill patterns which lead to potentially misleading low rates of poor MA.(13, 40) One study compared patient- with pharmacy reported outcomes and their results confirm this hypothesis.(30) However, our results do not fully confirm this.

Healthcare systems have a major influence on MA.(15-17, 35) One study showed that subjects from North America were more likely to discontinue their medication compared to subjects from Europe.(27) Another study executed in North America confirmed that the inability to afford medication was a major reason for poor MA.(32) Most European countries have similar healthcare systems that reimburse necessary health costs.(41)

Regarding patient-related factors, studies that include post-revascularized PAD patients might show slightly higher MA rates.(28, 30, 42) One study showed lower long-term secondary nonadherence compared to short-term nonadherence.(30) These patients underwent revascularisation at 6 months follow-up. The severity of the symptoms might affect patients' perception of treatments. However, the literature is ambiguous.(32) Equivocal evidence regarding the impact of patient-related factors on MA is common. Amongst the included studies, subanalyses of patient-related factors show heterogeneous results.(27, 28, 31, 32, 43)

To estimate the individual risk of poor MA, it is of interest whether nonadherence leads to nonpersistence. It seems that adherent and nonadherence patients are both highly at risk for nonpersistence and thus poor MA.(31) The reason given is the lack of awareness regarding the life-long indication for ATT in PAD patients. We advise physicians to discuss MA with PAD patients. Additional research on all subcategories of MA based on registries that use pharmacy refill records and have extensive follow-up are warranted to confirm our findings.

CONCLUSION

Studies regarding MA to ATT in PAD patients are scarce and heterogeneous designs create a wide dispersion in the proportions. However, poor MA to ATT was found in approximately one-third of the PAD patients and seemed to increase with longer duration of ATT use, which highlights the magnitude of this societal challenge.

AUTHOR CONTRIBUTIONS:

EW: Concept and design, screening, data collection, analyses and interpretation of data, writing of manuscript, final approval.

BM: Screening, data collection and analyses, final approval.

CU: Concept and design, revision of manuscript, final approval.

GJdB: Concept and design, revision of manuscript, final approval.

DATA STATEMENT:

Access to the data is available via the correspondence of this article.

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SUPPLEMENTARY FILE

Tables

Outcome measurements	Nr*	Specification examples [description]
pharmacist-reported outcome measurements	A	Medication Event Monitoring System (MEMS) [Use of electronic devices with microchips to record medication intake]
	B	Pharmacy records [Counting returned pills and tracking refill patterns]
	C	Prescription records registers [Tracking all dispensed drugs and tracking refill patterns]
Patient-reported outcome measurements	D	Morisky Medication Adherence Scale (MMAS-8)(44)
	E	Medication Adherence Report Scale (MARS)(12)
	F	Simplified Medication Adherence Questionnaire (SMAQ)(45)
	G	Brief Medication Questionnaire (BMQ)(18)
	H	Other
Biochemical or laboratory outcome measurements	I	INR, Platelet activity

- * This table does not include all existing measurements.

Table S1: Outcome measurements

	ROB arising from the randomisation process;	ROB due to deviations from intended interventions;	ROB due to missing outcome data	ROB in measurement of the outcome	ROB in selection of the reported result	Overall ROB judgment
Haile, 2022 (30)	✓	✓	✓	✓	✓	✓
Jivegard, 2005 (46)	✓	?	✓	?	✓	?
Weissler, 2022 (27)	✓	✓	✓	✓	✓	✓

ROB = risk of bias; x = high risk of Bias; ? = unclear risk of Bias; v = low risk of bias

Table S2. **Risk-of-bias summary of included RCTs following the Cochrane risk-of-bias tool**

	Clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate	Unbiased assessment of endpoint	FU period appropriate	Loss to follow-up < 5%	Calculation study size	Adequate control group	Contemporary groups	Baseline equivalence of groups	Statistical analyses	Total	Quality
Cassar, 2006 (42)	2	2	2	2	1	1	2	0	1	2	1	2	18/24	M

Ferreira, 2010 (43)	2	0	2	2	0	2	0	0	N/A	N/A	N/A	N/A	8/16	P
Halle, 2017 (32)	2	2	2	2	1	1	2	0	N/A	N/A	N/A	N/A	12/16	M
Hess, 2022 (28)	1	1	2	1	1	2	2	0	N/A	N/A	N/A	N/A	10/16	M
Kremers, 2023 (47)	2	1	2	2	1	2	2	0	N/A	N/A	N/A	N/A	12/16	M
Qvist, 2019 (29)	2	1	1	2	2	2	2	0	N/A	N/A	N/A	N/A	12/16	M
Wawruch, 2021 (31)	2	2	1	2	2	2	2	0	N/A	N/A	N/A	N/A	13/16	M

N/A = not applicable; P = Poor; M = Moderate; G = good

***Table S3*. Risk-of-bias of bias summary for the non-randomised controlled trials following the MINORs-score**

Figures

Search	Actions	Details	Query	Results	Time
#4	•••	! >	Search: **#1 AND #2 AND #3** Sort by: **Most Recent**	128	08:50:30
#3	•••	! >	Search: **"Treatment Adherence and Compliance"[Mesh] OR "Medication Adherence"[Mesh]] OR ''compliance" [tiab] OR ''adherence" [tiab] OR "refus*"[tiab] OR "nonadherence"[tiab] OR "noncompliance"[tiab]** Sort by: **Most Recent**	542,177	08:50:03
#2	•••	! >	Search: **"Platelet Aggregation Inhibitors"[Mesh] OR "Platelet Aggregation Inhibitors" [Pharmacological Action] OR "Dual Anti-Platelet Therapy"[Mesh] OR ''Platelet aggregation inhibitor*"[tiab] OR ''antiplatelet therap*"[tiab] OR "anti platelet therap*"[tiab] OR OR "platelet inhibitor*"[tiab] OR "platelet aggregant*"[tiab] OR ''acetylsalicylic acid''[tiab] OR "aspirin"[tiab] OR "paracetamol"[tiab] OR ''clopidogrel''[tiab] OR OR "Anticoagulants"[Mesh] OR "Anticoagulants" [Pharmacological Action] OR "Indirect thrombin inhibitor*"[tiab] OR "anti coagulant"[tiab] OR "Fibrinolytic Agents" [Mesh] OR "fibrinolytic agent*"[tiab] OR "fibrinolytic drug*"[tiab] OR "Thrombolytic drug*"[tiab] OR "Thrombolytic agent*"[tiab] OR "antithrombotic drug*"[tiab] OR "antithrombotic agent*"[tiab] OR ''anticoagulant*''[tiab] OR ''Factor Xa inhibitor*''[tiab] OR ''Rivaroxaban''[tiab]** Sort by: **Most Recent**	468,945	08:49:49
#1	•••	>	Search: **("Peripheral Arterial Disease"[Mesh] OR ''peripheral arterial disease*"[tiab] OR "peripheral artery disease*"[tiab] OR ''lower extremity arterial disease*"[tiab] OR "lower extremity artery disease*"[tiab] OR ''Chronic Limb-Threatening Ischemia*"[tiab] OR ''intermittent claudication*"[tiab] OR ''Peripheral Arterial Vascular Disease*"[tiab] OR ''peripheral artery occlusive disease*"[tiab] OR "peripheral arterial occlusive disease*"[tiab]) AND ("Peripheral Arterial Disease"[Mesh] OR ''peripheral arterial disease*"[tiab] OR "peripheral artery disease*"[tiab] OR ''lower extremity arterial disease*"[tiab] OR "lower extremity artery disease*"[tiab] OR ''Chronic Limb-Threatening Ischemia*"[tiab] OR ''intermittent claudication*"[tiab] OR ''Peripheral Arterial Vascular Disease*"[tiab] OR ''peripheral artery occlusive disease*"[tiab] OR "peripheral arterial occlusive disease*"[tiab])** Sort by: **Most Recent**	32,848	08:44:08

Figure S1. Search PubMed/MEDLINE

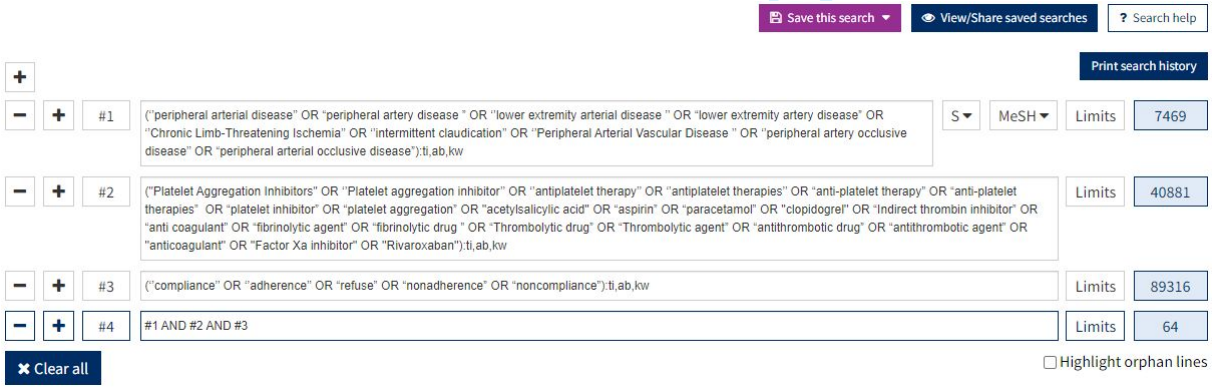

Figure S2. Search in Cochrane

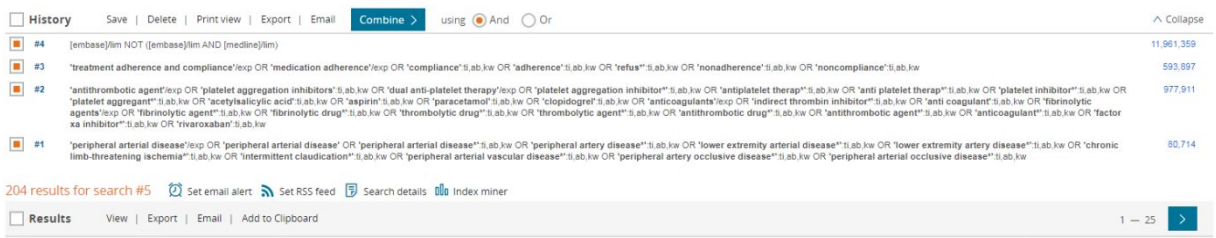

Figure S3. Search in Embase

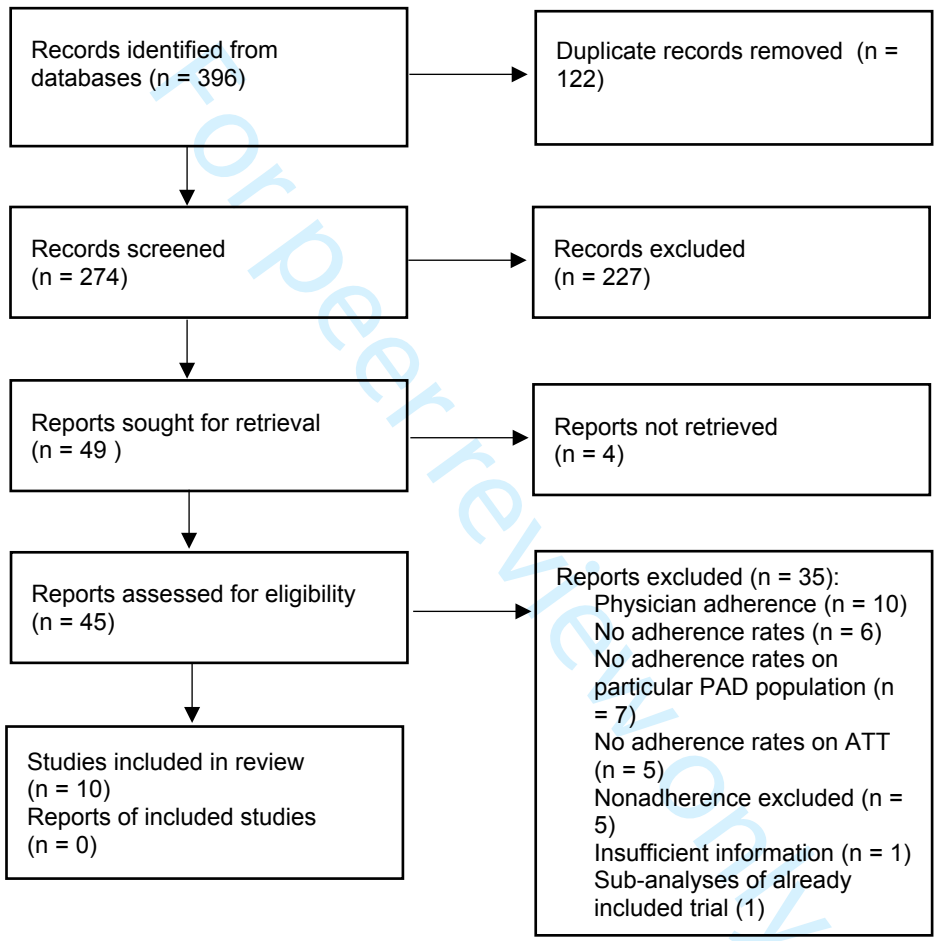

***Figure S4*. The flowchart of the selection process**

BMJ Open

Medication adherence of patients with peripheral arterial disease to antithrombotic therapy: a systematic review

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Medication adherence of patients with peripheral arterial disease to antithrombotic therapy: a systematic review

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Strengths and limitations of this study

- This review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-statement and contains a comprehensive search compiled by a medical database specialist.
- Studies regarding medication adherence of patients with peripheral arterial disease to antithrombotic therapy are scarce, leading to limited data.
- The included trials had rather heterogeneous study designs, making a meta-analysis infeasible and creating a wide dispersion in medication adherence proportions.
- This review provides insight into the extent of the patient's poor medication adherence which is an addition to the current literature focussing primarily on physician adherence.

