Medication Adherence After Acute Coronary Syndrome in Women Compared With Men: A Systematic Review and Meta-Analysis

Sophie H. Bots¹, Jose A. Inia² and Sanne A. E. Peters²,³*

¹Laboratory for Experimental Cardiology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands; ²Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands; ³Imperial College London, The George Institute for Global Health, London, United Kingdom

Introduction: Pharmacological treatment is an important component of secondary prevention in acute coronary syndrome (ACS) survivors. However, adherence to medication regimens is often suboptimal, reducing the effectiveness of treatment. It has been suggested that sex influences adherence to cardiovascular medication, but results differ across studies, and a systematic overview is lacking.

Methods: We performed a systematic search of PubMed and EMBASE on 16 October 2019. Studies that reported sex-specific adherence for one or more specific medication classes for ACS patients were included. Odds ratios, or equivalent, were extracted per medication class and combined using a random effects model.

Results: In total, we included 28 studies of which some had adherence data for more than one medication group. There were 7 studies for angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) (n = 100,909, 37% women), 8 studies for antiplatelet medication (n = 37,804, 27% women), 11 studies for beta-blockers (n = 191,339, 38% women), and 17 studies for lipid-lowering medication (n = 318,837, 35% women). Women were less adherent to lipid-lowering medication than men (OR = 0.87, 95% CI 0.82–0.92), but this sex difference was not observed for antiplatelet medication (OR = 0.95, 95% CI 0.83–1.09), ACEIs/ARBs (OR = 0.95, 95% CI 0.78–1.17), or beta-blockers (OR = 0.97, 95% CI 0.86–1.11).

Conclusion: Women with ACS have poorer adherence to lipid-lowering medication than men with the same condition. There are no differences in adherence to antiplatelet medication, ACEIs/ARBs, and beta-blockers between women and men with ACS.

Keywords: acute coronary syndrome, sex differences, medication adherence, cardiovascular medicine, women

INTRODUCTION

Patients who survive an acute coronary syndrome (ACS) are at high risk of recurrent events (1–3). Secondary prevention through pharmacological therapy reduces the risk of recurrent events and mortality in this population (1, 2), but its effectiveness is attenuated by suboptimal patient adherence (4, 5). Poor adherence to medication regimens is an important obstacle in
improving outcomes for ACS patients and has proven difficult to solve (6). Two large meta-analyses evaluating adherence to cardiovascular medication found that patient sex was an important factor in predicting adherence (7, 8). However, these meta-analyses did not investigate which sex was at higher risk of non-adherence.

There is some evidence on adherence to, for example, statins that suggests women have poorer adherence because they experience more adverse drug reactions (9), but a structured overview of the literature is still lacking. We performed a systematic review with meta-analyses on sex differences in adherence to cardiovascular medication in patients with ACS. We hypothesize that women, in general, have poorer adherence than men.

**METHODS**

**Terminology**

It is important to recognize that sex and gender describe two different concepts. Sex refers to the biological differences between females and males, whereas gender refers to social differences between women and men. Both play an important role in health and disease, although through different mechanisms (10). This manuscript evaluates sex differences, meaning the linguistically correct terms to use would be “female” and “male.” However, all studies included in our review used the terms “women” and “men” to refer to patient sex, as is common in medical literature. We therefore also use the terms “women” and “men” to refer to patients of the female and male sex, respectively.
### TABLE 1 | Overview of studies included in systematic review and meta-analysis.

