Systematic Review and Meta-Analysis

Sex Differences in Cardiovascular Medication Prescription in Primary Care: A Systematic Review and Meta-Analysis

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Background: Sex differences in the management of cardiovascular disease have been reported in secondary care. We conducted a systematic review with meta-analysis of systematically investigated sex differences in cardiovascular medication prescription among patients at high risk or with established cardiovascular disease in primary care.

Methods and Results: PubMed and Embase were searched between 2000 and 2019 for observational studies reporting on the sex-specific prevalence of aspirin, statins, and antihypertensive medication prescription, including beta blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and diuretics, in primary care. Random effects meta-analysis was used to obtain pooled women-to-men prevalence ratios for each cardiovascular medication prescription. Metaregression models assessed the impact of age and year on the findings. A total of 43 studies were included, involving 2,264,600 participants (28% women) worldwide. Participants’ mean age ranged from 51 to 76 years. The pooled prevalence of cardiovascular medication prescription for women was 41% for aspirin, 60% for statins, and 68% for any antihypertensive medications. Corresponding rates for men were 56%, 63%, and 69% respectively. The pooled women-to-men prevalence ratios were 0.81 (95% CI, 0.72–0.92) for aspirin, 0.90 (95% CI, 0.85–0.95) for statins, and 1.01 (95% CI, 0.95–1.08) for any antihypertensive medications. Women were less likely to be prescribed angiotensin-converting enzyme inhibitors (0.85; 95% CI, 0.81–0.89) but more likely with diuretics (1.27; 95% CI, 1.17–1.37). Mean age, mean age difference between the sexes, and year of study had no significant impact on findings.

Conclusions: Sex differences in the prescription of cardiovascular medication exist among patients at high risk or with established cardiovascular disease in primary care, with a lower prevalence of aspirin, statins, and angiotensin-converting enzyme inhibitors prescription in women and a lower prevalence of diuretics prescription in men.

Keywords: cardiovascular medication ■ meta-analysis ■ primary care ■ sex differences ■ systematic review

Cardiovascular disease (CVD) remains the leading cause of death worldwide, accounting for about a third of all deaths in both women and men.1 Historically, there has been a misperception that CVD predominantly affects men, which may have resulted in suboptimal management and treatment of CVD in women.2,3 Over recent decades, substantial efforts have been made to characterize CVD in women. As a result, important differences between women and men in the presentation, diagnosis, and medical treatment of CVD have been identified.2,4 Most studies on sex differences in CVD management have been performed in secondary care.3,5–7 For example, among all patients receiving statins after hospitalization for myocardial infarction in the United States, women were less likely than men to receive high-intensity statins, despite guideline recommendations.6 Also, a study of coronary heart
disease patients recruited from routine outpatient cardiology clinics in 11 countries across Europe, Asia, and the Middle East showed that women were less likely than men to reach all treatment targets set by clinical guidelines. Whether similar sex differences exist in primary care has not been systematically evaluated. Considering that both patients at high risk and with established CVD attended clinics in primary care to monitor their current CVD treatment, primary care visits are a key stage at which any sex inequities in treatment could and should be investigated. Comprehensive evidence on current sex differences in cardiovascular medication prescription in primary care would help to obtain a better understanding of the utilization of evidence-based medical treatment for both sexes and encourage all health professionals to strive for sex equity in providing CVD management to their patients.

In this study, we conducted a systematic review and meta-analysis to determine the prevalence of common cardiovascular medication prescription in women and men in primary care and to evaluate whether prescriptions for guideline-recommended cardiovascular medications differ between the sexes.

METHODS
The authors declare that all supporting data are available within the article and its online supplementary files.

Search Strategy
A systematic search of observational studies was performed in PubMed/MEDLINE and Embase for studies published between 2000 and 2019 using combined text word subject heading terms (Table S1). The reference lists of all related articles were screened for any other potentially relevant studies.

Study Selection and Data Extraction
All observational studies that reported the sex-specific prevalence of prescriptions of cardiovascular medications (aspirin, statins, and any antihypertensive medication including beta blockers, calcium channel blockers [CCBs], angiotensin-converting enzyme inhibitors [ACE inhibitors], and diuretics) for patients at high risk or with established CVD (coronary heart disease, stroke, heart failure, and atrial fibrillation) in primary care were included. Studies were excluded if they (1) were published in a language other than English; (2) presented an unrelated study population, outcome, or were not performed in primary care; (3) included <1000 patients; (4) reported cardiovascular medication prescription only for 1 sex; and (5) assessed cardiovascular medication not by prescription (such as self-report or pharmacy dispensing).

Duplicate records were removed before title and abstract screening. When there were multiple reports from the same study, the report involving the highest number of cases or most explicit participants characteristics and outcome measures was included. Four independent reviewers (M.Z., E.R.C.M., C.C., and K.H.) screened the papers by title and abstract against the inclusion and exclusion criteria. Any disagreement between reviewers was discussed and the full text was reviewed, if necessary. A similar process took place in reviewing the full text of selected papers. A tailor-made data extraction form was used to collect information on study and participant characteristics and sex-specific prevalence of prescriptions of cardiovascular medication (Table S2).

Quality Assessment
Study quality was assessed using the modified Newcastle-Ottawa scale for observational studies.
This scale consists of 6 items that assess the quality of participant selection, comparability, and outcome adjudication (Tables S3 and S4).^8^

**Outcomes**
The primary outcome was the women-to-men prescription prevalence ratio with 95% CI for each cardiovascular medication. The secondary outcomes were the sex-specific prescription rates of each cardiovascular medication.