ABSTRACT

Introduction: Patients with peripheral arterial disease (PAD) have a high risk of atherothrombotic events (AE). Antithrombotic therapy (ATT) is an important component in the treatment armamentarium to prevent AE. Poor medication adherence (MA) may compromise the preventive benefit. Most MA studies primarily concentrate on physician prescription adherence, patients without PAD diagnosis, and non-ATTs. We reviewed the data regarding poor MA of PAD patients to ATT.

Design: Systematic review

Method: Our protocol was based on the PRISMA statement. PubMed, EMBASE, and Cochrane Library were searched from 2000 to June 2023. Publications with a (sub)cohort of PAD patients that reported on patients' MA to ATT were included. The main exclusion criteria were reviews, expert opinions, and, case reports. All articles were reviewed on eligibility and methodological quality by 2 independent researchers. Primary objective was the proportion of patients with poor MA following patient-, pharmacy- or laboratory-reported outcome measurements. Poor MA is a combined endpoint of primary nonadherence (inability to initiate a prescription), secondary nonadherence (incorrect daily intake), and nonpersistence (discontinuation of daily intake).

Results: We identified 274 potentially relevant records of which 10 studies (32,628 patients) were included. Six studies were RCTs, 2 prospective-, and 2 retrospective studies. Most studies scored a moderate risk of bias and had heterogeneous study

designs. Poor MA rates ranged between 2-45%. Higher rates of poor MA were found in studies with longer follow-ups, pharmacy-reported outcome measurements, and registry-based cohorts.

Conclusion: Heterogeneous study designs create a wide dispersion in the proportions. However, poor MA to ATT was found in approximately one-third of the PAD patients and seemed to increase with longer therapy duration which highlights the magnitude of this societal challenge. Enhancing patients' MA to ATT might be a key element to reduce the risk of AE and, therefore, more attention to MA in clinical and research settings is warranted.

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INTRODUCTION

Peripheral arterial disease (PAD) is associated with a high risk of atherothrombotic events (AE).[1, 2] The annual cardiovascular mortality risk of patients with intermittent claudication is approximately 5% compared to 11.5% for patients with critical limb-threatening ischemia.[3] In contrast to other atherosclerotic diseases such as coronary artery disease and cerebrovascular diseases, the overall long-term risk of major adverse cardiovascular events (MACE) of PAD patients is 2-fold worse.[4, 5] Last decades, revascularisation techniques have been improved which resulted in a 40% reduction in major lower limb amputations, however, the high cardiovascular mortality risk has barely declined.[1, 2, 6, 7]

A cornerstone in PAD management is MACE prevention through pharmacological therapies through lifelong antihypertensives, statins, and antithrombotic therapy (ATT).[1, 2, 8] Medication adherence (MA), which is the ability to take medication following prescriptions, is believed to be an essential factor for pharmacological therapies to be effective.[9, 10] However, approximately 50% of patients with long-term medication due to chronic diseases in developed countries have a poor MA.[11] More specifically, in patients with cardiovascular protective medicines, poor MA was found in 25-80%.[12-17] Nevertheless, the majority of these studies are outdated, focus on physician prescription adherence, primarily concentrate on patients without PAD diagnosis, or non-ATTs. MA is partly influenced by overarching factors such as healthcare systems, but many factors are disease- and patient-related such as clinical symptoms, socioeconomic background, and, medication side effects.[15, 18, 19] This underscores the importance of reporting on MA rates in specific patient populations and medication groups.

MA comprises two main elements: 'adherence' (or 'compliance') and 'persistence'.[9, 15]. No universally accepted consensus exists, however, adherence is mainly used to describe correct daily intake and persistence represents the continuation of daily intake.[9, 15] Adherence can be subdivided into primary- (or initiation) and secondary adherence to differentiate between the ability to initiate a new prescription and the daily intake after initiating the first prescription. Patients are mostly considered adherent when approximately 80% of the intake is as prescribed.[20, 21] MA is measured through patient- (questionnaires), pharmacy- (counting pills, refill records), or biochemical/laboratory-reported outcome measurements (Table S1).[22]

The optimal ATT in PAD patients is still under debate.[1, 8, 23, 24] MA is generally not discussed in trials although poor MA might lead to substantial bias and thus erroneous outcomes. As far as we are aware, there are no systematic analyses regarding MA of PAD patients to ATT . Therefore, we initiated this study to assess medication adherence specifically for ATT in patients with PAD.

METHODS

The protocol of this systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-statement (PROSPERO: CRD42023431803).[25, 26]

Search strategy and study selection

The systematic literature search was performed from inception to June 7th, 2023. The bibliographic databases PubMed, Embase.com, and Wiley/Cochrane Library were used. The index terms "Peripheral Arterial Disease", ''Antithrombotic Drugs'', "Treatment Adherence and Compliance" along with their synonyms and/or closely related words, were included. The search was compiled by a medical database specialist (see Figures S1, S2, and S3).

The search results were first deduplicated to which all obtained articles were screened on title and abstract by two independent researchers (EW and BM). Subsequently, the remaining articles were fully reviewed for eligibility and the references were screened for relevant publications (Figure S4). In case of disagreement, the study was reviewed by a third reviewer (CU).

Eligible publications contained a (sub)population of adult PAD patients and reported on patients' (non)adherence and/or (non)persistence to ATT. Publications before the year 2000, review articles, expert opinions, case reports, use of polypills, only nurse-led intensified follow-up, and non-English articles were excluded (Figure S4).

Outcome definitions and measurements

The primary objective was the proportion of PAD patients with poor MA following patient-, pharmacy-, or biochemical/laboratory-reported outcome measurements (Table S1). Poor MA includes; primary nonadherence (the inability to initiate a new prescription), secondary nonadherence (incorrect daily dosage/timing/frequency after initiating a new prescription), and nonpersistence (discontinuation of the medication intake).[9, 15, 22]

Secondary objectives were the proportion of PAD patients with (1) poor MA following pharmacy-reported outcome measurements, (2) primary nonadherence following pharmacy-reported- and (3) all outcome measurements, (4) secondary (short- and long-term) nonadherence following pharmacy-reported- and (5) all outcome measurements, and (6) nonpersistence following pharmacy-reported- and (7) all outcome measurements. Short-term was defined as a maximum follow-up of 6 months and long-term follow-up was defined as more than 6 months.

Data extraction and data analysis

The extracted data included; first author, year of publication, study design, country, number of PAD subjects, disease stage, mean age, male-female ratio, type of ATT, type of MA subgroup(s), the proportions of the poor MA, threshold for poor MA, follow-up length, the MA outcome measurement.

The data were retrieved and collected in Review Manager Web (RevMan Web), version 4.14.0., The Cochrane Collaboration, Londen, UK. The number of patients who were adherent/persistent and nonadherent/nonpersistent were extracted from the articles. Subsequently, the proportions of adherence/persistence and nonadherence/nonpersistence were calculated and processed in tables. Clinical homogeneity was assessed based on the study designs and definitions of nonadherence and/or non-persistence.

Quality assessment

The Cochrane Risk-of-Bias (ROB) tool was applied to assess the quality of the included randomised controlled trials (RCTs) that reported MA as primary outcome. The Cochrane ROB tool identifies different domains of bias and classifies risk into high-, low-, or unclear risk.[27] The overall quality was deemed high if all domains had a low ROB or 1 domain was unclear. Unclear ROB was considered if 2≥ domains were unclear and high ROB was assigned if 1≥ domain had a high ROB.

For the non-RCTs and RCTs that report MA as a subanalysis, the methodological index for non-randomised studies (MINORS) score was used.[28] This method provides a 12-item list for comparative studies and an 8-item list for noncomparative studies. This score contains 3 classes; 0 (not reported), 1 (reported inadequate), and 2 (reported adequate). The overall quality for non-comparative trials was considered poor if the score was ≤8, moderate between 9-14, and good if ≥15. For the comparative trials, the score ranges were ≤15, 16-22, and ≥23.

Patient and public involvement

None

RESULTS

Screening process

The search identified 274 potentially relevant records after deduplicating. No articles were added by cross-linking. After reviewing the title and abstract, 227 articles were excluded and 4 articles could not be retrieved. The remaining 45 records were fully screened of which 10 records could be included; 6 RCTs, 2 prospective-, and 2

retrospective studies (Figure S1). In case of conflicting screening decisions, consensus was found between EW and BM.

Risk-of-bias assessment

Three articles were RCTs with MA as the main analysis of the trial and, therefore, the Cochrane ROB tool was used (Table S2). The MINOR-score was used for the other 7 articles (Table S3). Overall, most studies had a moderate ROB. Concerns regarding the ROB arise mostly due to patient-reported outcomes and non-adjudicated endpoints that could be easily influenced by knowledge of the intervention. Moreover, most articles did not calculate a sample size based on the MA outcome.

Study sample/study characteristics

The characteristics of the included studies are shown in Table 1. In total 32628 PAD patients were analysed. Most studies were executed in Europe, however, the two largest trials (EUCLID and VOYAGER PAD) that accounted for 63% of the included patients were executed in various countries and continents.[29, 30] MA was mostly reported as a sub-analysis. The included trials had rather heterogeneous study designs, making a meta-analysis infeasible.

	1st Author	Country	YOP	PAD cohort	Severity disease	ATT	Age	Female (%)	FU
Randomised controlled trials									
1	Cassar [31]	United Kingdom	2006	67	R1-3 w EVR	A w C or PLB	Mn 66 (R: 43-80)	15 (22)	1M
2	Haile [32]	Sweden	2022	105	R1-3 w EVR/SVR	Any ATT	Md 72 (IQR: 69-77)	54 (52)	1Y
3	Hess [30]	Multiple	2022	6564	R1-6 w EVR/SVR	ASA w PLB or DOAC	Mn 68 (IQR: 60-76)	1704 (26)	Md 28M (IQR: 22-34)
4	Jivegard [33]	Sweden	2005	281	R4-6	ASA w PLB or LMWH	Mn 74 (SD:9)	126 (45)	3M
5	Qvist [34]	Denmark	2019	2051	R 0-6 w/o EVR/SVR	Any ATT	Mn 70 (SD: 2.9)	0 (0)	5Y
6	Weissler [29]	Multiple	2022	13842	R1-6 w/o EVR/SVR	C or T	Mn 67 (IQR: 59-75)	3884 (28)	30M (up to 42 M)
Prospective trials									
7	Ferreira [35]	Spain	2010	194	NR	Any APT	Mn 64 (SD: 11.2)	43 (22)	1Y
8	Kremers [36]	Netherlands	2023	246	R1-4	Any APT	Mn 69 (SD: 9.2)	105 (43)	1Y
Retrospective studies									
9	Halle [37]	United States	2017	100	R1-6 w/o EVR/SVR	Any APT	Mn 64 (SD: 9.5)	42 (42)	NR
10	Wawruch [38]	Slovak Republic	2021	9178	R 0-6 w/o EVR/SVR	Any APT	Mn 75	5285 (58)	5Y
Total				32628				11258 (35)	

YOP = year of publication; w = with; w/o = with or without; A = acetylsalicylic acid; ATT = antithrombotic therapy; DOAC = direct-acting oral anticoagulant; PLB = placebo; LMWH = low molecule weight heparin; C = clopidogrel; APT = antiplatelet therapy; NR = not reported; EVR = endovascular revascularisation; SVR = surgical/open revascularisation; Mn = mean; Md = median; R = range; ±=standard deviation; ( ) = percentage, M = Months, Y = years.

Table 1: Articles eligible for this systematic review

Medication adherence

Poor MA following all outcome measurements ranged between 2-45% and following pharmacy-reported measurements between 9-45% (Table 2). One study, however, reported on all 3 subcategories of poor MA (i.e. primary-, secondary adherence, and persistence) and reported a total risk of 33%.[34] Overall, higher proportions of poor MA were found in studies with longer follow-ups, pharmacy-reported outcomes, and registry-based methods.[32, 34, 38]

One study reported on primary nonadherence based on a pharmacy-reported outcome measurement that occurred in 31% of the study population (Table 3). Short-term secondary nonadherence was reported in 3 articles and ranged between 9-26% (Table 4). Two of the 3 articles applied pharmacy-reported outcome measurement and found rates between 9-21%. Long-term secondary nonadherence, described in 5 articles, showed rates ranging between 5-26% comparable to short-term secondary nonadherence (Table 4). Following the pharmacy-reported outcome measurement long-term secondary nonadherence occurred in 14-20% of the patients. Lastly, nonpersistence was found between 2-33% (Table 5). Nonpersistence within the pharmacy-reported group ranged between 27-33%. Higher rates of nonpersistence were found in studies with longer follow-ups and registry-based methods.

Nr.	Ref.	Measurement (Table S1)	Poor MA	FU period
Pharmacy ROM				
1	Cassar [31]	Counting returned pills	9%	6 months
2	Haile [32]	Counting pills	30%	1,5 year
3	Qvist [34]	National prescription register	45%*	5 years
4	Wawruch [38]	Counting returned pills	43%	5 years
Pharmacy- and patient ROM				
5	Hess [30]	Interview NVQ and counting returned pills	8%	Md 28M (IQR: 22-34)
Patient ROM				
6	Ferreira [35]	Interview (NVQ)	2%	1 year
7	Halle [37]	Brief medication questionnaire	26%	NR
8	Jivegard [33]	Patient diary	26%	3 months
9	Kremers [36]	Morisky Medication Adherence Scale	5%	1 year

10	Weissler [29]	Interview (NR)	10%	30M (up to 42 M)

- MA = medication adherence; NVQ = non-validated questionnaire; NR = not reported; Md = median; M = months; IQR = interquartile range; ROM = reported outcome measurements

* Nonpersistence is excluded since the proportion of the patients who were nonadherent and nonpersistent is lacking.