| First author (year of publication) | Study population | Country | Measure of adherence; good adherence | Medication groups evaluated | Number of participants (% women) | Quality |
|-----------------------------------|------------------|---------|--------------------------------------|-----------------------------|-------------------------------|---------|
| Akincigil et al. (14)             | Patients hospitalized with AMI | USA     | Drug possession rate; ≤60 days elapsed between refills | Angiotensin system Beta-blocker | 526 (36.7) 499 (33.3) | High    |
| Allen LaPointe et al. (15)        | Patients with high-risk NSTE-ACS | USA     | Self-report; never missed a dose | Angiotensin system Beta-blocker Lipid-lowering | 702 (31.9) 882 (30.5) 873 (31.0) | Moderate |
| Alsabbagh et al. (16)             | Patients hospitalized with ACS | Canada  | PDC; ≥80%                            | Lipid-lowering              | 9,051 (30.8) | High    |
| Brogaard et al. (17)              | Patients discharged with ACS | Denmark | MPR; ≥80%                            | Lipid-lowering              | 1,024 (32.4) | High    |
| Butler et al. (18)                | Medicaid beneficiaries discharged with ACS | USA     | Maintain prescription                | Beta-blocker               | 305 (54.9) | High    |
| Colantonio et al. (19)            | Medicare beneficiaries hospitalized for MI | USA     | PDC; ≥80%                            | Lipid-lowering              | 29,125 (44.8) | Moderate |
| Degli-Espoti et al. (20)          | Patients discharged with ACS | Italy   | Maintain prescription                | Antiplatelet               | 5,919 (32.1) | High    |
| Eagle et al. (21)                 | Patients with ACS | GRACE registry (14 countries) | Maintain prescription | Angiotensin system Antiplatelet Beta-blocker Lipid-lowering | 2,364 (30.8) 12,393 (31.7) 7,686 (30.7) 6,277 (30.0) | Moderate |
| Fang et al. (22)                  | Medicare beneficiaries aged ≥65 years, alive 30 days after index AMI hospitalization | USA     | PDC; ≥80%                            | Angiotensin system Antiplatelet Beta-blocker Lipid-lowering | 47,124 (59.0) 64,939 (57.5) 52,185 (55.9) | Moderate |
| Green et al. (23)                 | Patients admitted to hospital with first-time MI | Denmark | PPC                                  | Antiplatelet               | 4,772 (33.0) | High    |
| Hickson et al. (24)               | Medicare beneficiaries aged ≥65 years with statin use prior to index AMI hospitalization | USA     | PDC; ≥80%                            | Lipid-lowering              | 113,296 (54.3) | Moderate |
| Holme et al. (25)                 | Patients with history of confirmed AMI | IDEAL (6 North-European countries) | Total medication exposure/total study follow-up; ≥80% | Lipid-lowering | 8,888 (19.1) | Moderate |
| Kramer et al. (26)                | Patients hospitalized with AMI who survived for at least 1 year | USA     | PDC; ≥75%                            | Beta-blocker               | 17,035 (29.5) | Moderate |
| Kubica et al. (27)                | Patients treated with PCI for AMI | Poland  | Quantity purchased/quantity prescribed; ≥80% | Antiplatelet               | 184 (25.0) | Moderate |
| Lauffenburger et al. (28)         | Medicare beneficiaries aged ≥65 years, alive 30 days after index AMI hospitalization | USA     | PDC; ≥75%                            | Angiotensin system Antiplatelet Beta-blocker Lipid-lowering | 46,286 (40.6) 63,856 (42.0) 51,321 (43.7) | Moderate |
| Luu et al. (29)                   | AMI patients who received coronary artery intervention | Vietnam | Self-report; never missed a dose | Antiplatelet               | 175 (27.0) | Poor    |
| McGinnis et al. (30)              | Kaiser Permanente Colorado beneficiaries with an incident coronary event | USA     | PDC; ≥80%                            | Lipid-lowering              | 2,201 (29.4) | Moderate |
| Monaldi et al. (31)               | Patients discharged with main diagnosis of MI | Italy   | MPR; ≥80%                            | Lipid-lowering              | 2,629 (27.3) | Moderate |
| Nordstrom et al. (32)             | Patients discharged from hospital after ACS-PCI | USA     | MPR; ≥80%                            | Antiplatelet               | 1,340 (20.5) | Moderate |
| Ohlsson et al. (33)               | Patients with discharge diagnosis of AMI | Sweden  | Fill prescription within 3 months after discharge | Angiotensin system Lipid-lowering | 1,346 (31.9) 1,346 (31.9) | Moderate |