**Statistical Analysis**
In general, the included studies reported unadjusted numbers, rates, or percentages of women and men with cardiovascular medication prescriptions. If a measure of variability was not reported, these were estimated from the rate and the sample size. The women-to-men prevalence ratios with 95% CI were pooled across studies using random-effects meta-analyses with inverse-variance weighting for each medication. In sensitivity analysis, we pooled the results from studies that had adjusted for age. As different studies reported on different antihypertensive medications, we also restricted the analyses on individual antihypertensive medications to studies that reported on each of the 4 antihypertensive medications. Metaregression analyses were performed to assess the impact of mean age and age difference (women minus men) on our findings. We further investigated whether there was a trend in sex differences in cardiovascular medication prescription over time. In subgroup analysis, we assessed whether the findings differed by CVD status (high risk only, prevalent CVD, and high risk and prevalent CVD combined). P<0.05 were considered statistically significant. Statistical analyses were performed by using the “metafor” package in R version 3.2.2.

**RESULTS**

**Study Characteristics**
Of the 10 803 studies identified through the systematic search, 900 studies were reviewed in full text (Figure 1). Of these, 43 studies were included, including a total of 2 264 600 participants, of whom 630 111 (28%) were
women. The mean age ranged from 51 to 76 years (where reported). Table shows the key characteristics of the included studies. Of the 43 studies, 18 included information on aspirin, 14 on any antihypertensive medications, 13 on CCBs, 21 on ACE inhibitors, and 14 on diuretics. Eight out of 43 studies reported cardiovascular medication prescription for high-risk patients, 24 for patients with established CVD, and 11 for both high-risk and CVD patients.

**Sex Differences in Prevalence of Cardiovascular Medication Prescription**

In women, the pooled prevalence of cardiovascular medication prescription was 41% for aspirin, 60% for statins, and 68% for overall antihypertensive medications. The corresponding rates for men were 56%, 63%, and 69%, respectively. The pooled women-to-men prevalence ratios were 0.81 (95% CI, 0.72–0.92) for aspirin, 0.90 (95% CI, 0.85–0.95) for statins, and 1.01 (95% CI, 0.95–1.08) for any antihypertensive medications (Figure 2).

Figure 3 shows the women-to-men prevalence ratios of individual antihypertensive medication prescription. Women were less likely to be prescribed with ACE inhibitors (women-to-men prevalence ratio: 0.85; 95% CI, 0.81–0.89) whereas the prevalence of diuretics prescription was higher than in men (women-to-men prevalence ratio: 1.27; 95% CI, 1.17–1.37). There were no significant sex differences in the prescription of beta blockers and CCBs. Findings were similar in analyses restricted to studies that reported on all 4 individual antihypertensive medications (Figure S1). Findings were similar in age-adjusted analyses, available for 31 studies (Tables S5 through S10).

**Impact of Age on the Sex Differences in Prevalence of Cardiovascular Medication**

Among the 31 studies that reported a sex-combined mean age of the study population, there was no evidence that the women-to-men prevalence ratio varied systematically according to the mean age (Figure S2; P value: 0.57 for aspirin; 0.24 for beta blockers; 0.27 for CCBs; 0.41 for ACE inhibitors; 0.85 for diuretics). The only exception was that in studies with older patients, women were less likely than men to be prescribed statins whereas women had a higher prevalence of statin prescription compared with men in studies including younger patients (P=0.003).

Among the 17 studies that reported sex-specific mean ages, there was no evidence that the prevalence ratio varied systematically according to the women to men age difference (Figure S3; P values: 0.34 for aspirin; 0.21 for statins; 0.93 for beta blockers; 0.91 for CCBs; 0.89 for ACE inhibitors). The exception was the higher prevalence of diuretics prescription in women increased as the difference between the mean age of women and the mean age of men increased (P=0.006).

**Sex Differences in the Prevalence of Cardiovascular Medication Prescription Over Time**

The sex differences in prevalence ratio of prescription did not significantly change over time for aspirin (P=0.92), any antihypertensive medications (P=0.99), beta blockers (P=0.43), CCBs (P=0.44), ACE inhibitors (P=0.39), and diuretics (P=0.58) (Figure S4). However, the pattern and magnitude of the sex differences in statin prescription changed over time, with an increased women-to-men prevalence ratio (P=0.003).

**Sex Differences in Cardiovascular Medication Prescription by CVD Status**

Among patients with established CVD, women were less likely to be prescribed with aspirin (0.89, 95% CI, 0.84–0.94), statins (0.85; 95% CI, 0.80–0.90), beta blockers (0.90, 95% CI, 0.85–0.96), and ACE inhibitors (0.88, 95% CI, 0.84–0.93) (Figure S5, Table S11). In contrast, women with established CVD were more likely to be prescribed with diuretics than their male counterparts (1.25; 95% CI, 1.09–1.43). Similar pooled estimates, but with wider CIs, were found when studies included only high-risk participants, or when studies included both participants at high risk of and with established CVD. Time trends in the women-to-men prevalence ratio in medication prescription did not differ materially by CVD status (Figures S6 through S11). However, the women-to-men ratio of statin prescription increased over time in studies among high-risk patients but not in studies including patients with established CVD or in studies including both high-risk and CVD patients (P for interaction=0.002).