Table 2: Medication adherence

Nr	Ref.	Threshold nonadherence	Nonadherence	FU period
Pharmacy ROM				
1	Qvist [34]	Filling prescription ≤ 120 days	31%	6 months

ROM = reported outcome measurements

Table 3: Primary nonadherence

Nr.	Ref.	Threshold nonadherence	Nonadherence	FU period
Short-term secondary nonadherence				
Pharmacy ROM				
1	Cassar [31]	NR	9%	6 months
2	Haile [32]	< 80%	21%	6 month
Patient ROM				
3	Jivegard [33]	NR	26%	3 months
Long-term secondary outcome				
Pharmacy ROM				
1	Haile [32]	< 80%	14%	1,5 year
2	Qvist [34]	< 80%	20%	5 year
3	Wawruch [38]	< 80%	20%	5 year
Patient ROM				
4	Halle [37]	< 80%	26%	NR
5	Kremers [36]	8 points	5%	1 year

NVQ = non-validated questionnaire; ROM = reported outcome measurements

Table 4: Secondary nonadherence

Nr.	Ref.	Threshold nonadherence	Nonpersistence*	FU period
Pharmacy ROM				
1	Qvist [34]	< 80%	27%	5 years
2	Wawruch [38]	< 80%	33%	5 years
Pharmacy- and patient ROM				
3	Hess [30]	NR	8%	Md 28M (IQR: 22-34)
Patient ROM				
4	Ferreira [35]	NR	2%	1 year
5	Weissler [29]	NR	10%	30M (up to 42 M)

- * Non-persistent due to patients' decisions. The proportion of persistence and nonpersistence might not be 100% due to other trial-related reasons such as major bleeding.

- NVQ = non-validated questionnaire; NR = not reported; Md = median; M = months; IQR = interquartile range; ROM = reported outcome measurements

Table 5: Nonpersistence

DISCUSSION

This systematic review provides an overview of the literature about MA to ATT in patients with PAD. The results demonstrate a poor MA rate of approximately one-third. Despite the variability in poor MA rates, it shows the magnitude of poor MA. Higher rates of poor MA were found in studies with longer follow-ups, pharmacy-reported outcomes, and registry-based methods. The secondary objectives show that all subcategories seem to have a nearly equal share in the overall risk of nonadherence.

Trial designs influence participant burdens which might partly explain the dispersion in MA amongst trials.[39, 40] In this review, 3 articles required minimum effort from participants because of the registry-based or retrospective design compared to the other articles including extensive follow-up, additional injections, and/or blood samples. Designs that required minimum effort, showed the highest rate of poor MA, nonadherence, and/or nonpersistence.[34, 37, 38] In the field of PAD, it is plausible that the likelihood of creating a more representative sample rises as the required effort for patients decreases. Literature shows that PAD patients are frequently precarious which is related to lower socioeconomic status and, therefore, less likely to participate in trials[12, 41-44] Reducing the complexity of trials leads to better understanding, fewer transfers, time commitment, and risk of additional (transfer) costs, resulting in a lower threshold for participation in this population.[40]

Regarding the length of follow-up, the literature shows a tendency for poor MA to increase as the duration of medication use increases.[45-47] This review shows similar results (Tables 2, 4, and 5). One study showed that the highest proportion of nonadherence predominantly occurred between 13 and 24 months with 44% and 35.5% respectively compared to 17% within the first 12 months. This pattern corresponds with the dispersion in our long-term nonadherence results (Table 4).[38]

Additionally, the heterogeneity of the reporting methods, such as the definition of MA and outcome measurements, might contribute to the variety in proportions between studies. MA includes 3 subcategories; primary nonadherence, secondary nonadherence, and nonpersistence. Most articles, except one, researched only nonpersistence and/or secondary nonadherence. This might underestimate the proportion of poor MA by not identifying all categories of MA. The study that distinguished all 3 subcategories reported the highest proportion of poor MA.[34]

Healthcare systems have a major influence on MA.[15, 18, 19, 41] One study showed that participants from North America were more likely to discontinue their medication compared to participants from Europe.[29] Another study executed in North America confirmed that the inability to afford medication was a major reason for

poor MA.[37] Most European countries have similar healthcare systems that reimburse necessary health costs.[48]

Regarding patient-related factors, studies that include post-revascularized PAD patients might show slightly higher MA rates.[30-32] One study showed lower long-term secondary nonadherence compared to short-term nonadherence.[32] These patients underwent revascularisation at 6 months follow-up. The severity of the symptoms might affect patients' perception of treatments. However, the literature is ambiguous.[37] Equivocal evidence regarding the impact of patient-related factors on MA is common. Amongst the included studies, subanalyses of patient-related factors show heterogeneous results.[29, 30, 35, 37, 38]

To estimate the individual risk of poor MA, it is of interest whether nonadherence leads to nonpersistence. It seems that adherent and nonadherence patients are both highly at risk for nonpersistence and thus poor MA.[38] The reason given is the lack of awareness regarding the life-long indication for ATT in PAD patients. We advise physicians to discuss MA with PAD patients. Additional research on all subcategories of MA based on registries that use pharmacy refill records and have extensive follow-up are warranted to confirm our findings.

The main strengths of this study are the selected inclusion of trials that include medication adherence of patients with PAD regarding antithrombotic therapies and the distinction between different types of adherence which is clinically relevant when prescribing and discussing antithrombotic treatment. However, this review has a few limitations. Most articles were at moderate risk for bias and a few studies did not mention its thresholds for non-adherence. Moreover, the heterogeneous study designs made a meta-analysis infeasible. Most of the included studies used patient-reported outcome measurements, i.e. questionnaires and interviews, which are at risk for multiple biases such as recall bias leading to potentially misleading low rates of poor MA.[13, 32, 49]

CONCLUSION

Studies regarding MA in PAD patients to ATT are scarce and contain heterogeneous designs creating a wide dispersion in MA proportions. However, poor MA to ATT was found in approximately one-third of the PAD patients and seemed to increase with longer duration of ATT use, which highlights the magnitude of this societal challenge.

AUTHOR CONTRIBUTIONS:

EW: Concept and design, screening, data collection, analyses and interpretation of data, writing of manuscript, final approval.

BM: Screening, data collection, and analyses, final approval.

CU: Concept and design, revision of manuscript, final approval.

GJdB: Concept and design, revision of manuscript, final approval, and is the guarantor.

DATA STATEMENT:

Access to the data is available via the correspondence of this article.

ETHICS APPROVAL:

Ethical approval was not considered as this review involved only previously published data.

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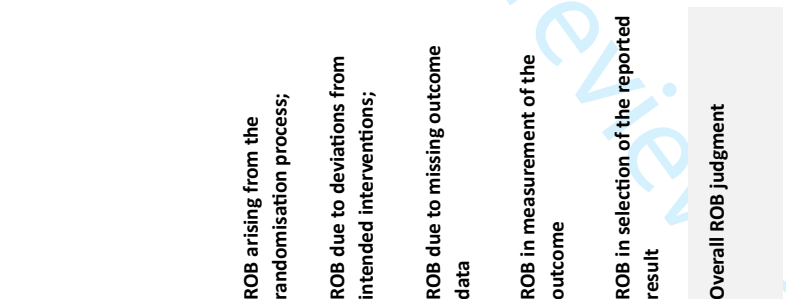
SUPPLEMENTARY FILE

Tables

Outcome measurements	Specification examples [description]*
pharmacist-reported outcome measurements	Medication Event Monitoring System (MEMS) [Use of electronic devices with microchips to record medication intake]
	Pharmacy records [Counting returned pills and tracking refill patterns]
	Prescription records registers [Tracking all dispensed drugs and tracking refill patterns]
Patient-reported outcome measurements	Morisky Medication Adherence Scale (MMAS-8)[1]
	Medication Adherence Report Scale (MARS)[2]
	Simplified Medication Adherence Questionnaire (SMAQ)[3]
	Brief Medication Questionnaire (BMQ)[4]
	Other
Biochemical or laboratory outcome measurements	INR, Platelet activity

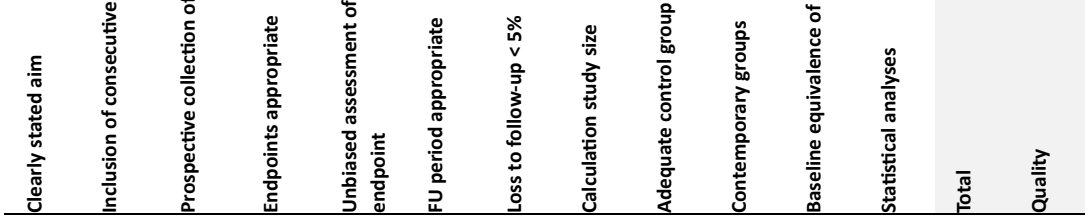
- * This table does not include all existing measurements.

Table S1: Outcome measurements



ROB = risk of bias; x = high risk of Bias; ? = unclear risk of Bias; v = low risk of bias

Table S2. **Risk-of-bias summary of included RCTs following the Cochrane risk-of-bias tool**



Cassar, 2006 [8]	2	2	2	2	1	1	2	0	1	2	1	2	18/24	M
Ferreira, 2010 [9]	2	0	2	2	0	2	0	0	N/A	N/A	N/A	N/A	8/16	P
Halle, 2017 [10]	2	2	2	2	1	1	2	0	N/A	N/A	N/A	N/A	12/16	M
Hess, 2022 [11]	1	1	2	1	1	2	2	0	N/A	N/A	N/A	N/A	10/16	M
Kremers, 2023 [12]	2	1	2	2	1	2	2	0	N/A	N/A	N/A	N/A	12/16	M
Qvist, 2019 [13]	2	1	1	2	2	2	2	0	N/A	N/A	N/A	N/A	12/16	M
Wawruch, 2021 [14]	2	2	1	2	2	2	2	0	N/A	N/A	N/A	N/A	13/16	M

N/A = not applicable; P = Poor; M = Moderate; G = good

***Table S3*. Risk-of-bias of bias summary for the non-randomised controlled trials following the MINORs-score**

Figures

Search	Actions	Details	Query	Results	Time
#4	•••	! >	Search: **#1 AND #2 AND #3** Sort by: **Most Recent**	128	08:50:30
#3	•••	! >	Search: **"Treatment Adherence and Compliance"[Mesh] OR "Medication Adherence"[Mesh]] OR ''compliance" [tiab] OR ''adherence" [tiab] OR "refus*"[tiab] OR "nonadherence"[tiab] OR "noncompliance"[tiab]** Sort by: **Most Recent**	542,177	08:50:03
#2	•••	! >	Search: **"Platelet Aggregation Inhibitors"[Mesh] OR "Platelet Aggregation Inhibitors" [Pharmacological Action] OR "Dual Anti-Platelet Therapy"[Mesh] OR ''Platelet aggregation inhibitor*"[tiab] OR ''antiplatelet therap*"[tiab] OR "anti platelet therap*"[tiab] OR OR "platelet inhibitor*"[tiab] OR "platelet aggregant*"[tiab] OR ''acetylsalicylic acid''[tiab] OR "aspirin"[tiab] OR "paracetamol"[tiab] OR ''clopidogrel''[tiab] OR OR "Anticoagulants"[Mesh] OR "Anticoagulants" [Pharmacological Action] OR "Indirect thrombin inhibitor*"[tiab] OR "anti coagulant"[tiab] OR "Fibrinolytic Agents" [Mesh] OR "fibrinolytic agent*"[tiab] OR "fibrinolytic drug*"[tiab] OR "Thrombolytic drug*"[tiab] OR "Thrombolytic agent*"[tiab] OR "antithrombotic drug*"[tiab] OR "antithrombotic agent*"[tiab] OR ''anticoagulant*''[tiab] OR ''Factor Xa inhibitor*''[tiab] OR ''Rivaroxaban''[tiab]** Sort by: **Most Recent**	468,945	08:49:49
#1	•••	>	Search: **("Peripheral Arterial Disease"[Mesh] OR ''peripheral arterial disease*"[tiab] OR "peripheral artery disease*"[tiab] OR ''lower extremity arterial disease*"[tiab] OR "lower extremity artery disease*"[tiab] OR ''Chronic Limb-Threatening Ischemia*"[tiab] OR ''intermittent claudication*"[tiab] OR ''Peripheral Arterial Vascular Disease*"[tiab] OR ''peripheral artery occlusive disease*"[tiab] OR "peripheral arterial occlusive disease*"[tiab]) AND ("Peripheral Arterial Disease"[Mesh] OR ''peripheral arterial disease*"[tiab] OR "peripheral artery disease*"[tiab] OR ''lower extremity arterial disease*"[tiab] OR "lower extremity artery disease*"[tiab] OR ''Chronic Limb-Threatening Ischemia*"[tiab] OR ''intermittent claudication*"[tiab] OR ''Peripheral Arterial Vascular Disease*"[tiab] OR ''peripheral artery occlusive disease*"[tiab] OR "peripheral arterial occlusive disease*"[tiab])** Sort by: **Most Recent**	32,848	08:44:08

