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

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## 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 patients with PAD with poor MA in literature following patient-reported, pharmacy-reported or laboratory-reported outcome measurements. Poor MA is a combined outcome of primary non-adherence (inability to initiate a prescription), secondary non-adherence (incorrect daily intake) and non-persistence (discontinuation of daily intake).

**Design** Systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

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

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

**Data extraction and synthesis** All articles were reviewed on eligibility and methodological quality by two independent researchers. The data were retrieved and collected in Review Manager Web and the percentages were calculated per subgroup. The 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 score for non-RCTs.

**Results** We identified 274 potential records of which 10 studies (32 628 patients) were included. Six studies were RCTs and two prospective and two retrospective studies. Most studies scored a moderate risk of bias and had heterogeneous study designs. Poor MA rates ranged between 2% and 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 patients with PAD 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 in reducing the risk of AE, and therefore, more attention to MA in clinical and research settings is warranted.

**PROSPERO registration number** CRD42023431803.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 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 focusing primarily on physician adherence.

## INTRODUCTION

Peripheral arterial disease (PAD) is associated with a high risk of atherothrombotic events.[1 2] The annual cardiovascular mortality risk of patients with intermittent claudication is approximately 5% compared with 11.5% for patients with critical limb-threatening ischaemia.[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) in patients with PAD is twofold worse.[4 5] In the 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 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-related 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-reported (questionnaires), pharmacy-reported (counting pills, refill records) or biochemical/laboratory-reported outcome measurements (online supplemental table S1).[22]

The optimal ATT in patients with PAD 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 patients with PAD 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 statement (PROSPERO: CRD42023431803).[25 26]

### Search strategy and study selection

The systematic literature search was performed from inception to 7 June 2023. The bibliographic databases PubMed, Embase.com and Wiley/Cochrane Library were used. The index terms 'Peripheral Arterial Disease', 'Antithrombotic Drugs' and '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 online supplemental figures S1–S3).

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

Eligible publications contained a (sub)population of adult patients with PAD 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 (online supplemental figure S4).

### Outcome definitions and measurements

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

Secondary objectives were the proportion of patients with PAD with (1) poor MA following pharmacy-reported outcome measurements, (2) primary non-adherence following pharmacy-reported and (3) all outcome measurements, (4) secondary (short- and long-term) non-adherence following pharmacy-reported and (5) all outcome measurements and (6) non-persistence 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 patients with PAD, disease stage, mean age, male–female ratio, type of ATT, type of MA subgroup(s), number of patients with PAD that had poor MA per subgroup, number of patients with PAD 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), V.4.14.0, The Cochrane Collaboration, London, UK. Based on the number of patients with PAD with poor MA per subgroup and the total number of patients with PAD, the proportions of non-adherence/non-persistence were calculated per subgroup and processed in the table. For the primary objective, that is, 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 non-adherence 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 the 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 non-comparative studies. This score contains three 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 (online supplemental figure S1). In case of conflicting screening decisions, consensus was reached between ECJW and BMM.

### 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 (online supplemental table S2). The MINORS score was used for the other seven articles (online supplemental 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, 32 628 patients with PAD 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 subanalysis. The included trials had rather heterogeneous study designs, making a meta-analysis infeasible.

### Medication adherence

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

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

## 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 non-adherence.

Trial designs influence participant burdens, which might partly explain the dispersion in MA among trials.[34 35] In this review, three articles required minimum effort from participants because of the registry-based or retrospective design compared with 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, non-adherence and/or non-persistence.[31 33 36] 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 patients with PAD are frequently precarious, which is related to lower socioeconomic status and, therefore, less likely to participate in trials.[12 37–40] 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.[35]