**DISCUSSION**

In this systematic review and meta-analysis of 43 studies including over 2 million participants, we found that there were sex differences in cardiovascular medication prescription among patients at high risk or with established CVD in primary care. Compared with men, women were less likely to have a prescription for
Table. Key Characteristics of Selected Studies

| Study                        | Year | Country | Prevention Type | Sample Size | Women | Men | Age, y | Cardiovascular Medications |
|------------------------------|------|---------|-----------------|-------------|-------|-----|--------|-----------------------------|
| Al-Lawati et al<sup>10</sup> | 2007 | Oman    | Mixed           | 2551        | 1352  | 1199| 54     | Aspirin Statin Antihtn BB CCB ACEI Diuretics |
| Alberts et al<sup>28</sup>  | 2004 | Multiple| Secondary       | 55 499      | 18 315| 37 184| 69     | X X X X X X |
| Brady et al<sup>11</sup>    | 1998 | UK      | Secondary       | 24 431      | 9898  | 14 533| 67     | X X X X X X |
| Brady et al<sup>20</sup>    | 2002 | UK      | Secondary       | 12 045      | 4457  | 7588 | 67     | X X X X X X |
| Bull et al<sup>16</sup>     | 2003*| UK      | Secondary       | 13 929      | 5827  | 8102 | >40    | X X X X X X |
| Carlsson et al<sup>21</sup> | 2013*| Sweden  | Secondary       | 7408        | 3330  | 4078 | 76     | X X X X X X |
| Carroll et al<sup>22</sup>  | 2001 | UK      | Secondary       | 6778        | 2787  | 3991 | NA     | X X X |
| Catalán-Ramos et al<sup>12</sup> | 2009 | Spain   | Primary         | 696 073     | 358 218| 337 855| 51     | X X X X X X |
| Critty et al<sup>13</sup>   | 2001 | UK      | Secondary       | 1162        | 552   | 610 | 69     | X X X X X X |
| Dodhia et al<sup>23</sup>   | 2013 | UK      | Secondary       | 6711        | 2828  | 4564 | 70     | X X X X X X |
| Dreyer et al<sup>34</sup>   | 2007 | Australia| Secondary      | 2005        | 721   | 1284 | 70     | X X X X X X |
| Driscoll et al<sup>24</sup> | 2007 | Australia| Secondary      | 12 509      | 5267  | 7242 | 73     | X X X X X X |
| Emberson et al<sup>25</sup> | 2001 | UK      | Mixed           | 8538        | 4286  | 4252 | NA     | X X X X X X |
| Forster et al<sup>25</sup>  | 2000 | NL      | Primary         | 7550        | 4774  | 2776 | 63     | X X X X X X |
| Gulliford et al<sup>26</sup> | 2010*| UK      | Secondary       | 7065        | 3816  | 3249 | 73     | X X X |
| Hawkins et al<sup>30</sup>  | 2007 | UK      | Secondary       | 13 330      | 6603  | 6527 | 68     | X X |
| Hendrix et al<sup>29</sup>  | 2005*| US      | Mixed           | 72 508      | 29 208| 43 300| NA     | X X X X X X |
| Hippisley-Cox et al<sup>17</sup> | 2001*| UK      | Mixed           | 5891        | 2783  | 3128 | NA     | X X X |
| Hyun et al<sup>37</sup>     | 2012 | Australia| Mixed          | 13 294      | 6202  | 7092 | 61     | X X |
| Journath et al<sup>38</sup> | 2005 | Sweden  | Primary         | 6537        | 3410  | 3127 | 66     | X X X X X X |
| Lahoz et al<sup>22</sup>    | 2008*| Spain   | Secondary       | 8817        | 2319  | 6498 | 65     | X X X X X X |
| Law et al<sup>19</sup>      | 2010 | Canada  | Primary         | 390         | 128   | 262 | 58     | X X X X X X |
| Lawlor et al<sup>29</sup>   | 2000 | UK      | Secondary       | 1314        | 483   | 831 | NA     | X X X X X X |
| Lee et al<sup>31</sup>      | 2018 | Australia| Secondary      | 130 926     | 61 142| 69 784| 67     | X X X X X X |
| Macchia et al<sup>13</sup>  | 2012*| Italy   | Secondary       | 21 423      | 6928  | 14 495| NA     | X X X X X X |
| Majeed et al<sup>26</sup>   | 1996 | UK      | Secondary       | 63 259      | 34 545| 28 714| NA     | X X X X X X |
| Majeed et al<sup>12</sup>   | 2002 | UK      | Secondary       | 2129        | 1224  | 905 | NA     | X X X X X X |
| Murphy et al<sup>27</sup>   | 2004*| UK      | Secondary       | 2186        | 1213  | 973 | NA     | X X X X X X |
| Nanna et al<sup>16</sup>    | 2015 | US      | Mixed           | 5693        | 2460  | 3233 | 68     | X X X |
| Nilsson et al<sup>25</sup>  | 2004*| Sweden  | Mixed           | 9375        | 4293  | 5062 | 65     | X X X |
| Nilsson et al<sup>27</sup>  | 2007*| Sweden  | Primary         | 1135        | 714   | 421 | 52     | X X X |

(Continued)
Zhao et al. Sex Differences in CVD Drug Prescription

Aspirin, statins, or ACE inhibitors but more likely to have a prescription for diuretics. Sex differences did not vary materially by age, but there was some evidence to suggest that the magnitude of sex differences in statin prescription increased over time.