Figure S1. Search PubMed/MEDLINE

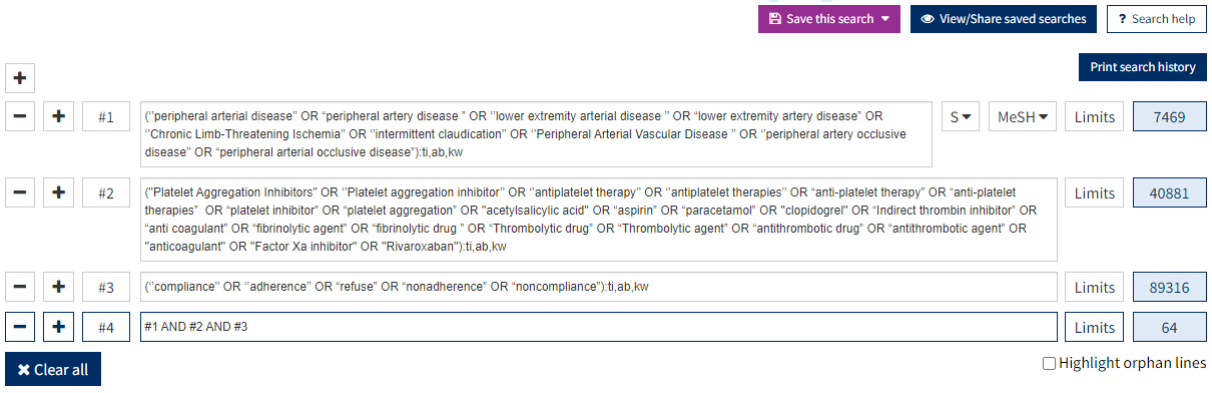


Figure S2. Search in Cochrane

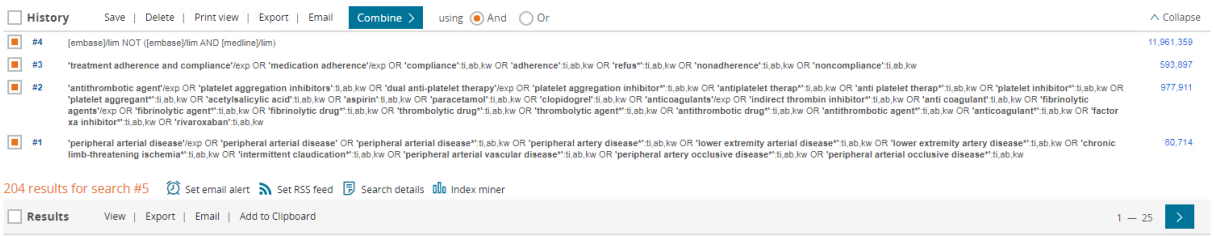


Figure S3. Search in Embase

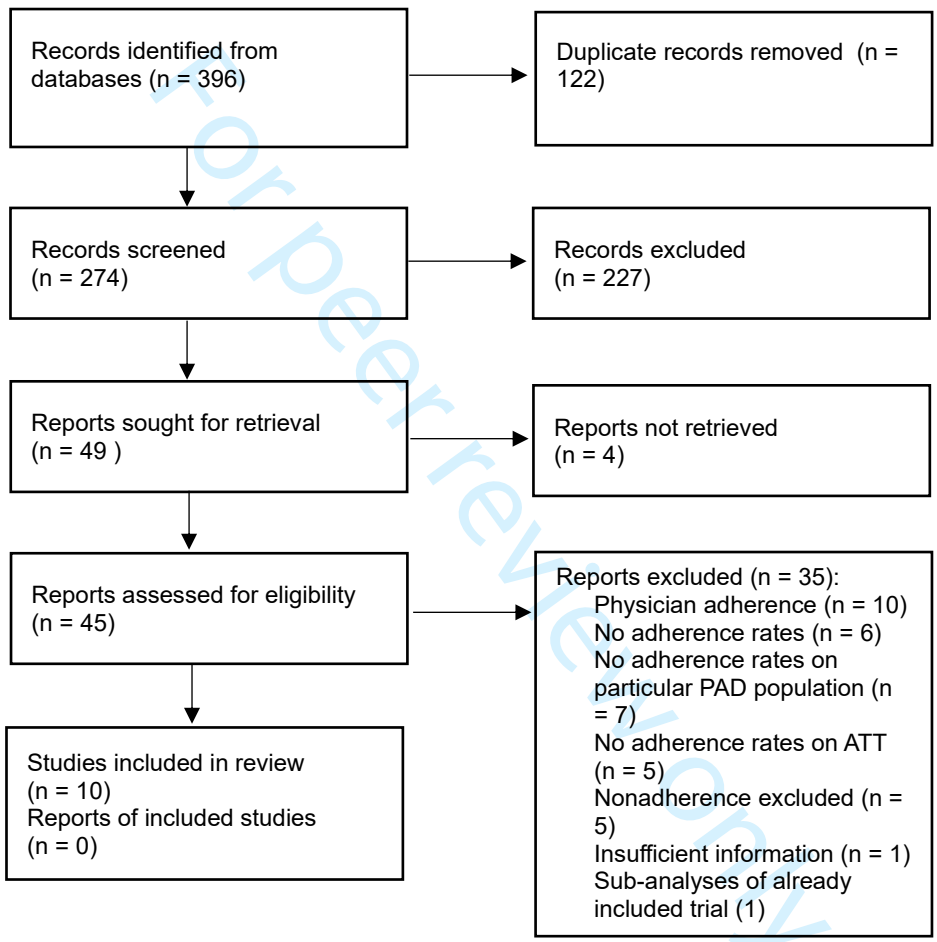


***Figure S4.* The flowchart of the selection process**

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Medication adherence of patients with peripheral arterial disease to antithrombotic therapy: a systematic review

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Secondary Subject Heading:	Cardiovascular medicine, Patient-centred medicine
Keywords:	Medication Adherence, Medication Persistence < Medication Adherence, Medication Review, Systematic Review, Vascular surgery < SURGERY, VASCULAR MEDICINE

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Medication adherence of patients with peripheral arterial disease to antithrombotic therapy: a systematic review

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Strengths and limitations of this study

- This review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-statement and contains a comprehensive search compiled by a medical database specialist.
- Studies regarding medication adherence of patients with peripheral arterial disease to antithrombotic therapy are scarce, leading to limited data.
- The included trials had rather heterogeneous study designs, making a meta-analysis infeasible and creating a wide dispersion in medication adherence proportions.
- This review provides insight into the extent of the patient's poor medication adherence which is an addition to the current literature focussing primarily on physician adherence.

ABSTRACT

Introduction: Patients with peripheral arterial disease (PAD) have a high risk of atherothrombotic events (AE). Antithrombotic therapy (ATT) is an important component in the treatment armamentarium to prevent AE. Poor medication adherence (MA) may compromise the preventive benefit. Most MA studies primarily concentrate on physician prescription adherence, patients without PAD diagnosis, and non-ATTs. We reviewed the data regarding poor MA of PAD patients to ATT.

Design: Systematic review

Method: Our protocol was based on the PRISMA statement. PubMed, EMBASE, and Cochrane Library were searched from 2000 to June 2023. Publications with a (sub)cohort of PAD patients that reported on patients' MA to ATT were included. The main exclusion criteria were reviews, expert opinions, and, case reports. All articles were reviewed on eligibility and methodological quality by 2 independent researchers. Primary objective was the proportion of patients with poor MA following patient-, pharmacy- or laboratory-reported outcome measurements. Poor MA is a combined endpoint of primary nonadherence (inability to initiate a prescription), secondary nonadherence (incorrect daily intake), and nonpersistence (discontinuation of daily intake).

Results: We identified 274 potentially relevant records of which 10 studies (32,628 patients) were included. Six studies were RCTs, 2 prospective-, and 2 retrospective studies. Most studies scored a moderate risk of bias and had heterogeneous study

designs. Poor MA rates ranged between 2-45%. Higher rates of poor MA were found in studies with longer follow-ups, pharmacy-reported outcome measurements, and registry-based cohorts.

Conclusion: Heterogeneous study designs create a wide dispersion in the proportions. However, poor MA to ATT was found in approximately one-third of the PAD patients and seemed to increase with longer therapy duration, which highlights the magnitude of this societal challenge. Enhancing patients' MA to ATT might be a key element to reducing the risk of AE, and therefore, more attention to MA in clinical and research settings is warranted.

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INTRODUCTION

Peripheral arterial disease (PAD) is associated with a high risk of atherothrombotic events (AE).[1, 2] The annual cardiovascular mortality risk of patients with intermittent claudication is approximately 5% compared to 11.5% for patients with critical limb-threatening ischemia.[3] In contrast to other atherosclerotic diseases such as coronary artery disease and cerebrovascular diseases, the overall long-term risk of major adverse cardiovascular events (MACE) of PAD patients is 2-fold worse.[4, 5] Last decades, revascularisation techniques have been improved which resulted in a 40% reduction in major lower limb amputations, however, the high cardiovascular mortality risk has barely declined.[1, 2, 6, 7]

A cornerstone in PAD management is MACE prevention through pharmacological therapies through lifelong antihypertensives, statins, and antithrombotic therapy (ATT).[1, 2, 8] Medication adherence (MA), which is the ability to take medication following prescriptions, is believed to be an essential factor for pharmacological therapies to be effective.[9, 10] However, approximately 50% of patients with long-term medication due to chronic diseases in developed countries have a poor MA.[11] More specifically, in patients with cardiovascular protective medicines, poor MA was found in 25-80%.[12-17] Nevertheless, the majority of these studies are outdated, focus on physician prescription adherence, primarily concentrate on patients without PAD diagnosis, or non-ATTs. MA is partly influenced by overarching factors such as healthcare systems, but many factors are disease- and patient-related such as clinical symptoms, socioeconomic background, and, medication side effects.[15, 18, 19] This underscores the importance of reporting on MA rates in specific patient populations and medication groups.

MA comprises two main elements: 'adherence' (or 'compliance') and 'persistence'.[9, 15]. No universally accepted consensus exists, however, adherence is mainly used to describe correct daily intake and persistence represents the continuation of daily intake.[9, 15] Adherence can be subdivided into primary- (or initiation) and secondary adherence to differentiate between the ability to initiate a new prescription and the daily intake after initiating the first prescription. Patients are mostly considered adherent when approximately 80% of the intake is as prescribed.[20, 21] MA is measured through patient- (questionnaires), pharmacy- (counting pills, refill records), or biochemical/laboratory-reported outcome measurements (Table S1).[22]

The optimal ATT in PAD patients is still under debate.[1, 8, 23, 24] MA is generally not discussed in trials although poor MA might lead to substantial bias and thus erroneous outcomes. As far as we know, there are no systematic analyses regarding MA of PAD patients to ATT. Therefore, we initiated this study to assess medication adherence specifically for ATT in patients with PAD.

METHODS

The protocol of this systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-statement (PROSPERO: CRD42023431803).[25, 26]

Search strategy and study selection

The systematic literature search was performed from inception to June 7th, 2023. The bibliographic databases PubMed, Embase.com, and Wiley/Cochrane Library were used. The index terms "Peripheral Arterial Disease", ''Antithrombotic Drugs'', "Treatment Adherence and Compliance" along with their synonyms and/or closely related words, were included. The search was compiled by a medical database specialist (see Figures S1, S2, and S3).

The search results were first deduplicated to which all obtained articles were screened on title and abstract by two independent researchers (EW and BM). Subsequently, the remaining articles were fully reviewed for eligibility and the references were screened for relevant publications (Figure S4). In case of disagreement, the study was reviewed by a third reviewer (CU).

Eligible publications contained a (sub)population of adult PAD patients and reported on patients' (non)adherence and/or (non)persistence to ATT. Publications before the year 2000, review articles, expert opinions, case reports, use of polypills, only nurse-led intensified follow-up, and non-English articles were excluded (Figure S4).

Outcome definitions and measurements

The primary objective was the proportion of PAD patients with poor MA following patient-, pharmacy-, or biochemical/laboratory-reported outcome measurements (Table S1). Poor MA includes; primary nonadherence (the inability to initiate a new prescription), secondary nonadherence (incorrect daily dosage/timing/frequency after initiating a new prescription), and nonpersistence (discontinuation of the medication intake).[9, 15, 22]

Secondary objectives were the proportion of PAD patients with (1) poor MA following pharmacy-reported outcome measurements, (2) primary nonadherence following pharmacy-reported- and (3) all outcome measurements, (4) secondary (short- and long-term) nonadherence following pharmacy-reported- and (5) all outcome measurements, and (6) nonpersistence following pharmacy-reported- and (7) all outcome measurements. Short-term was defined as a maximum follow-up of 6 months and long-term follow-up was defined as more than 6 months.

Data extraction and data analysis

The extracted data included; first author, year of publication, study design, country, number of PAD patients, disease stage, mean age, male-female ratio, type of ATT, type of MA subgroup(s), number of PAD patients that had poor MA per subgroup, number of PAD patients with overlap between two or more MA subgroups, threshold for poor MA, follow-up length, and MA outcome measurement.

The data were retrieved and collected in Review Manager Web (RevMan Web), version 4.14.0., The Cochrane Collaboration, Londen, UK. Based on the number of PAD patients with poor MA per subgroup and the total number of PAD patients, the proportions of nonadherence/nonpersistence were calculated per subgroup and processed in the table. For the primary objective, i.e. general poor MA, a separate calculation was made to adjust for patients with two or more kinds of poor MA to avoid overestimation of the general poor MA. Clinical homogeneity was assessed based on the study designs and definitions of nonadherence and/or non-persistence.

Quality assessment

The Cochrane Risk-of-Bias (ROB) tool was applied to assess the quality of the included randomised controlled trials (RCTs) that reported MA as primary outcome. The Cochrane ROB tool identifies different domains of bias and classifies risk into high-, low-, or unclear risk.[27] The overall quality was deemed high if all domains had a low ROB or if 1 domain was unclear. Unclear ROB was considered if 2≥ domains were unclear and high ROB was assigned if 1≥ domain had a high ROB.

For the non-RCTs and RCTs that report MA as a subanalysis, the methodological index for non-randomised studies (MINORS) score was used.[28] This method provides a 12-item list for comparative studies and an 8-item list for noncomparative studies. This score contains 3 classes; 0 (not reported), 1 (reported inadequate), and 2 (reported adequate). The overall quality for non-comparative trials was considered poor if the score was ≤8, moderate between 9-14, and good if ≥15. For the comparative trials, the score ranges were ≤15, 16-22, and ≥23.

Patient and public involvement

None

RESULTS

Screening process

The search identified 274 potentially relevant records after deduplicating. No articles were added by cross-linking. After reviewing the title and abstract, 227 articles were excluded and 4 articles could not be retrieved. The remaining 45 records were fully

screened of which 10 records could be included; 6 RCTs, 2 prospective-, and 2 retrospective studies (Figure S1). In case of conflicting screening decisions, consensus was reached between EW and BM.

Risk-of-bias assessment

Three articles were RCTs with MA as the main analysis of the trial and, therefore, the Cochrane ROB tool was used (Table S2). The MINOR-score was used for the other 7 articles (Table S3). Overall, most studies had a moderate ROB. Concerns regarding the ROB arise mostly due to patient-reported outcomes and non-adjudicated endpoints that could be easily influenced by knowledge of the intervention. Moreover, most articles did not calculate a sample size based on the MA outcome.

Study sample/study characteristics

The characteristics of the included studies are shown in Table 1. In total 32628 PAD patients were analysed. Most studies were executed in Europe, however, the two largest trials (EUCLID and VOYAGER PAD) that accounted for 63% of the included patients were executed in various countries and continents.[29, 30] MA was mostly reported as a sub-analysis. The included trials had rather heterogeneous study designs, making a meta-analysis infeasible.