(Continued)
TABLE 1 | Continued

| First author (year of publication) | Study population | Country | Measure of adherence; good adherence | Medication groups evaluated | Number of participants (% women) | Quality |
|-----------------------------------|------------------|---------|--------------------------------------|-----------------------------|----------------------------------|---------|
| Phan et al. (34)                  | Kaiser Permanente South Colorado beneficiaries aged ≥80 years hospitalized for AMI | USA     | PDC; ≥80%                             | Lipid-lowering              | 5,629 (50.0)                    | Moderate |
| Rasmussen et al. (35)             | Patients aged >65 years who survived at least 1 year and 3 months after index AMI hospitalization | Canada  | PDC; ≥80%                             | Beta-blocker Lipid-lowering | 24,319 (44.3) 17,823 (41.9)    | High    |
| Sanfelix et al. (36)              | Patients discharged after MI hospitalization | USA     | Days when drug available; ≥75%       | Beta-blocker                | 8,872 (28.5)                   | High    |
| Sun et al. (37)                   | Patients discharged after ACS at discharge          | China   | PDC; ≥50%                             | Angiotensin system           | 2,561 (25.1)                   | Moderate |
|                                  |                                                               |         |                                       | Antiplatelet                 | 3,318 (25.1)                   |         |
|                                  |                                                               |         |                                       | Beta-blocker                 | 2,757 (26.4)                   |         |
|                                  |                                                               |         |                                       | Lipid-lowering               | 3,648 (25.4)                   |         |
| Turner et al. (38)               | Patients discharged on high-intensity statin after index NSTE-ACS hospital admission | UK      | Self-report; never missed a dose      | Lipid-lowering               | 1,005 (24.2)                   | Poor    |
| Wei et al. (39)                  | Patients who survived for 1 year after their first MI hospitalization | UK      | MPR; ≥80%                             | Beta-blocker                | 386 (34.5)                     | High    |
| Xie et al. (40)                  | Patients hospitalized with ACS who survived for 6 months without recurrent MI or stroke | China   | Usage and dose over time; continuous use without dose decline | Lipid-lowering               | 12,516 (29.9)                  | Moderate |
| Zhu et al. (41)                  | MarketScan beneficiaries aged 18–65 years hospitalized with primary diagnosis of ACS who underwent PCI | USA     | MPR; ≥80%                             | Antiplatelet                | 9,703 (22.4)                   | Moderate |

ACS, acute coronary syndrome; AMI, acute myocardial infarction; MPR, medication possession ratio; NSTE, non-ST elevation; PCI, percutaneous coronary intervention; PDC, proportion of days covered; PPC, proportion of patients covered; UK, United Kingdom; USA, United States of America.

Search Strategy and Selection Criteria
We searched both PubMed and EMBASE on 16 October 2019 using a pre-defined search term consisting of both text words and MeSH headings (Supplementary Files). The text words were limited to title and abstract only. The retrieved articles were screened by two independent reviewers who also resolved any conflicts that arose with help of a third reviewer, if necessary. The reference lists of relevant articles were screened for any additional articles. A modified version of the Newcastle-Ottawa Scale was used to assess the quality of included studies (Supplementary Files).

Only original research articles written in English that evaluated adherence at the individual patient-level were eligible for inclusion. Articles were included if they reported sex-specific data on medication adherence in patients with ACS, defined as either myocardial infarction or unstable angina (11). We excluded studies with too few participants to evaluate sex differences (n < 100), studies where ACS was included alongside other cardiovascular diseases and results could not be separated based on disease subgroup, and studies that included only men or only women. We also excluded studies that evaluated adherence to a combination of medications instead of per specific medication group. Finally, we excluded all studies for which the full text could not be retrieved.

We extracted population size, the percentage of women, mean age, total duration of follow-up, and measure of adherence used from all included studies. In addition, we extracted the number of adherent and non-adherent women and men or, if unavailable, unadjusted relative risk estimates (or equivalent). We also extracted adjusted relative risk estimates when available.

Statistical Analysis
The meta-analysis was conducted conforming with the Meta-Analyses and Systematic Reviews of Observational studies (MOOSE) guidelines (12). We chose “good adherence,” as defined by each study, as our outcome and men as the reference category to facilitate interpretation of the results. We pooled the sex-specific odds ratios (ORs) using random effects meta-analysis because the included studies applied varying definitions of adherence and thus the estimated effect of sex on adherence can vary across these studies. In these situations, it is recommended...
to apply random effects meta-analysis instead of fixed effects meta-analyses (13).

We calculated the average sex-specific adherence across studies weighted by study size. We calculated unadjusted ORs for studies that presented number of adherent and non-adherent women and men. We converted the risk estimates from studies that used either a different outcome (poor adherence) or reference category (women) to fit our analysis. When studies stratified their analysis by subgroups, we pooled reported risk estimates using fixed effects meta-analysis and included the pooled risk estimate in our overall meta-analysis. We performed an additional analysis using only adjusted ORs to see whether adjustment would affect our crude estimates. We created funnel plots to check for publication bias.

All analyses were performed in R (R Core Team, Vienna, Austria). A p < 0.05 was considered statistically significant.
RESULTS

Study Characteristics
In total, we included 28 studies of which some had adherence data for more than one medication group (Figure 1). The medication groups included were angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ACEIs/ARBs), antiplatelet therapy, beta-blockers, and lipid-lowering medication. Nine studies were of high quality (4 stars), 17 studies were of moderate quality (2 or 3 stars), and two studies were of poor quality (0 or 1 star). A complete overview of the included studies can be found in Table 1.