Previous studies in secondary care have demonstrated that women are generally less likely than men to have a prescription of guideline-recommended cardiovascular medications after a cardiac event. A recent study in the United States confirmed that women were less likely than men to be prescribed with aspirin, statins, or ACE inhibitors but more likely to have a prescription for diuretics. Sex differences did not vary materially by age, but there was some evidence to suggest that the magnitude of sex differences in statin prescription increased over time.

There are several other possible explanations for the lower prescription rates of some cardiovascular medications in women compared to men. First, the incidence of CVD in women is typically about a third that of men in midlife and occurs in men about a decade earlier than women, which might have led to the misconception that CVD is less common in women and does not have to be prevented as intensively as in men. Additionally, women may have a lower awareness of the severity of CVD and are more likely to be on diuretics but less likely to be on ACE inhibitors, which is in line with other studies. Sex differences in progression and presentation of CVD and comorbidities, the efficiency of treatment, and/or adverse drug effects may lead to different requirements and/or adverse drug effects and presentation of CVD and comorbidities, the efficiency of treatment, and/or adverse drug effects may lead to different requirements and/or adverse drug effects.
their disease and of appropriate CVD treatment and receive less support from healthy providers, compared with men, resulting in lower health consciousness and less frequent use of healthcare services.\textsuperscript{5,62–64}

Although beyond the scope of the current investigation, studies have reported a considerable delay in receiving appropriate medical treatment to reduce the risk of incident or recurrent cardiac event in women.\textsuperscript{2,23,62,63} Also, women may have less belief than men in the safety and effectiveness of cardiovascular medications and have been reported to have a greater risk of suffering adverse drug reactions, which may lead to a higher discontinuation rate of cardiovascular medications.\textsuperscript{60,65–67} Indeed, studies have shown that women have a poorer adherence to cardiovascular medication than men in primary

Figure 2. Women-to-men prevalence ratio of aspirin, statins, and any antihypertensive medications prescription.
For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% CI. The diamond indicates the pooled summary and its 95% CI.

Figure 3. Women-to-men prevalence ratio of individual antihypertensive medication prescription.
For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% CI. The diamond indicates the pooled summary and its 95% CI.
care. These factors would be expected to produce a wider disparity between the usage of cardiovascular medications than our study of prescriptions suggests.

We conducted a large-scale systematic review with meta-analyses on sex differences in cardiovascular medication prescription among patients at high risk or with established CVD in a primary care setting. We included all major cardiovascular medications and found that our results were generally robust across patient characteristics. Limitations of this study are inherent to its design and include the differences across studies in design, population, and end point definition. We had no information on potential combinations of cardiovascular medications prescribed, nor were we able to adjust our findings to potentially important comorbidities or other characteristics. However, some cardiovascular medications target the same risk factor and the lower use of ACE inhibitors among women, relative to men, could be explained by women’s higher use of diuretics. Also, we considered sex differences only in medication prescription and were not able to determine whether those differences, where found, resulted in different levels of risk factor control and event rates. Furthermore, patients with established CVD seen in primary care may also receive treatment from secondary care. Also, it is not clear whether general practitioners or cardiologists would be the main source of prescriptions in any individual case. Finally, as the studies included in this review were conducted in mostly high-income countries, the generalizability of our findings to low- and middle-income countries needs to be assessed.

In conclusion, this meta-analysis, summarizing all recent literature, shows that sex differences in cardiovascular medication prescription persist in primary care. Future research is needed to determine the underlying causes of observed sex differences and to develop tailored strategies to optimize the use of evidence-based cardiovascular medication for both women and men.

ARTICLE INFORMATION
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Disclosures
Woodward is a consultant to Amgen and Kirin. The remaining authors have no disclosures to report.

Supplementary Materials
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Supplemental Material
### Table S1. Search terms.