1st Author, YOP	Country	PAD cohort	Severity disease	ATT	Age	Female (%)	FU
Randomised controlled trials							
Cassar 2006 [31]	United Kingdom	67	R1-3 w EVR	A w C or PLB	Mn 66 (R: 43-80)	15 (22)	1M
Haile 2022 [32]	Sweden	105	R1-3 w EVR/SVR	Any ATT	Md 72 (IQR: 69-77)	54 (52)	1Y
Hess 2022 [30]	Multiple	6564	R1-6 w EVR/SVR	ASA w PLB or DOAC	Mn 68 (IQR: 60-76)	1704 (26)	Md 28M (IQR: 22-34)
Jivegard 2005 [33]	Sweden	281	R4-6	ASA w PLB or LMWH	Mn 74 (SD:9)	126 (45)	3M
Qvist 2019 [34]	Denmark	2051	R 0-6 w/o EVR/SVR	Any ATT	Mn 70 (SD: 2.9)	0 (0)	5Y
Weissler 2022 [29]	Multiple	13842	R1-6 w/o EVR/SVR	C or T	Mn 67 (IQR: 59-75)	3884 (28)	30M (up to 42 M)
Prospective trials							
Ferreira 2010 [35]	Spain	194	NR	Any APT	Mn 64 (SD: 11.2)	43 (22)	1Y
Kremers 2023 [36]	Netherlands	246	R1-4	Any APT	Mn 69 (SD: 9.2)	105 (43)	1Y
Retrospective studies							
Halle 2017 [37]	United States	100	R1-6 w/o EVR/SVR	Any APT	Mn 64 (SD: 9.5)	42 (42)	NR
Wawruch 2021 [38]	Slovak Republic	9178	R 0-6 w/o EVR/SVR	Any APT	Mn 75	5285 (58)	5Y
Total		32628				11258 (35)	

YOP = year of publication; w = with; w/o = with or without; A = acetylsalicylic acid; ATT = antithrombotic therapy; DOAC = direct-acting oral anticoagulant; PLB = placebo; LMWH = low molecule weight heparin; C = clopidogrel; APT = antiplatelet therapy; NR = not reported; EVR = endovascular revascularisation; SVR = surgical/open

revascularisation; Mn = mean; Md = median; R = range; ±=standard deviation; ( ) = percentage, M = Months, Y = years,

Table 1: Articles eligible for this systematic review

Medication adherence

Poor MA following all outcome measurements ranged between 2-45% and following pharmacy-reported measurements between 9-45% (Table 2). One study, however, reported on all 3 subcategories of poor MA (i.e. primary-, secondary adherence, and persistence) and reported a total risk of 33%.[34] Overall, higher proportions of poor MA were found in studies with longer follow-ups, pharmacy-reported outcomes, and registry-based methods.[32, 34, 38]

One study reported on primary nonadherence based on a pharmacy-reported outcome measurement that occurred in 31% of the study population (Table 2). Short-term secondary nonadherence was reported in 3 articles and ranged between 9-26% (Table 2). Two of the 3 articles applied pharmacy-reported outcome measurement and found rates between 9-21%. Long-term secondary nonadherence, described in 5 articles, showed rates ranging between 5-26% comparable to short-term secondary nonadherence (Table 2). Following the pharmacy-reported outcome measurement long-term secondary nonadherence occurred in 14-20% of the patients. Lastly, nonpersistence was found between 2-33% (Table 2). Nonpersistence within the pharmacy-reported group ranged between 27-33%. Higher rates of nonpersistence were found in studies with longer follow-ups and registry-based methods.

Nr.	Reference	Nonadherence/ Nonpersistence	Follow-up	Measurement method	Threshold NA
Poor medication adherence					
Pharmacy ROM					
1	Cassar [31]	9%	6M	Counting returned pills	NR
2	Haile [32]	30%	1,5Y	Counting pills	<80%
3	Qvist [34]	45%*	5Y	National prescription register	Primary NA: filling prescription >120 days. Other: <80%
4	Wawruch [38]	43%	5Y	Counting retuned pills	<80%
Pharmacy- and patient ROM					
5	Hess [30]	8%	Md 28M (IQR: 22-34)	Interview NVQ and counting returned pills	NR
Patient ROM					
6	Ferreira [35]	2%	1Y	Interview (NVQ)	NR
7	Halle [37]	26%	NR	Morisky Medication Adherence Scale	8 Points
8	Jivegard [33]	26%	3M	Patient dairy	NR
9	Kremers [36]	5%	1Y	Morisky Medication Adherence Scale	8 Points
10	Weissler [29]	10%	30M (up to 42 M)	Interview	NR
Primary nonadherence					
1	Qvist [34]	31%	6M	National prescription register	Filling prescription >120 days
Secondary nonadherence					
Short-term secondary nonadherence					
Pharmacy ROM					
1	Cassar [31]	9%	6M	Counting returned pills	NR
2	Haile [32]	21%	6M	Counting pills	<80%
Patient ROM					
1	Jivegard	26%	3M	Patient diary	NR
Long-term secondary outcome					
Pharmacy ROM					
1	Haile [32]	14%	1.5Y	Counting pills	<80%
2	Qvist [34]	20%	5Y	National prescription register	<80%
3	Wawruch [38]	20%	5Y	Counting returned pills	<80%
Patient ROM					
4	Halle [37]	26%	NR	Counting pills	<80%
5	Kremers [36]	5%	NR	Morisky Medication Adherence Scale	8 points

Nonpersistence**					
Pharmacy ROM					
1	Qvist [34]	27%	5Y	National prescription register	<80%
2	Wawruch [38]	33%	5Y	Counting returned pills	<80%
Pharmacy- and patient ROM					
3	Hess [30]	8%	Md 28M (IQR 22-34)	Interview NVQ and counting returned pills	NR
Patient ROM					
4	Ferreira [35]	2%	1Y	Interview (NVQ)	NR
5	Weissler [29]	10%	30M (up to 42M)	Interview	NR

- NR = not reported; Md = median; M = months; IQR = interquartile range; ROM = reported outcome measurements, NA = nonadherence, NVQ = non-validated questionnaire

* Nonpersistence is excluded since the proportion of the patients who were nonadherent and nonpersistent is lacking.

** Non-persistent due to patients' decisions.

Table 2: Medication adherence

DISCUSSION

This systematic review provides an overview of the literature about MA to ATT in patients with PAD. The results demonstrate a poor MA rate of approximately one-third. Despite the variability in poor MA rates, it shows the magnitude of poor MA. Higher rates of poor MA were found in studies with longer follow-ups, pharmacy-reported outcomes, and registry-based methods. The secondary objectives show that all subcategories seem to have a nearly equal share in the overall risk of nonadherence.

Trial designs influence participant burdens which might partly explain the dispersion in MA amongst trials.[39, 40] In this review, 3 articles required minimum effort from participants because of the registry-based or retrospective design compared to the other articles including extensive follow-up, additional injections, and/or blood samples. Designs that required minimum effort, showed the highest rate of poor MA, nonadherence, and/or nonpersistence.[34, 37, 38] In the field of PAD, it is plausible that the likelihood of creating a more representative sample rises as the required effort for patients decreases. Literature shows that PAD patients are frequently precarious which is related to lower socioeconomic status and, therefore, less likely to participate in trials[12, 41-44] Reducing the complexity of trials leads to better understanding, fewer transfers, time commitment, and risk of additional (transfer) costs, resulting in a lower threshold for participation in this population.[40]

Regarding the length of follow-up, the literature shows a tendency for poor MA to increase as the duration of medication use increases.[45-47] This review shows similar results (Tables 2). One study provided a subanalysis (data not uptaken in our table) revealing that the highest proportion of nonadherence predominantly occurred between 13 and 24 months with 44% and 35.5% respectively compared to 17% within the first 12 months.[38] This pattern corresponds with the dispersion in our long-term nonadherence results (Table 2).

Additionally, the heterogeneity of the reporting methods, such as the definition of MA and outcome measurements, might contribute to the variety in proportions between studies. MA includes 3 subcategories; primary nonadherence, secondary nonadherence, and nonpersistence. Most articles, except one, researched only nonpersistence and/or secondary nonadherence. This might underestimate the proportion of poor MA by not identifying all categories of MA. The study that distinguished all 3 subcategories reported the highest proportion of poor MA.[34]

Healthcare systems have a major influence on MA.[15, 18, 19, 41] One study showed that participants from North America were more likely to discontinue their medication compared to participants from Europe.[29] Another study executed in North America confirmed that the inability to afford medication was a major reason for poor MA.[37] Most European countries have similar healthcare systems that reimburse necessary health costs.[48]

Regarding patient-related factors, studies that include post-revascularized PAD patients might show slightly higher MA rates.[30-32] One study showed lower long-term secondary nonadherence compared to short-term nonadherence.[32] These patients underwent revascularisation at 6 months follow-up. The severity of the symptoms might affect patients' perception of treatments. However, the literature is ambiguous.[37] Equivocal evidence regarding the impact of patient-related factors on MA is common. Amongst the included studies, subanalyses of patient-related factors show heterogeneous results.[29, 30, 35, 37, 38]

To estimate the individual risk of poor MA, it is of interest whether nonadherence leads to nonpersistence. It seems that adherent and nonadherence patients are both highly at risk for nonpersistence and thus poor MA.[38] The reason given is the lack of awareness regarding the life-long indication for ATT in PAD patients. We advise physicians to discuss MA with PAD patients. Additional research on all subcategories of MA based on registries that use pharmacy refill records and have extensive follow-up are warranted to confirm our findings.

The main strengths of this study are the selected inclusion of trials that include medication adherence of patients with PAD regarding antithrombotic therapies and

the distinction between different types of adherence which is clinically relevant when prescribing and discussing antithrombotic treatment. However, this review has a few limitations. Six out of the 10 included articles are RCTs. RCTs may not reflect real-world adherence as these patients are often more closely monitored, and therefore, more motivated. Most articles were at moderate risk for bias and a few studies did not mention its thresholds for non-adherence. Moreover, the heterogeneous study designs made a meta-analysis infeasible. Most of the included studies used patient-reported outcome measurements, i.e. questionnaires and interviews, which are at risk for multiple biases such as recall bias leading to potentially misleading low rates of poor MA.[13, 32, 49]

CONCLUSION

Studies regarding MA in PAD patients to ATT are scarce and contain heterogeneous designs creating a wide dispersion in MA proportions. However, poor MA to ATT was found in approximately one-third of the PAD patients and seemed to increase with longer duration of ATT use, which highlights the magnitude of this societal challenge.

AUTHOR CONTRIBUTIONS:

EW: Concept and design, screening, data collection, analyses and interpretation of data, writing of manuscript, final approval.

BM: Screening, data collection, and analyses, final approval.

CU: Concept and design, revision of manuscript, final approval.

GJdB: Concept and design, revision of manuscript, final approval, and is the guarantor.

DATA STATEMENT:

Access to the data is available via the correspondence of this article.

ETHICS APPROVAL:

Ethical approval was not considered as this review involved only previously published data.

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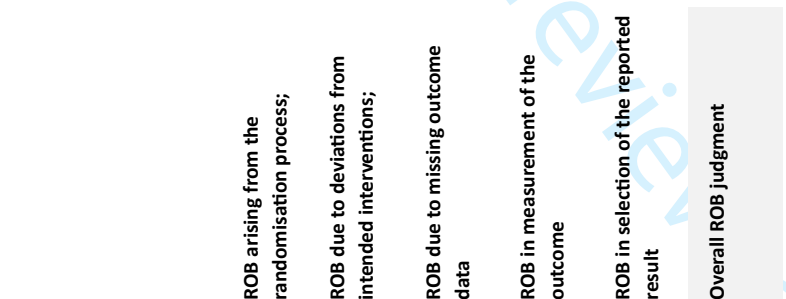
SUPPLEMENTARY FILE

Tables

Outcome measurements	Specification examples [description]*
pharmacist-reported outcome measurements	Medication Event Monitoring System (MEMS) [Use of electronic devices with microchips to record medication intake]
	Pharmacy records [Counting returned pills and tracking refill patterns]
	Prescription records registers [Tracking all dispensed drugs and tracking refill patterns]
Patient-reported outcome measurements	Morisky Medication Adherence Scale (MMAS-8)[1]
	Medication Adherence Report Scale (MARS)[2]
	Simplified Medication Adherence Questionnaire (SMAQ)[3]
	Brief Medication Questionnaire (BMQ)[4]
	Other
Biochemical or laboratory outcome measurements	INR, Platelet activity

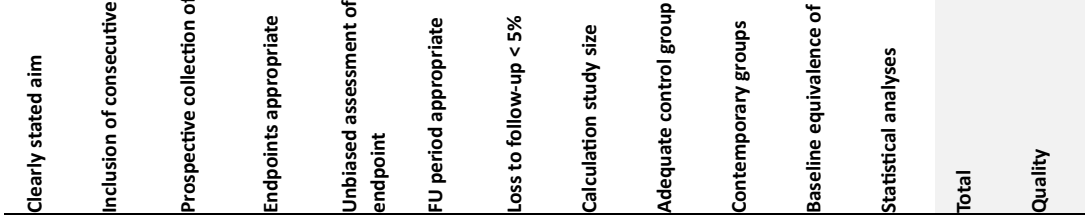
- * This table does not include all existing measurements.