Sex-Specific Adherence
In the crude analyses, we included 7 studies with adherence information for ACEIs/ARBs (n = 100,909, 37% women), 8 for antiplatelet medication (n = 37,804, 27% women), 11 for beta-blockers (n = 191,339, 38% women), and 17 for lipid-lowering medication (n = 318,837, 35% women). Across all included studies, 62.7% of women and 63.9% of men had good ACEIs/ARBs adherence. These percentages were 64.5 and 66.0% for antiplatelet medication, 60.8 and 61.0% for beta-blockers, and 73.6 and 75.3% for lipid-lowering medication, respectively.

There was no significant sex difference in adherence for ACEIs/ARBs (OR = 0.95, 95% CI 0.78–1.17; Figure 2A),
antiplatelet medication (OR = 0.95, 95% CI 0.83–1.09; Figure 2B), and beta-blockers (OR = 0.97, 95% CI 0.86–1.11; Figure 2C). However, women had significantly poorer adherence to lipid-lowering medications than men (OR = 0.87, 95% CI 0.82–0.92; Figure 2D).

In the adjusted analyses, we included three studies for ACEIs/ARBs and beta-blockers and six studies for lipid-lowering medication. There was only one study with adjusted risk estimates for antiplatelet medication. These analyses showed a significantly poorer adherence in women for ACEIs/ARBs (OR = 0.88, 95% CI 0.80–0.96) and beta-blockers (OR = 0.91, 95% CI 0.88–0.93) but not for lipid-lowering medication (OR = 0.97, 95% CI 0.89–1.05) (Figure 3).

The funnel plots for ACEIs/ARBs and lipid-lowering medication were relatively balanced, suggesting little publication bias. For antiplatelet medication and beta-blockers, however, smaller studies showing poorer adherence in women seemed to be lacking compared with the number of such studies showing poorer adherence in men (Figure 4).

**DISCUSSION**

Adherence to ACEIs/ARBs, antiplatelet medication, beta-blockers, and lipid-lowering medication lies between 60 and 70% in both women and men surviving an ACS. Women had poorer adherence than men for lipid-lowering medication but not for the other medication groups, where adherence was similar between the sexes.

A previous systematic review on adherence to cardiovascular medication in coronary heart disease patients also found adherence to be 60–70% (42), suggesting that adherence is reasonable in secondary prevention of ACS. However, they did not find any sex differences (42), whereas our results suggest that those may be present at least for lipid-lowering drugs. This finding is supported by previous work showing that women have poorer adherence to statins in both primary and secondary prevention (43). This may be due to biological or social reasons, or a combination of both. There are known biological differences in drug metabolism between women and men (44), which may increase the risk of statin-related adverse drug reactions in women (45). This may also be true for the other medication groups included in our review, but the lack of sex-specific data on medication efficacy, safety, and metabolism prevents researchers from drawing sound conclusions on this topic (46–48). Gender differences may also play a role in adherence, with women for example more often refusing or discontinuing statins because they do not believe the medication is safe (49). Given that women derive equal benefit from statin therapy as men (50), it is important to improve statin adherence in women through both collecting more high-quality sex-specific data on this topic and adapting treatment to individual patients by for example using lower dosages to reduce the risk of side effects (45).

The main strength of this review is that it combines data from 28 studies. However, it is limited by the quality of the available data. The majority of studies included in this review were of moderate quality, and the data were heterogeneous on several important points. Both the chosen measure of adherence and the definition of “good adherence” varied greatly across studies. Approximately half of the included studies used a standardized measure of adherence, such as the medication possession ratio (18% of studies) or proportion of days covered (36%), but others used either self-report (11%) or another, sometimes self-devised, measure (35%). This makes meta-analyzing such data and interpreting the results difficult. To alleviate this issue, it is important that future studies use both standardized measures of adherence and standardized cut-off values to denote good and poor adherence. We also saw that smaller studies showing poorer adherence in women were less likely to be published, and that studies showing poorer adherence in women more often provided adjusted risk estimates. This differential approach may introduce bias in meta-analyses such as ours and complicate the interpretation of our findings.

In conclusion, we show that adherence to cardiovascular medication is reasonable in women and men surviving an ACS. Women had poorer adherence to lipid-lowering medication than men, but this difference was not observed for the other cardiovascular medication groups. However, a standardized approach to the measurement and evaluation of adherence is needed to improve the quality of research performed in this field.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

**AUTHOR CONTRIBUTIONS**

SB and JI performed the systematic search. SB analyzed the data and wrote the manuscript. SP conceived the project, supported data analyses, and critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

**FUNDING**

SP was supported by a UK Medical Research Council Skills Development Fellowship (MR/P014550/1).

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgwh.2021.637398/full#supplementary-material
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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