| Category          | Pubmed                                                                 | EMBASE                                                                 | Search names                        |
|-------------------|------------------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------|
| **Primary care**  | Primary Health Care [Mesh]                                             | (primary adj3 care*).tw.                                               | Primary care v1                     |
|                   | Primary service [tiab]                                                | primary service*.tw.                                                  | Primary care v2                     |
|                   | GP [tiab]                                                              | GP.tw.                                                                |                                     |
|                   | Primary Health Care [tiab]                                             | General practice*.tw.                                                 |                                     |
|                   | Primary healthcare [tiab]                                              | Primary health?care.tw.                                               |                                     |
|                   | Primary medical care [tiab]                                            | exp primary medical care/                                              |                                     |
|                   | General practitioner [tiab]                                            | exp general practitioner/                                             |                                     |
|                   | General practice [tiab]                                               | exp general practice/                                                 |                                     |
|                   | Family doctor [tiab]                                                  | (family adj (doctor or practitioner or physician)).tw.                |                                     |
|                   | Family practitioner [tiab]                                            |                                                                        |                                     |
|                   | Family physician [tiab]                                               |                                                                        |                                     |
| **CVD risk scores** | Cardiovascular score [tiab]                                           | Exp cardiovascular risk/                                              | Cvd risk scores v1                   |
|                   | Cardiovascular risk score [tiab]                                       | (cardiovascular adj2 score).tw.                                       | *risk factor will go in risk factor |
|                   | ASSIGN score [tiab]                                                   | (assign adj score).tw.                                                | section.                            |
|                   | Qrisk [tiab]                                                           | QRisk.tw.                                                             |                                     |
|                   | Systematic Coronary Risk Evaluation [tiab]                            | Systematic Coronary Risk Evaluation.tw.                              |                                     |
|                   | Framingham score [tiab]                                               | (Framingham adj4 (score or risk or index)).tw.                        |                                     |
|                   | Framingham risk [tiab]                                                | pooled cohort equation.tw.                                           |                                     |
|                   | Framingham index [tiab]                                               |                                                                        |                                     |
|                   | Pooled cohort equation [tiab]                                          |                                                                        |                                     |
| **Primary**        | Primary prevention [MeSH]                                             | exp primary prevention/                                              | Primary prevention v1                |
| prevention         | Primary prevention [tiab]                                             | (primary adj2 prevention).tw.                                         | Primary prevention v2                |
| **Secondary**      | Secondary prevention [MeSH]                                           | exp secondary prevention/                                             | Secondary prevention v1              |
| prevention         | Secondary prevention [tiab]                                           | (secondary adj2 prevention).tw.                                       | Secondary prevention v2              |
| Sex | Pubmed                          | EMBASE                                      | Search names                  |
|-----|--------------------------------|---------------------------------------------|-------------------------------|
|     | Male[MeSH]                     | male/                                       | Men and women v2             |
|     | Male[tiab]                     | (mean or man or male).tw.                   | Sex gender v2                |
|     | Men[tiab]                      | female/                                     |                              |
|     | Man[tiab]                      | (woman or women or female).tw.              |                              |
|     | Female[MeSH]                   | gender/                                     |                              |
|     | Female[tiab]                   | sex/                                        |                              |
|     | Women[tiab]                    | (gender* or sex*).tw.                       |                              |
|     | Woman[tiab]                    |                                             |                              |
|     | Sex[MeSH]                      |                                             |                              |
|     | Sex[tiab]                      |                                             |                              |
|     | Gender[tiab]                   |                                             |                              |
| Risk assess | Risk factors[MeSH] | Exp risk factor/                             | Risk assess v2               |
|     | Risk factors [tiab]            | Exp risk assessment/                        | Risk assess v4               |
|     | Risk assessment [MeSH]         | (risk adj5 (assess* or measure* or screen*)).tw. |                              |
|     | Risk assessment [tiab]         | (absolute adj5 risk*).tw.                   |                              |
|     | Absolute risk [tiab]           | exp health care disparity/                  |                              |
|     | Health screen [tiab]           | (health? Care adj3 disparit*).tw.           |                              |
|     | Health screening [tiab]        |                                             |                              |
|     | Health measurement [tiab]      |                                             |                              |
|     | Health assessment [tiab]       |                                             |                              |
|     | Health care disparity [MeSH]   |                                             |                              |
|     | Health care disparity [tiab]   |                                             |                              |
|     | Health care disparities [tiab]  |                                             |                              |
| Drugs | (statin* or lipid lowering).tw.| cardiovascular drugs/therapeutic use [Mesh]| standalone:                  |
|      | exp hydroxymethylglutaryl coenzyme | cardiovascular diseases/therapy [mesh]      | combined with drugs tab:     |
|      | A reductase inhibitor/         | Hydroxymethylglutaryl-CoA Reductase Inhibitors [Mesh] | all drug terns and meds v2  |
|      | ([blood pressure adj3 medication*]) |                                             | same as angiotensin II receptor |
| Pubmed                                                                 | EMBASE                                                                 | Search names                     |
|-----------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------|
| blood pressure lowering or bp?lowering).tw.                          | statin [tiab]                                                          | blocker [mesh]                   |
| exp antihypertensive agent/ (angiotensin II receptor blocker* or ARB*).tw. | statins [tiab]                                                         | CVD meds v2                      |
| (angiotensin?converting enzyme inhibitor* or ACE* or ACEI* or ACEi*).tw. | lipid lowering [tiab]                                                  |                                  |
| exp dipeptidyl carboxypeptidase inhibitor/ (beta blocker* or b?blocker*).tw. | blood pressure lowering [tiab]                                         |                                  |
| exp beta adrenergic receptor blocking agent/ antiplatelet.tw.         | bp lowering [tiab]                                                     |                                  |
| exp antithrombocytic agent/ aspirin.tw                               | antihypertensive agent [Mesh]                                          |                                  |
| antithrombotic*.tw                                                   | antihypertensive [tiab]                                                |                                  |
| exp nonsteroid antiinflammatory agent/ ((calcium?channel and (blocker* or blocking)) or (calcium adj2 antagonist*) or calcium?antagonist* or CCB*).tw. | Angiotensin Receptor Antagonists [Mesh] |                                  |
| exp calcium channel blocking agent/ exp diuretic agent/ diuretic*.tw. | Angiotensin Receptor Antagonist [tiab]                                 |                                  |
|                                                                        | Angiotensin Receptor Antagonists [tiab]                                 |                                  |
|                                                                        | angiotensin II receptor blocker [tiab]                                  |                                  |
|                                                                        | angiotensin II receptor blockers [tiab]                                 |                                  |
|                                                                        | angiotensin 2 receptor blocker [tiab]                                   |                                  |
|                                                                        | angiotensin 2 receptor blockers [tiab]                                  |                                  |
|                                                                        | ARB[tiab]                                                              |                                  |
|                                                                        | ARBs[tiab]                                                             |                                  |
|                                                                        | Angiotensin Converting Enzyme Inhibitors [Mesh]                         |                                  |
|                                                                        | Angiotensin Converting Enzyme Inhibitor [tiab]                          |                                  |
|                                                                        | Angiotensin Converting Enzyme Inhibitors [tiab]                         |                                  |
|                                                                        | ACE inhibitor [tiab]                                                   |                                  |
|                                                                        | ACE inhibitors [tiab]                                                  |                                  |
|                                                                        | ACEI [tiab]                                                            |                                  |
|                                                                        | Adrenergic beta-Antagonists [Mesh]                                     |                                  |
|                | PubMed                                      | EMBASE                                      | Search names                                      |
|----------------|---------------------------------------------|---------------------------------------------|---------------------------------------------------|
|                | beta blocker [tiab]                          |                                             |                                                   |
|                | beta blockers [tiab]                          |                                             |                                                   |
|                | b blocker [tiab]                              |                                             |                                                   |
|                | b blockers [tiab]                             |                                             |                                                   |
|                | Anti-Inflammatory Agents, Non-Steroidal [Mesh]|                                             |                                                   |
|                | antithrombotic [tiab]                         |                                             |                                                   |
|                | antithrombotics [tiab]                        |                                             |                                                   |
|                | antiplatelet [tiab]                           |                                             |                                                   |
|                | aspirin [MeSH]                                |                                             |                                                   |
|                | aspirin [tiab]                                |                                             |                                                   |
|                | Calcium Channel Blockers [MeSH]               |                                             |                                                   |
|                | Calcium Channel Blocker [tiab]                |                                             |                                                   |
|                | Calcium Channel Blockers [tiab]               |                                             |                                                   |
|                | calcium antagonist [tiab]                     |                                             |                                                   |
|                | calcium antagonists [tiab]                    |                                             |                                                   |
|                | CCB [tiab]                                    |                                             |                                                   |
|                | CCBs [tiab]                                   |                                             |                                                   |
|                | diuretics [Mesh]                              |                                             |                                                   |
|                | diuretic [tiab]                               |                                             |                                                   |
|                | diuretics [tiab]                              |                                             |                                                   |
Table S2. Data extraction form.