**Table 1** Articles eligible for this systematic review

| First author, YOP | Country | Sample size | Disease severity | ATT | Age | Female (%) | Follow-up |
|---|---|---|---|---|---|---|---|
| Randomised controlled trials | | | | | | | |
| Cassar, 2006[45] | UK | 67 | R 1–3 w EVR | A w C or PLB | Mn 66 (R: 43–80) | 15 (22) | 1 M |
| Haile, 2022[32] | Sweden | 105 | R 1–3 w EVR/SVR | Any ATT | Md 72 (IQR: 69–77) | 54 (52) | 1.5 Y |
| Hess, 2022[30] | Multiple | 6564 | R 1–6 w EVR/SVR | ASA w PLB or DOAC | Mn 68 (IQR: 60–76) | 1704 (26) | Md 28 M (IQR: 22–34) |
| Jivegård, 2005[48] | Sweden | 281 | R 4–6 | ASA w PLB or LMWH | Mn 74 (SD:9) | 126 (45) | 3 M |
| Qvist, 2019[31] | Denmark | 2051 | R 0–6 w/o EVR/SVR | Any ATT | Mn 70 (SD: 2.9) | 0 (0) | 5 Y |
| Weissler, 2022[29] | Multiple | 13 842 | R 1–6 w/o EVR/SVR | C or T | Mn 67 (IQR: 59–75) | 3884 (28) | 30 M (up to 42 M) |
| Prospective trials | | | | | | | |
| Ferreira, 2010[46] | Spain | 194 | NR | Any APT | Mn 64 (SD: 11.2) | 43 (22) | 1 Y |
| Kremers, 2023 [49] | Netherlands | 246 | R 1–4 | Any APT | Mn 69 (SD: 9.2) | 105 (43) | 1 Y |
| Retrospective studies | | | | | | | |
| Halle, 2017[36] | USA | 100 | R 1–6 w/o EVR/SVR | Any APT | Mn 64 (SD: 9.5) | 42 (42) | NR |
| Wawruch, 2021[33] | Slovak Republic | 9178 | R 0–6 w/o EVR/SVR | Any APT | Mn 75 | 5285 (58) | 5 Y |
| Total | | 32 628 | | | | 11 258 (35) | |

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

**Table 2** Medication adherence

| No. | Reference | Non-adherence/ non-persistence | Follow-up | Measurement method | Threshold NA |
|---|---|---|---|---|---|
| Poor medication adherence | | | | | |
| Pharmacy ROM | | | | | |
| 1 | Cassar *et al*[45] | 9% | 1 M | Counting returned pills | NR |
| 2 | Haile *et al*[32] | 30% | 1.5 Y | Counting pills | <80% |
| 3 | Qvist *et al*[31] | 45%* | 5Y | National prescription register | Primary NA: filling prescription >120 days. Other: <80% |
| 4 | Wawruch *et al*[33] | 43% | 5 Y | Counting returned pills | <80% |
| Pharmacy and patient ROM | | | | | |
| 5 | Hess *et al*[30] | 8% | Md 28 M (IQR: 22–34) | Interview NVQ and counting returned pills | NR |
| Patient ROM | | | | | |
| 6 | Ferreira-González *et al*[46] | 2% | 1 Y | Interview (NVQ) | NR |
| 7 | Halle *et al*[36] | 26% | NR | Morisky Medication Adherence Scale | 8 points |
| 8 | Jivegård *et al*[48] | 26% | 3 M | Patient diary | NR |
| 9 | Kremers *et al*[49] | 5% | 1 Y | Morisky Medication Adherence Scale | 8 points |
| 10 | Weissler *et al*[29] | 10% | 30 M (up to 42 M) | Interview | NR |
| Primary non-adherence | | | | | |
| 1 | Qvist *et al*[31] | 31% | 6 M | National prescription register | Filling prescription >120 days |
| Secondary non-adherence | | | | | |
| Short-term secondary non-adherence | | | | | |
| Pharmacy ROM | | | | | |
| 1 | Cassar *et al*[45] | 9% | 1 M | Counting returned pills | NR |
| 2 | Haile *et al*[32] | 21% | 6 M | Counting pills | <80% |
| Patient ROM | | | | | |
| 1 | Jivegård | 26% | 3 M | Patient diary | NR |
| Long-term secondary outcome | | | | | |
| Pharmacy ROM | | | | | |
| 1 | Haile *et al*[32] | 14% | 1 Y | Counting pills | <80% |
| 2 | Qvist *et al*[31] | 20% | 5 Y | National prescription register | <80% |
| 3 | Wawruch *et al*[33] | 20% | 5 Y | Counting returned pills | <80% |
| Patient ROM | | | | | |
| 4 | Halle *et al*[36] | 26% | NR | Counting pills | <80% |
| 5 | Kremers *et al*[49] | 5% | 1 Y | Morisky Medication Adherence Scale | 8 points |
| Non-persistence† | | | | | |
| Pharmacy ROM | | | | | |
| 1 | Qvist *et al*[31] | 27% | 5 Y | National prescription register | <80% |
| 2 | Wawruch *et al*[33] | 33% | 5 Y | Counting returned pills | <80% |
| Pharmacy and patient ROM | | | | | |
| 3 | Hess *et al*[30] | 8% | Md 28 M (IQR 22–34) | Interview NVQ and counting returned pills | NR |
| Patient ROM | | | | | |
| 4 | Ferreira-González *et al*[46] | 2% | 1 Y | Interview (NVQ) | NR |
| 5 | Weissler *et al*[29] | 10% | 30 M (up to 42M) | Interview | NR |