Table S1: Outcome measurements



ROB = risk of bias; x = high risk of Bias; ? = unclear risk of Bias; v = low risk of bias

Table S2. **Risk-of-bias summary of included RCTs following the Cochrane risk-of-bias tool**



Cassar, 2006 [8]	2	2	2	2	1	1	2	0	1	2	1	2	18/24	M
Ferreira, 2010 [9]	2	0	2	2	0	2	0	0	N/A	N/A	N/A	N/A	8/16	P
Halle, 2017 [10]	2	2	2	2	1	1	2	0	N/A	N/A	N/A	N/A	12/16	M
Hess, 2022 [11]	1	1	2	1	1	2	2	0	N/A	N/A	N/A	N/A	10/16	M
Kremers, 2023 [12]	2	1	2	2	1	2	2	0	N/A	N/A	N/A	N/A	12/16	M
Qvist, 2019 [13]	2	1	1	2	2	2	2	0	N/A	N/A	N/A	N/A	12/16	M
Wawruch, 2021 [14]	2	2	1	2	2	2	2	0	N/A	N/A	N/A	N/A	13/16	M

N/A = not applicable; P = Poor; M = Moderate; G = good

***Table S3*. Risk-of-bias of bias summary for the non-randomised controlled trials following the MINORs-score**

Figures

Search	Actions	Details	Query	Results	Time
#4	•••	! >	Search: **#1 AND #2 AND #3** Sort by: **Most Recent**	128	08:50:30
#3	•••	! >	Search: **"Treatment Adherence and Compliance"[Mesh] OR "Medication Adherence"[Mesh]] OR ''compliance" [tiab] OR ''adherence" [tiab] OR "refus*"[tiab] OR "nonadherence"[tiab] OR "noncompliance"[tiab]** Sort by: **Most Recent**	542,177	08:50:03
#2	•••	! >	Search: **"Platelet Aggregation Inhibitors"[Mesh] OR "Platelet Aggregation Inhibitors" [Pharmacological Action] OR "Dual Anti-Platelet Therapy"[Mesh] OR ''Platelet aggregation inhibitor*"[tiab] OR ''antiplatelet therap*"[tiab] OR "anti platelet therap*"[tiab] OR OR "platelet inhibitor*"[tiab] OR "platelet aggregant*"[tiab] OR ''acetylsalicylic acid''[tiab] OR "aspirin"[tiab] OR "paracetamol"[tiab] OR ''clopidogrel''[tiab] OR OR "Anticoagulants"[Mesh] OR "Anticoagulants" [Pharmacological Action] OR "Indirect thrombin inhibitor*"[tiab] OR "anti coagulant"[tiab] OR "Fibrinolytic Agents" [Mesh] OR "fibrinolytic agent*"[tiab] OR "fibrinolytic drug*"[tiab] OR "Thrombolytic drug*"[tiab] OR "Thrombolytic agent*"[tiab] OR "antithrombotic drug*"[tiab] OR "antithrombotic agent*"[tiab] OR ''anticoagulant*''[tiab] OR ''Factor Xa inhibitor*''[tiab] OR ''Rivaroxaban''[tiab]** Sort by: **Most Recent**	468,945	08:49:49
#1	•••	>	Search: **("Peripheral Arterial Disease"[Mesh] OR ''peripheral arterial disease*"[tiab] OR "peripheral artery disease*"[tiab] OR ''lower extremity arterial disease*"[tiab] OR "lower extremity artery disease*"[tiab] OR ''Chronic Limb-Threatening Ischemia*"[tiab] OR ''intermittent claudication*"[tiab] OR ''Peripheral Arterial Vascular Disease*"[tiab] OR ''peripheral artery occlusive disease*"[tiab] OR "peripheral arterial occlusive disease*"[tiab]) AND ("Peripheral Arterial Disease"[Mesh] OR ''peripheral arterial disease*"[tiab] OR "peripheral artery disease*"[tiab] OR ''lower extremity arterial disease*"[tiab] OR "lower extremity artery disease*"[tiab] OR ''Chronic Limb-Threatening Ischemia*"[tiab] OR ''intermittent claudication*"[tiab] OR ''Peripheral Arterial Vascular Disease*"[tiab] OR ''peripheral artery occlusive disease*"[tiab] OR "peripheral arterial occlusive disease*"[tiab])** Sort by: **Most Recent**	32,848	08:44:08

Figure S1. Search PubMed/MEDLINE

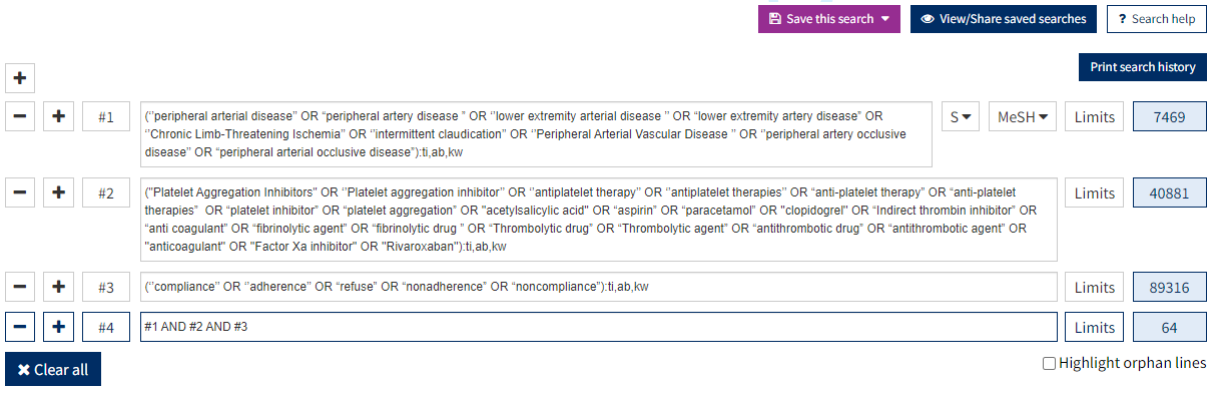


Figure S2. Search in Cochrane

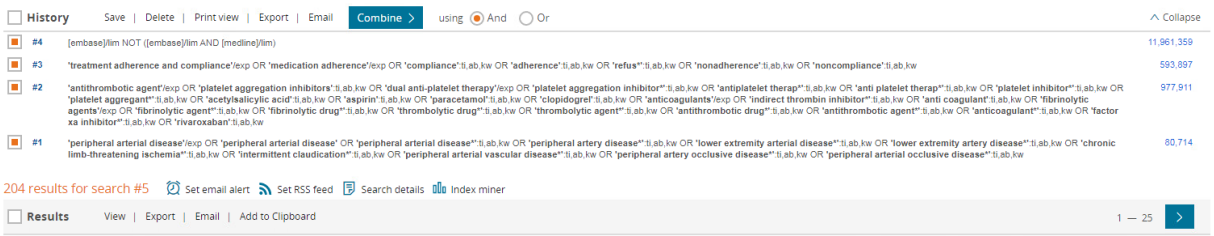


Figure S3. Search in Embase

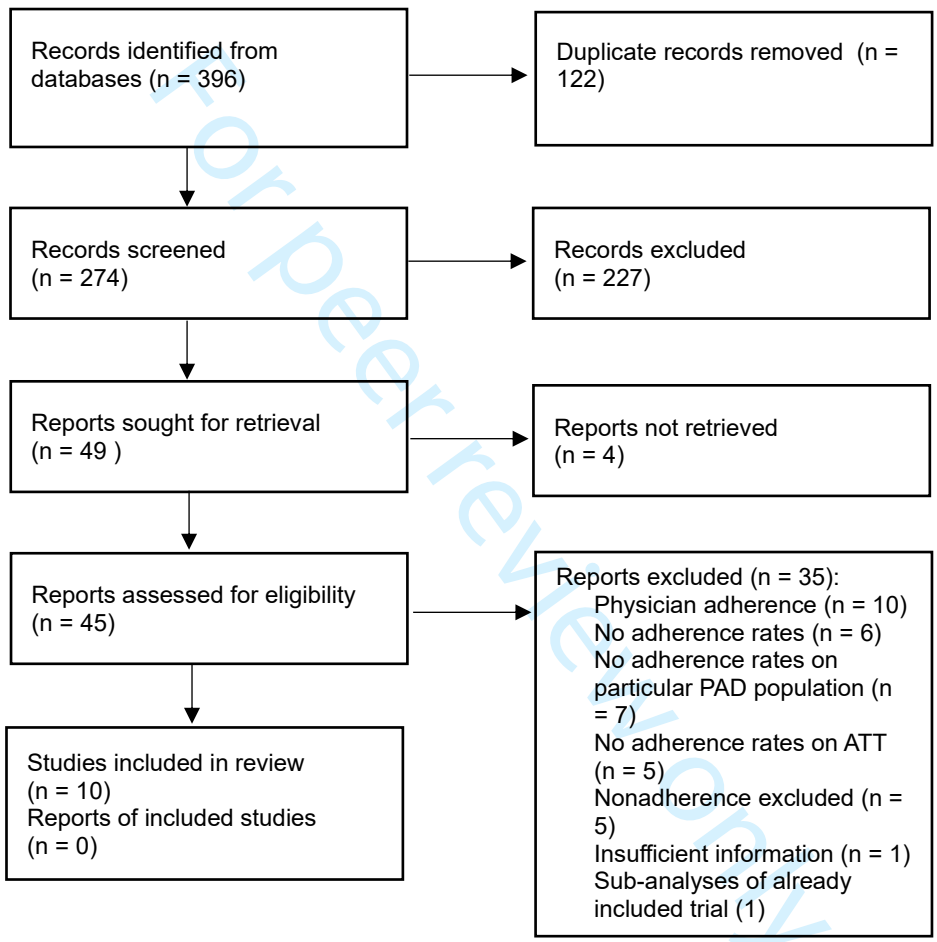


***Figure S4.* The flowchart of the selection process**

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BMJ Open

Medication adherence of patients with peripheral arterial disease to antithrombotic therapy: a systematic review

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Secondary Subject Heading:	Cardiovascular medicine, Patient-centred medicine
Keywords:	Medication Adherence, Medication Persistence < Medication Adherence, Medication Review, Systematic Review, Vascular surgery < SURGERY, VASCULAR MEDICINE

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Medication adherence of patients with peripheral arterial disease to antithrombotic therapy: a systematic review

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Keywords: Medication Adherence, Treatment Adherence and Compliance, Peripheral Arterial Disease, Platelet Aggregation Inhibitors, Anticoagulants, Systematic Review.

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Strengths and limitations of this study

- This review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-statement and contains a comprehensive search compiled by a medical database specialist.
- Studies regarding medication adherence of patients with peripheral arterial disease to antithrombotic therapy are scarce, leading to limited data.
- The included trials had rather heterogeneous study designs, making a meta-analysis infeasible and creating a wide dispersion in medication adherence proportions.
- This review provides insight into the extent of the patient's poor medication adherence which is an addition to the current literature focussing primarily on physician adherence.

ABSTRACT

Objectives: Antithrombotic therapy (ATT) prevents atherothrombotic events (AE) in patients with peripheral arterial disease (PAD). However, the benefit may be compromised by poor medication adherence (MA). Therefore, our primary objective was the proportion of PAD patients with poor MA in literature following patient-, pharmacy- or laboratory-reported outcome measurements. Poor MA is a combined outcome of primary nonadherence (inability to initiate a prescription), secondary nonadherence (incorrect daily intake), and nonpersistence (discontinuation of daily intake).

Design: Systematic review based on the PRISMA statement.

Data sources: PubMed, EMBASE, and Cochrane Library were searched from 2000 to June 2023.

Eligibility criteria: Publications with a (sub)cohort of PAD patients that reported on patients' MA to ATT were included.

Data extraction and synthesis: All articles were reviewed on eligibility and methodological quality by 2 independent researchers. The data were retrieved and collected in Review Manager Web and the percentages were calculated per subgroup. Risk of bias was assessed by using the Cochrane Risk-of-Bias tool for randomised controlled trials (RCT) and the methodological index for non-randomised studies (MINORS) score for non-RCTs.

Results: We identified 274 potential records of which 10 studies (32,628 patients) were included. Six studies were RCTs, 2 prospective-, and 2 retrospective studies. Most studies scored a moderate risk of bias and had heterogeneous study designs. Poor MA rates ranged between 2-45%. Higher rates of poor MA were found in studies with longer follow-ups, pharmacy-reported outcome measurements, and registry-based cohorts.

Conclusion: Heterogeneous study designs create a wide dispersion in the proportions. However, poor MA to ATT was found in approximately one-third of the PAD patients and seemed to increase with longer therapy duration, which highlights the magnitude of this societal challenge. Enhancing patients' MA to ATT might be a key element to reducing the risk of AE, and therefore, more attention to MA in clinical and research settings is warranted.

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PROSPERO registration number: CRD42023431803

INTRODUCTION

Peripheral arterial disease (PAD) is associated with a high risk of atherothrombotic events (AE).[1, 2] The annual cardiovascular mortality risk of patients with intermittent claudication is approximately 5% compared to 11.5% for patients with critical limb-threatening ischemia.[3] In contrast to other atherosclerotic diseases such as coronary artery disease and cerebrovascular diseases, the overall long-term risk of major adverse cardiovascular events (MACE) of PAD patients is 2-fold worse.[4, 5] Last decades, revascularisation techniques have been improved which resulted in a 40% reduction in major lower limb amputations, however, the high cardiovascular mortality risk has barely declined.[1, 2, 6, 7]

A cornerstone in PAD management is MACE prevention through pharmacological therapies through lifelong antihypertensives, statins, and antithrombotic therapy (ATT).[1, 2, 8] Medication adherence (MA), which is the ability to take medication following prescriptions, is believed to be an essential factor for pharmacological therapies to be effective.[9, 10] However, approximately 50% of patients with long-term medication due to chronic diseases in developed countries have a poor MA.[11] More specifically, in patients with cardiovascular protective medicines, poor MA was found in 25-80%.[12-17] Nevertheless, the majority of these studies are outdated, focus on physician prescription adherence, primarily concentrate on patients without PAD diagnosis, or non-ATTs. MA is partly influenced by overarching factors such as healthcare systems, but many factors are disease- and patient-related such as clinical symptoms, socioeconomic background, and, medication side effects.[15, 18, 19] This underscores the importance of reporting on MA rates in specific patient populations and medication groups.

MA comprises two main elements: 'adherence' (or 'compliance') and 'persistence'.[9, 15]. No universally accepted consensus exists, however, adherence is mainly used to describe correct daily intake and persistence represents the continuation of daily intake.[9, 15] Adherence can be subdivided into primary- (or initiation) and secondary adherence to differentiate between the ability to initiate a new prescription and the daily intake after initiating the first prescription. Patients are mostly considered adherent when approximately 80% of the intake is as prescribed.[20, 21] MA is measured through patient- (questionnaires), pharmacy- (counting pills, refill records), or biochemical/laboratory-reported outcome measurements (Table S1).[22]

The optimal ATT in PAD patients is still under debate.[1, 8, 23, 24] MA is generally not discussed in trials although poor MA might lead to substantial bias and thus erroneous outcomes. As far as we know, there are no systematic analyses regarding MA of PAD patients to ATT. Therefore, we initiated this study to assess medication adherence specifically for ATT in patients with PAD.