| Study (author) | Study ID (Corresponding with reference software) | Reviewer ID (MZ, EM, or KH) |
|----------------|--------------------------------------------------|----------------------------|
| **Publication year** |                                                   |                            |
| **Source** | Study type | Year of study | Performed country |
| **Study characteristics** | CVD status | Prevention type | Age | Women | Mean women | Men | Mean men |
| **Patient characteristics** | Study sample | Study women | Number of women on medications | Percentage of women on medications | Number of men on medications | Percentage of women on medications | Differences (women-men) | Women-to-men prevalence ratio | Maximum adjustment available |
| **Aspirin** | Study sample | Study women | Number of women on medications | Percentage of women on medications | Number of men on medications | Percentage of women on medications | Differences (women-men) | Women-to-men prevalence ratio | Maximum adjustment available |
| **Statins** | Study sample | Study women | Number of women on medications | Percentage of women on medications | Number of men on medications | Percentage of women on medications | Differences (women-men) | Women-to-men prevalence ratio | Maximum adjustment available |
| **Beta blockers** | Study sample | Study women | Number of women on medications | Percentage of women on medications | Number of men on medications | Percentage of women on medications |
| Study (author) | Differences (women-men) | Women-to-men prevalence ratio | Maximum adjustment available |
|---------------|-------------------------|-------------------------------|-----------------------------|
| Calcium channel blockers | Study sample | Study women | Number of women on medications | Percentage of women on medications | Number of men on medications | Percentage of women on medications | Differences (women-men) | Women-to-men prevalence ratio | Maximum adjustment available |
| ACE-inhibitors | Study sample | Study women | Number of women on medications | Percentage of women on medications | Number of men on medications | Percentage of women on medications | Differences (women-men) | Women-to-men prevalence ratio | Maximum adjustment available |
| Diuretics | Study sample | Study women | Number of women on medications | Percentage of women on medications | Number of men on medications | Percentage of women on medications | Differences (women-men) | Women-to-men prevalence ratio | Maximum adjustment available |

Key findings
Table S3. Quality assessment tool: Newcastle-Ottawa Scale.

Selection: (Maximum 3 stars)

1) Representativeness of the sample:
   a) Truly representative of the average in the target population. * (all subjects or random sampling)
   b) Somewhat representative of the average in the target population. * (non-random sampling)
   c) Selected group of users.
   d) No description of the sampling strategy.

2) Sample size:
   a) Justified and satisfactory. *
   b) Not justified.

3) Non-respondents:
   a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *
   b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
   c) No description of the response rate or the characteristics of the responders and the non-responders.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
   a) The study controls for the most important factor (age). *
   b) The study control for any additional factor. *

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
   a) Independent blind assessment. **
   b) Record linkage. **
   c) Self report. *
   d) No description.

2) Statistical test:
   a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *
   b) The statistical test is not appropriate, not described or incomplete.