*Non-persistence is excluded since the proportion of the patients who were non-adherent and non-persistent is lacking.
†Non-persistent due to patients' decisions.
M, months; Md, median; NA, non-adherence; NR, not reported; NVQ, non-validated questionnaire; ROM, reported outcome measurements.

Regarding the length of follow-up, the literature shows a tendency for poor MA to increase as the duration of medication use increases.[41–43] This review shows similar results (table 2). One study provided a subanalysis (data not included in our tables) revealing that the highest proportion of non-adherence predominantly occurred between 13 and 24 months with 44% and 35.5%, respectively, compared with 17% within the first 12 months.[33]

This pattern corresponds with the dispersion in our long-term non-adherence 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 three subcategories: primary non-adherence, secondary non-adherence and non-persistence. Most articles, except one, researched only non-persistence and/or secondary non-adherence. This might underestimate the proportion of poor MA by not identifying all categories of MA. The study that distinguished all three subcategories reported the highest proportion of poor MA.[31]

Healthcare systems have a major influence on MA.[15 18 19 37] One study showed that participants from North America were more likely to discontinue their medication compared with participants from Europe.[29] Another study executed in North America confirmed that the inability to afford medication was a major reason for poor MA.[36] Most European countries have similar healthcare systems that reimburse necessary health costs.[44]

Regarding patient-related factors, studies that include postrevascularised patients with PAD might show slightly higher MA rates.[30 32 45] One study showed lower long-term secondary non-adherence compared with short-term non-adherence.[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.[36] Equivocal evidence regarding the impact of patient-related factors on MA is common. Among the included studies, subanalyses of patient-related factors show heterogeneous results.[29 30 33 36 46]

To estimate the individual risk of poor MA, it is of interest whether non-adherence leads to non-persistence. It seems that adherent and non-adherent patients are both highly at risk for non-persistence and thus poor MA.[33] The reason given is the lack of awareness regarding the life-long indication for ATT in patients with PAD. We advise physicians to discuss MA with patients with PAD. 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 their thresholds for non-adherence. Moreover, the heterogeneous study designs made a meta-analysis infeasible. Most of the included studies used patient-reported outcome measurements, that is, 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 47]

## CONCLUSION

Studies regarding MA in patients with PAD 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 patients with PAD and seemed to increase with longer duration of ATT use, which highlights the magnitude of this societal challenge.

**Contributors** ECJW: Concept and design, screening, data collection, analyses and interpretation of data, writing of manuscript and final approval. BMM: Screening, data collection and analyses, and final approval. CU: Concept and design, revision of manuscript and final approval. G-JdB: Concept and design, revision of manuscript, final approval and is the guarantor.

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