METHODS

The protocol of this systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-statement (PROSPERO: CRD42023431803).[25, 26]

Search strategy and study selection

The systematic literature search was performed from inception to June 7th, 2023. The bibliographic databases PubMed, Embase.com, and Wiley/Cochrane Library were used. The index terms "Peripheral Arterial Disease", ''Antithrombotic Drugs'', "Treatment Adherence and Compliance" along with their synonyms and/or closely related words, were included. The search was compiled by a medical database specialist (see Figures S1, S2, and S3).

The search results were first deduplicated to which all obtained articles were screened on title and abstract by two independent researchers (EW and BM). Subsequently, the remaining articles were fully reviewed for eligibility and the references were screened for relevant publications (Figure S4). In case of disagreement, the study was reviewed by a third reviewer (CU).

Eligible publications contained a (sub)population of adult PAD patients and reported on patients' (non)adherence and/or (non)persistence to ATT. Publications before the year 2000, review articles, expert opinions, case reports, use of polypills, only nurse-led intensified follow-up, and non-English articles were excluded (Figure S4).

Outcome definitions and measurements

The primary objective was the proportion of PAD patients with poor MA following patient-, pharmacy-, or biochemical/laboratory-reported outcome measurements (Table S1). Poor MA includes; primary nonadherence (the inability to initiate a new prescription), secondary nonadherence (incorrect daily dosage/timing/frequency after initiating a new prescription), and nonpersistence (discontinuation of the medication intake).[9, 15, 22]

Secondary objectives were the proportion of PAD patients with (1) poor MA following pharmacy-reported outcome measurements, (2) primary nonadherence following pharmacy-reported- and (3) all outcome measurements, (4) secondary (short- and long-term) nonadherence following pharmacy-reported- and (5) all outcome measurements, and (6) nonpersistence following pharmacy-reported- and (7) all outcome measurements. Short-term was defined as a maximum follow-up of 6 months and long-term follow-up was defined as more than 6 months.

Data extraction and data analysis

The extracted data included; first author, year of publication, study design, country, number of PAD patients, disease stage, mean age, male-female ratio, type of ATT, type of MA subgroup(s), number of PAD patients that had poor MA per subgroup, number of PAD patients with overlap between two or more MA subgroups, threshold for poor MA, follow-up length, and MA outcome measurement.

The data were retrieved and collected in Review Manager Web (RevMan Web), version 4.14.0., The Cochrane Collaboration, Londen, UK. Based on the number of PAD patients with poor MA per subgroup and the total number of PAD patients, the proportions of nonadherence/nonpersistence were calculated per subgroup and processed in the table. For the primary objective, i.e. general poor MA, a separate calculation was made to adjust for patients with two or more kinds of poor MA to avoid overestimation of the general poor MA. Clinical homogeneity was assessed based on the study designs and definitions of nonadherence and/or non-persistence.

Quality assessment

The Cochrane Risk-of-Bias (ROB) tool was applied to assess the quality of the included randomised controlled trials (RCTs) that reported MA as primary outcome. The Cochrane ROB tool identifies different domains of bias and classifies risk into high-, low-, or unclear risk.[27] The overall quality was deemed high if all domains had a low ROB or if 1 domain was unclear. Unclear ROB was considered if 2≥ domains were unclear and high ROB was assigned if 1≥ domain had a high ROB.

For the non-RCTs and RCTs that report MA as a subanalysis, the methodological index for non-randomised studies (MINORS) score was used.[28] This method provides a 12-item list for comparative studies and an 8-item list for noncomparative studies. This score contains 3 classes; 0 (not reported), 1 (reported inadequate), and 2 (reported adequate). The overall quality for non-comparative trials was considered poor if the score was ≤8, moderate between 9-14, and good if ≥15. For the comparative trials, the score ranges were ≤15, 16-22, and ≥23.

Patient and public involvement

None

RESULTS

Screening process

The search identified 274 potentially relevant records after deduplicating. No articles were added by cross-linking. After reviewing the title and abstract, 227 articles were excluded and 4 articles could not be retrieved. The remaining 45 records were fully

screened of which 10 records could be included; 6 RCTs, 2 prospective-, and 2 retrospective studies (Figure S1). In case of conflicting screening decisions, consensus was reached between EW and BM.

Risk-of-bias assessment

Three articles were RCTs with MA as the main analysis of the trial and, therefore, the Cochrane ROB tool was used (Table S2). The MINOR-score was used for the other 7 articles (Table S3). Overall, most studies had a moderate ROB. Concerns regarding the ROB arise mostly due to patient-reported outcomes and non-adjudicated endpoints that could be easily influenced by knowledge of the intervention. Moreover, most articles did not calculate a sample size based on the MA outcome.

Study sample/study characteristics

The characteristics of the included studies are shown in Table 1. In total 32628 PAD patients were analysed. Most studies were executed in Europe, however, the two largest trials (EUCLID and VOYAGER PAD) that accounted for 63% of the included patients were executed in various countries and continents.[29, 30] MA was mostly reported as a sub-analysis. The included trials had rather heterogeneous study designs, making a meta-analysis infeasible.

1st Author, YOP	Country	Sample size	Disease severity	ATT	Age	Female (%)	Follow-up
Randomised controlled trials							
Cassar 2006 [31]	United Kingdom	67	R1-3 w EVR	A w C or PLB	Mn 66 (R: 43-80)	15 (22)	1M
Haile 2022 [32]	Sweden	105	R1-3 w EVR/SVR	Any ATT	Md 72 (IQR: 69-77)	54 (52)	1,5Y
Hess 2022 [30]	Multiple	6564	R1-6 w EVR/SVR	ASA w PLB or DOAC	Mn 68 (IQR: 60-76)	1704 (26)	Md 28M (IQR: 22-34)
Jivegard 2005 [33]	Sweden	281	R4-6	ASA w PLB or LMWH	Mn 74 (SD:9)	126 (45)	3M
Qvist 2019 [34]	Denmark	2051	R 0-6 w/o EVR/SVR	Any ATT	Mn 70 (SD: 2.9)	0 (0)	5Y
Weissler 2022 [29]	Multiple	13842	R1-6 w/o EVR/SVR	C or T	Mn 67 (IQR: 59-75)	3884 (28)	30M (up to 42 M)
Prospective trials							
Ferreira 2010 [35]	Spain	194	NR	Any APT	Mn 64 (SD: 11.2)	43 (22)	1Y
Kremers 2023 [36]	Netherlands	246	R1-4	Any APT	Mn 69 (SD: 9.2)	105 (43)	1Y
Retrospective studies							
Halle 2017 [37]	United States	100	R1-6 w/o EVR/SVR	Any APT	Mn 64 (SD: 9.5)	42 (42)	NR
Wawruch 2021 [38]	Slovak Republic	9178	R 0-6 w/o EVR/SVR	Any APT	Mn 75	5285 (58)	5Y
Total		32628				11258 (35)	

YOP = year of publication; w = with; w/o = with or without; A = acetylsalicylic acid; ATT = antithrombotic therapy; DOAC = direct-acting oral anticoagulant; PLB = placebo; LMWH = low molecule weight heparin; C = clopidogrel; APT = antiplatelet therapy; R = Rutherford classification; NR = not reported; EVR = endovascular revascularisation;

SVR = surgical/open revascularisation; Mn = mean; Md = median; R = range; ±=standard deviation; ( ) = percentage, M = Months, Y = years,

Table 1: Articles eligible for this systematic review

Medication adherence

Poor MA following all outcome measurements ranged between 2-45% and following pharmacy-reported measurements between 9-45% (Table 2). One study, however, reported on all 3 subcategories of poor MA (i.e. primary-, secondary adherence, and persistence) and reported a total risk of 33%.[34] Overall, higher proportions of poor MA were found in studies with longer follow-ups, pharmacy-reported outcomes, and registry-based methods.[32, 34, 38]

One study reported on primary nonadherence based on a pharmacy-reported outcome measurement that occurred in 31% of the study population (Table 2). Short-term secondary nonadherence was reported in 3 articles and ranged between 9-26% (Table 2). Two of the 3 articles applied pharmacy-reported outcome measurement and found rates between 9-21%. Long-term secondary nonadherence, described in 5 articles, showed rates ranging between 5-26% comparable to short-term secondary nonadherence (Table 2). Following the pharmacy-reported outcome measurement long-term secondary nonadherence occurred in 14-20% of the patients. Lastly, nonpersistence was found between 2-33% (Table 2). Nonpersistence within the pharmacy-reported group ranged between 27-33%. Higher rates of nonpersistence were found in studies with longer follow-ups and registry-based methods.

Nr.	Reference	Nonadherence/ Nonpersistence	Follow-up	Measurement method	Threshold NA
Poor medication adherence					
Pharmacy ROM					
1	Cassar [31]	9%	1M	Counting returned pills	NR
2	Haile [32]	30%	1,5Y	Counting pills	<80%
3	Qvist [34]	45%*	5Y	National prescription register	Primary NA: filling prescription >120 days. Other: <80%
4	Wawruch [38]	43%	5Y	Counting retuned pills	<80%
Pharmacy- and patient ROM					
5	Hess [30]	8%	Md 28M (IQR: 22-34)	Interview NVQ and counting returned pills	NR
Patient ROM					
6	Ferreira [35]	2%	1Y	Interview (NVQ)	NR
7	Halle [37]	26%	NR	Morisky Medication Adherence Scale	8 Points
8	Jivegard [33]	26%	3M	Patient dairy	NR
9	Kremers [36]	5%	1Y	Morisky Medication Adherence Scale	8 Points
10	Weissler [29]	10%	30M (up to 42 M)	Interview	NR
Primary nonadherence					
1	Qvist [34]	31%	6M	National prescription register	Filling prescription >120 days
Secondary nonadherence					
Short-term secondary nonadherence					
Pharmacy ROM					
1	Cassar [31]	9%	1M	Counting returned pills	NR
2	Haile [32]	21%	6M	Counting pills	<80%
Patient ROM					
1	Jivegard	26%	3M	Patient diary	NR
Long-term secondary outcome					
Pharmacy ROM					
1	Haile [32]	14%	1Y	Counting pills	<80%
2	Qvist [34]	20%	5Y	National prescription register	<80%
3	Wawruch [38]	20%	5Y	Counting returned pills	<80%
Patient ROM					
4	Halle [37]	26%	NR	Counting pills	<80%
5	Kremers [36]	5%	1Y	Morisky Medication Adherence Scale	8 points

Nonpersistence**					
Pharmacy ROM					
1	Qvist [34]	27%	5Y	National prescription register	<80%
2	Wawruch [38]	33%	5Y	Counting returned pills	<80%
Pharmacy- and patient ROM					
3	Hess [30]	8%	Md 28M (IQR 22-34)	Interview NVQ and counting returned pills	NR
Patient ROM					
4	Ferreira [35]	2%	1Y	Interview (NVQ)	NR
5	Weissler [29]	10%	30M (up to 42M)	Interview	NR

- NR = not reported; Md = median; M = months; IQR = interquartile range; ROM = reported outcome measurements, NA = nonadherence, NVQ = non-validated questionnaire

* Nonpersistence is excluded since the proportion of the patients who were nonadherent and nonpersistent is lacking.

** Non-persistent due to patients' decisions.

Table 2: Medication adherence

DISCUSSION

This systematic review provides an overview of the literature about MA to ATT in patients with PAD. The results demonstrate a poor MA rate of approximately one-third. Despite the variability in poor MA rates, it shows the magnitude of poor MA. Higher rates of poor MA were found in studies with longer follow-ups, pharmacy-reported outcomes, and registry-based methods. The secondary objectives show that all subcategories seem to have a nearly equal share in the overall risk of nonadherence.

Trial designs influence participant burdens which might partly explain the dispersion in MA amongst trials.[39, 40] In this review, 3 articles required minimum effort from participants because of the registry-based or retrospective design compared to the other articles including extensive follow-up, additional injections, and/or blood samples. Designs that required minimum effort, showed the highest rate of poor MA, nonadherence, and/or nonpersistence.[34, 37, 38] In the field of PAD, it is plausible that the likelihood of creating a more representative sample rises as the required effort for patients decreases. Literature shows that PAD patients are frequently precarious which is related to lower socioeconomic status and, therefore, less likely to participate in trials[12, 41-44] Reducing the complexity of trials leads to better understanding, fewer transfers, time commitment, and risk of additional (transfer) costs, resulting in a lower threshold for participation in this population.[40]

Regarding the length of follow-up, the literature shows a tendency for poor MA to increase as the duration of medication use increases.[45-47] This review shows similar results (Tables 2). One study provided a subanalysis (data not uptaken in our tables) revealing that the highest proportion of nonadherence predominantly occurred between 13 and 24 months with 44% and 35.5% respectively compared to 17% within the first 12 months.[38] This pattern corresponds with the dispersion in our long-term nonadherence results (Table 2).

Additionally, the heterogeneity of the reporting methods, such as the definition of MA and outcome measurements, might contribute to the variety in proportions between studies. MA includes 3 subcategories; primary nonadherence, secondary nonadherence, and nonpersistence. Most articles, except one, researched only nonpersistence and/or secondary nonadherence. This might underestimate the proportion of poor MA by not identifying all categories of MA. The study that distinguished all 3 subcategories reported the highest proportion of poor MA.[34]

Healthcare systems have a major influence on MA.[15, 18, 19, 41] One study showed that participants from North America were more likely to discontinue their medication compared to participants from Europe.[29] Another study executed in North America confirmed that the inability to afford medication was a major reason for poor MA.[37] Most European countries have similar healthcare systems that reimburse necessary health costs.[48]

Regarding patient-related factors, studies that include post-revascularized PAD patients might show slightly higher MA rates.[30-32] One study showed lower long-term secondary nonadherence compared to short-term nonadherence.[32] These patients underwent revascularisation at 6 months follow-up. The severity of the symptoms might affect patients' perception of treatments. However, the literature is ambiguous.[37] Equivocal evidence regarding the impact of patient-related factors on MA is common. Amongst the included studies, subanalyses of patient-related factors show heterogeneous results.[29, 30, 35, 37, 38]

To estimate the individual risk of poor MA, it is of interest whether nonadherence leads to nonpersistence. It seems that adherent and nonadherence patients are both highly at risk for nonpersistence and thus poor MA.[38] The reason given is the lack of awareness regarding the life-long indication for ATT in PAD patients. We advise physicians to discuss MA with PAD patients. Additional research on all subcategories of MA based on registries that use pharmacy refill records and have extensive follow-up are warranted to confirm our findings.