Studies with more than four stars will be counted as satisfactory and thus can be included in systematic review.
Table S4. Quality assessment.

| Study                | Year | Selection (3) | Comparability (2) | Outcome(3) | Total |
|----------------------|------|----------------|-------------------|------------|-------|
|                      |      | Representativeness | Sample size | Non-respondent | Adjustment | Outcome | Statistical test |
| Carlsson A.C. et al  | 2012 | 1              | 1                 | 1          | 1     | 2      | 1              | 7       |
| Carroll K et al      | 2003 | 1              | 1                 | 1          | 1     | 2      | 1              | 7       |
| Catalan-Ramos A et al| 2014 | 1              | 1                 | 1          | 0     | 2      | 1              | 6       |
| Al-Lawati J.A. et al | 2012 | 1              | 1                 | 1          | 0     | 2      | 1              | 6       |
| Crilly M et al       | 2007 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Dodhia H et al       | 2015 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Dreyer R et al       | 2009 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Driscoll A. et al    | 2011 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Emberson J.R. et al  | 2005 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Forster A.S. et al   | 2014 | 1              | 1                 | 1          | 0     | 2      | 1              | 6       |
| Greving J.P. et al   | 2004 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Gulliford M.C. et al | 2010 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Hawkins N.M. et al   | 2012 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Hendrix K.H. et al   | 2005 | 1              | 1                 | 1          | 0     | 2      | 0              | 5       |
| Hippisley-Cox J et al| 2001 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Hyun K. et al        | 2012 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Journath G. et al    | 2008 | 1              | 1                 | 1          | 2     | 2      | 1              | 7       |
| Brady A.J.B. et al   | 2005 | 1              | 1                 | 1          | 0     | 2      | 0              | 5       |
| Weler D.J. et al     | 2005 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Paulsen M.S. et al   | 2011 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Lahoz C. et al       | 2009 | 1              | 1                 | 1          | 2     | 2      | 1              | 8       |
| Study                  | Year | Selection (3) | Comparability (2) | Outcome(3) | Total |
|-----------------------|------|---------------|-------------------|------------|-------|
| Sheppard J.P. et al\(^1\) | 2014 | 1             | 0                 | 2          | 5     |
| Svilaas A et al\(^2\)  | 2000 | 1             | 0                 | 2          | 6     |
| Tabenkin H et al\(^3\) | 2010 | 1             | 2                 | 2          | 8     |
| Turnbull F et al\(^4\) | 2010 | 1             | 1                 | 1          | 6     |
| Virani S.S. et al\(^5\) | 2011 | 1             | 2                 | 2          | 8     |
| Majeed A. et al\(^6\) | 2000 | 1             | 0                 | 2          | 5     |
| Majeed A. et al\(^7\) | 2005 | 1             | 2                 | 2          | 8     |
| Murphy N. et al\(^8\) | 2004 | 1             | 1                 | 2          | 6     |
| Nilsson P.M. et al\(^9\) | 2007 | 1             | 2                 | 2          | 7     |
| Nilsson P.M. et al\(^10\) | 2004 | 1             | 2                 | 2          | 6     |
| Owen A. et al\(^11\) | 2009 | 0             | 0                 | 2          | 8     |
| Lawlor D.A. et al\(^12\) | 2004 | 1             | 2                 | 2          | 8     |
| Bull N et al\(^13\) | 2003 | 2             | 2                 | 2          | 8     |
| Macchia A et al\(^14\) | 2012 | 1             | 2                 | 2          | 8     |
| Qato D.M et al\(^15\) | 2016 | 1             | 1                 | 2          | 7     |
| Saposnik G. et al\(^16\) | 2009 | 1             | 1                 | 1          | 5     |
| Brady A.J. et al\(^17\) | 2001 | 1             | 0                 | 2          | 5     |
| Alberts M.J. et al\(^18\) | 2009 | 0             | 0                 | 2          | 6     |
| Lee C. et al\(^19\) | 2019 | 1             | 2                 | 2          | 8     |
| Wandell P. et al\(^20\) | 2018 | 1             | 1                 | 2          | 7     |
| Law T.K. et al\(^21\) | 2015 | 1             | 1                 | 1          | 5     |
Table S5. Sex difference on aspirin prescription.