The main strengths of this study are the selected inclusion of trials that include medication adherence of patients with PAD regarding antithrombotic therapies and

the distinction between different types of adherence which is clinically relevant when prescribing and discussing antithrombotic treatment. However, this review has a few limitations. Six out of the 10 included articles are RCTs. RCTs may not reflect real-world adherence as these patients are often more closely monitored, and therefore, more motivated. Most articles were at moderate risk for bias and a few studies did not mention its thresholds for non-adherence. Moreover, the heterogeneous study designs made a meta-analysis infeasible. Most of the included studies used patient-reported outcome measurements, i.e. questionnaires and interviews, which are at risk for multiple biases such as recall bias leading to potentially misleading low rates of poor MA.[13, 32, 49]

CONCLUSION

Studies regarding MA in PAD patients to ATT are scarce and contain heterogeneous designs creating a wide dispersion in MA proportions. However, poor MA to ATT was found in approximately one-third of the PAD patients and seemed to increase with longer duration of ATT use, which highlights the magnitude of this societal challenge.

AUTHOR CONTRIBUTIONS:

EW: Concept and design, screening, data collection, analyses and interpretation of data, writing of manuscript, final approval.

BM: Screening, data collection, and analyses, final approval.

CU: Concept and design, revision of manuscript, final approval.

GJdB: Concept and design, revision of manuscript, final approval, and is the guarantor.

DATA STATEMENT:

Access to the data is available via the correspondence of this article.

ETHICS APPROVAL:

Ethical approval was not considered as this review involved only previously published data.

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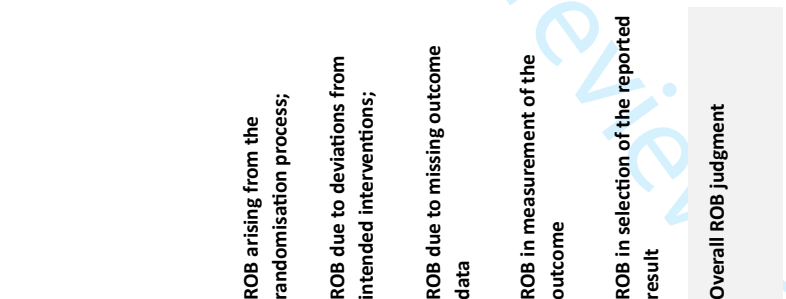
SUPPLEMENTARY FILE

Tables

Outcome measurements	Specification examples [description]*
pharmacist-reported outcome measurements	Medication Event Monitoring System (MEMS) [Use of electronic devices with microchips to record medication intake]
	Pharmacy records [Counting returned pills and tracking refill patterns]
	Prescription records registers [Tracking all dispensed drugs and tracking refill patterns]
Patient-reported outcome measurements	Morisky Medication Adherence Scale (MMAS-8)[1]
	Medication Adherence Report Scale (MARS)[2]
	Simplified Medication Adherence Questionnaire (SMAQ)[3]
	Brief Medication Questionnaire (BMQ)[4]
	Other
Biochemical or laboratory outcome measurements	INR, Platelet activity

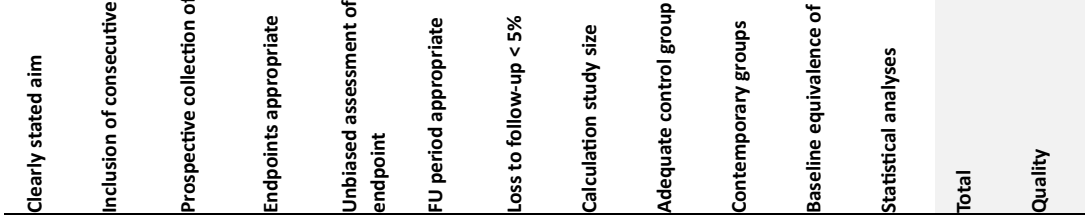
- * This table does not include all existing measurements.

Table S1: Outcome measurements



ROB = risk of bias; x = high risk of Bias; ? = unclear risk of Bias; v = low risk of bias

Table S2. **Risk-of-bias summary of included RCTs following the Cochrane risk-of-bias tool**



Cassar, 2006 [8]	2	2	2	2	1	1	2	0	1	2	1	2	18/24	M
Ferreira, 2010 [9]	2	0	2	2	0	2	0	0	N/A	N/A	N/A	N/A	8/16	P
Halle, 2017 [10]	2	2	2	2	1	1	2	0	N/A	N/A	N/A	N/A	12/16	M
Hess, 2022 [11]	1	1	2	1	1	2	2	0	N/A	N/A	N/A	N/A	10/16	M
Kremers, 2023 [12]	2	1	2	2	1	2	2	0	N/A	N/A	N/A	N/A	12/16	M
Qvist, 2019 [13]	2	1	1	2	2	2	2	0	N/A	N/A	N/A	N/A	12/16	M
Wawruch, 2021 [14]	2	2	1	2	2	2	2	0	N/A	N/A	N/A	N/A	13/16	M

N/A = not applicable; P = Poor; M = Moderate; G = good

***Table S3*. Risk-of-bias of bias summary for the non-randomised controlled trials following the MINORs-score**

Figures

Search	Actions	Details	Query	Results	Time
#4	•••	! >	Search: **#1 AND #2 AND #3** Sort by: **Most Recent**	128	08:50:30
#3	•••	! >	Search: **"Treatment Adherence and Compliance"[Mesh] OR "Medication Adherence"[Mesh]] OR ''compliance" [tiab] OR ''adherence" [tiab] OR "refus*"[tiab] OR "nonadherence"[tiab] OR "noncompliance"[tiab]** Sort by: **Most Recent**	542,177	08:50:03
#2	•••	! >	Search: **"Platelet Aggregation Inhibitors"[Mesh] OR "Platelet Aggregation Inhibitors" [Pharmacological Action] OR "Dual Anti-Platelet Therapy"[Mesh] OR ''Platelet aggregation inhibitor*"[tiab] OR ''antiplatelet therap*"[tiab] OR "anti platelet therap*"[tiab] OR OR "platelet inhibitor*"[tiab] OR "platelet aggregant*"[tiab] OR ''acetylsalicylic acid''[tiab] OR "aspirin"[tiab] OR "paracetamol"[tiab] OR ''clopidogrel''[tiab] OR OR "Anticoagulants"[Mesh] OR "Anticoagulants" [Pharmacological Action] OR "Indirect thrombin inhibitor*"[tiab] OR "anti coagulant"[tiab] OR "Fibrinolytic Agents" [Mesh] OR "fibrinolytic agent*"[tiab] OR "fibrinolytic drug*"[tiab] OR "Thrombolytic drug*"[tiab] OR "Thrombolytic agent*"[tiab] OR "antithrombotic drug*"[tiab] OR "antithrombotic agent*"[tiab] OR ''anticoagulant*''[tiab] OR ''Factor Xa inhibitor*''[tiab] OR ''Rivaroxaban''[tiab]** Sort by: **Most Recent**	468,945	08:49:49
#1	•••	>	Search: **("Peripheral Arterial Disease"[Mesh] OR ''peripheral arterial disease*"[tiab] OR "peripheral artery disease*"[tiab] OR ''lower extremity arterial disease*"[tiab] OR "lower extremity artery disease*"[tiab] OR ''Chronic Limb-Threatening Ischemia*"[tiab] OR ''intermittent claudication*"[tiab] OR ''Peripheral Arterial Vascular Disease*"[tiab] OR ''peripheral artery occlusive disease*"[tiab] OR "peripheral arterial occlusive disease*"[tiab]) AND ("Peripheral Arterial Disease"[Mesh] OR ''peripheral arterial disease*"[tiab] OR "peripheral artery disease*"[tiab] OR ''lower extremity arterial disease*"[tiab] OR "lower extremity artery disease*"[tiab] OR ''Chronic Limb-Threatening Ischemia*"[tiab] OR ''intermittent claudication*"[tiab] OR ''Peripheral Arterial Vascular Disease*"[tiab] OR ''peripheral artery occlusive disease*"[tiab] OR "peripheral arterial occlusive disease*"[tiab])** Sort by: **Most Recent**	32,848	08:44:08

Figure S1. Search PubMed/MEDLINE

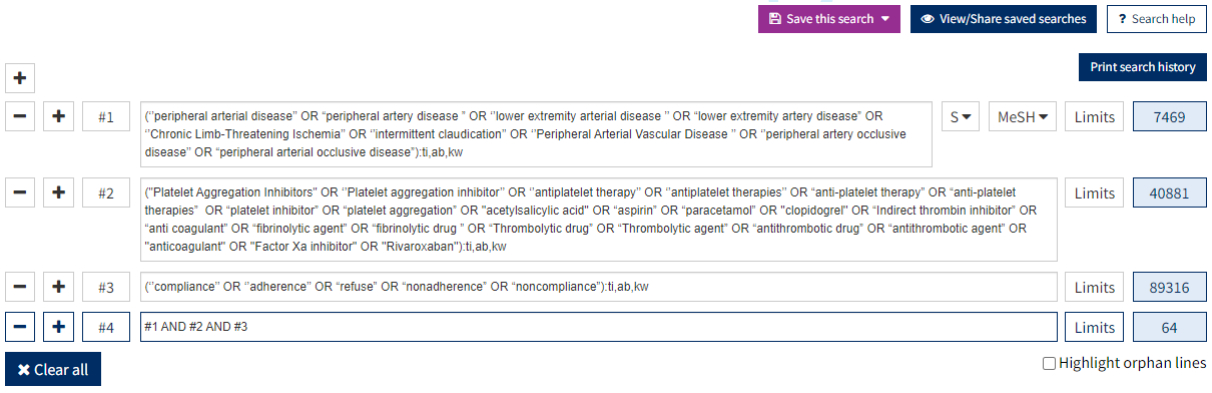


Figure S2. Search in Cochrane

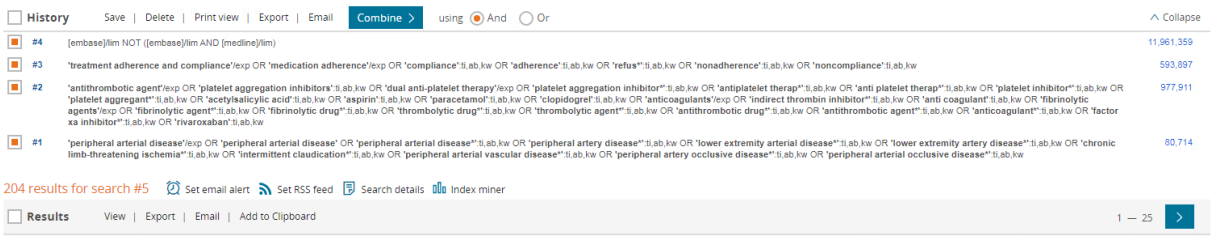


Figure S3. Search in Embase

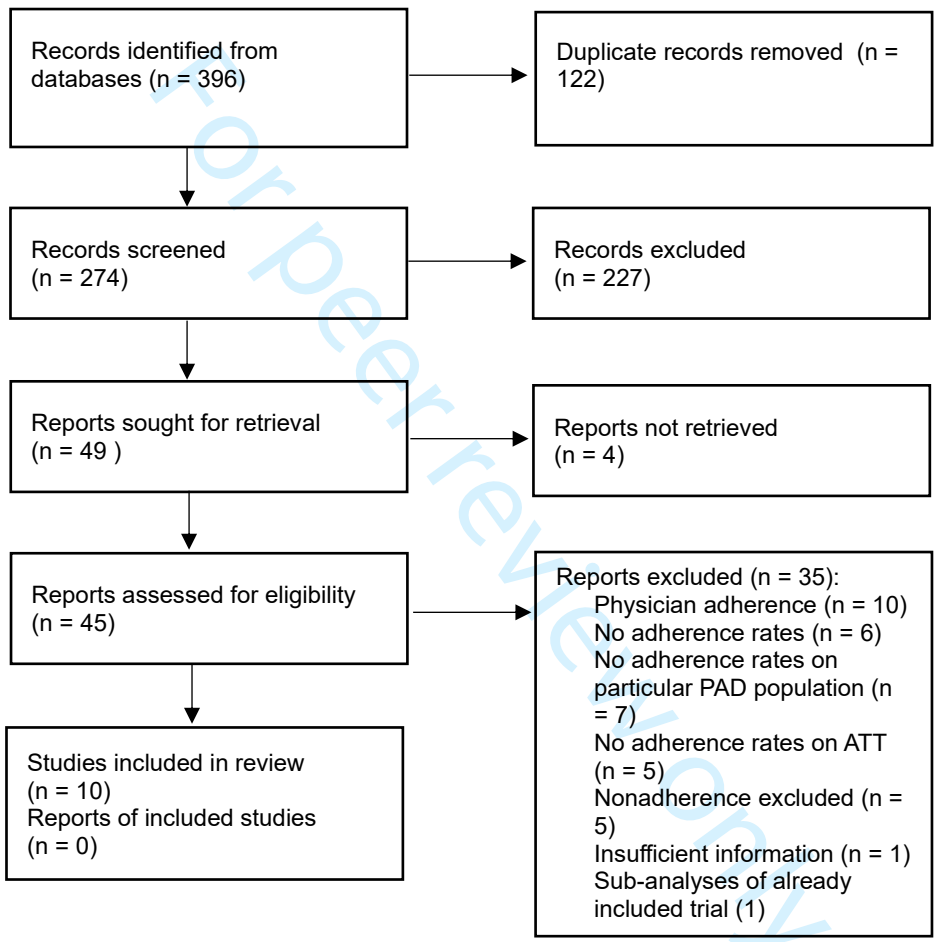


***Figure S4.* The flowchart of the selection process**

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