| Study, year        | CVD status                          | Age | Age of women | Age of men | % for women | % for men | Unadjusted PR       | Adjusted PR         |
|--------------------|-------------------------------------|-----|--------------|------------|-------------|-----------|---------------------|---------------------|
| Brady, 1998<sup>11</sup> | CVD                                 | 67  | NA           | NA         | 46%         | 53%       | 0.86 (0.83-0.88)    | 0.88 (0.81-0.95)    |
| Macchia, 2005<sup>13</sup> | CVD                                 | NA  | NA           | NA         | 78%         | 85%       | 0.92 (0.91-0.93)    | NA                  |
| Qato D.M, 2011<sup>15</sup> | Mixed (CVD+High-risk**)             | 52  | NA           | NA         | 60%         | 63%       | 0.96 (0.91-1.01)    | 0.84 (0.71-0.98)    |
| Al-Lawati, 2012<sup>10</sup> | Mixed (CVD+DM)                       | 54  | 54           | 54         | 67%         | 67%       | 1.00 (0.95-1.06)    | 0.85 (0.74-0.97)    |
| Brady, 2002<sup>20</sup>  | CVD                                 | 67  | NA           | NA         | 74%         | 80%       | 0.92 (0.90-0.94)    | 0.88 (0.81-0.95)    |
| Carlsson, 2002<sup>21</sup> | CVD                                 | 76  | 75           | 74         | 35%         | 32%       | 1.09 (1.02-1.16)    | 0.91 (0.79-1.04)    |
| Carroll, 2001<sup>22</sup> | CVD                                 | NA  | NA           | NA         | 59%         | 65%       | 0.90 (0.87-0.94)    | NA                  |
| Crilly, 2001<sup>23</sup>  | CVD                                 | 69  | NA           | NA         | 81%         | 86%       | 0.94 (0.89-0.99)    | 0.89 (0.81-0.97)    |
| Driscoll, 2007<sup>24</sup> | CVD                                 | 73  | 74           | 72         | 71%         | 80%       | 0.89 (0.87-0.91)    | 0.90 (0.80-1.01)    |
| Emberson, 2001<sup>25</sup> | Mixed (CVD+DM)                       | NA  | NA           | NA         | 14%         | 27%       | 0.51 (0.47-0.56)    | NA                  |
| Hendrix, 2005<sup>26</sup> | Mixed (CVD+HTN)                      | NA  | NA           | NA         | 15%         | 39%       | 0.38 (0.37-0.39)    | NA                  |
| Hippisley-Cox, 2001<sup>27</sup> | Mixed, (CVD+High-risk**)            | NA  | NA           | NA         | 71%         | 76%       | 0.94 (0.91-0.97)    | NA                  |
| Weler, 2003<sup>18</sup>   | Mixed (CVD+DM)                       | 65  | 66           | 63         | 46%         | 57%       | 0.80 (0.75-0.85)    | 0.88 (0.81-0.94)    |
| Lahoz, 2008<sup>12</sup>   | CVD                                 | 65  | NA           | NA         | 55%         | 64%       | 0.87 (0.83-0.90)    | 0.88 (0.82-0.94)    |
| Majeed, 2002<sup>24</sup>  | CVD                                 | NA  | NA           | NA         | 59%         | 66%       | 0.89 (0.83-0.95)    | NA                  |
| Sivilas, 1997<sup>16</sup> | CVD                                 | 69  | NA           | NA         | 47%         | 58%       | 0.81 (0.74-0.89)    | 0.89 (0.82-0.97)    |
| Tabenkin, 2004<sup>17</sup> | Mixed (CVD+HTN)                      | 53  | 52           | 53         | 35%         | 55%       | 0.64 (0.51-0.80)    | 0.84 (0.73-0.98)    |
| Lee, 2018<sup>19</sup>     | CVD                                 | 67  | 65           | 68         | 41%         | 57%       | 0.72 (0.71, 0.73)   | 0.88 (0.81, 0.95)   |
| Pooled                 |                                     | 64  | 67           | 65         | 41%         | 56%       | 0.81 (0.73-0.92)    | 0.87 (0.81-0.94)    |
CVD: cardiovascular disease; PR: prevalence ratio; NA: not available; %: percentage of using medication; mixed: patients at high-risks and with established cardiovascular disease; DM: diabetes; HTN: hypertension

*Publication year

** No high-risk assessment tool is available

¶ Mean age of study population in each study was adjusted.
### Table S6. Sex difference on statin prescription.

| Study, year          | CVD status             | Age  | Age of Women | Age of men | % for women | % for men | Unadjusted PR   | Adjusted PR ¶  |
|----------------------|------------------------|------|--------------|------------|-------------|-----------|----------------|----------------|
| Alberts, 2004        | CVD                    | 69   | NA           | NA         | 66%         | 69%       | 0.96 (0.94-0.97)| 0.87 (0.82-0.92)|
| Brady, 1998          | CVD                    | 69   | NA           | NA         | 13%         | 18%       | 0.73 (0.69-0.78)| 0.87 (0.82-0.92)|
| Lawlor, 2000         | CVD                    | 60-79| NA           | NA         | 27%         | 24%       | 1.12 (0.93-1.36)| NA             |
| Macchia, 2005        | CVD                    | 68.1 | 74           | 65         | 67%         | 80%       | 0.84 (0.83-0.86)| 0.88 (0.83-0.93)|
| Qato, 2011           | High-risk**            | 52.2 | NA           | NA         | 25%         | 25%       | 1.00 (0.90-1.11)| 1.05 (0.94-1.18)|
| Saposnik, 2004       | CVD                    | 67   | NA           | NA         | 79%         | 78%       | 1.01 (0.95-1.08)| 0.89 (0.84-0.93)|
| Brady, 2002          | CVD                    | 67   | NA           | NA         | 45%         | 52%       | 0.87 (0.83-0.90)| 0.89 (0.84-0.93)|
| Bull, 2003           | CVD                    | >40  | NA           | NA         | 21%         | 28%       | 0.75 (0.70-0.79)| NA             |
| Carlsson, 2002       | CVD                    | 75.5 | 75           | 74         | 18%         | 24%       | 0.78 (0.71-0.85)| 0.81 (0.73-0.89)|
| Carroll K, 2001      | CVD                    | >44  | NA           | NA         | 38%         | 49%       | 0.77 (0.73-0.82)| NA             |
| Catalan-Ramos, 2009  | High-risk, defined by FRS | 51   | NA           | NA         | 71%         | 70%       | 1.01 (1.00-1.02)| 1.07 (0.94, 1.20)|
| Crilly, 2001         | CVD                    | 69   | 71           | 67         | 53%         | 56%       | 0.93 (0.84-1.04)| 0.87 (0.82-0.92)|
| Dodhia, 2013         | CVD                    | 70   | NA           | NA         | 75%         | 83%       | 0.90 (1.03-1.09)| 0.86 (0.81-0.91)|
| Dreyer, 2007         | CVD                    | 70   | NA           | NA         | 76%         | 85%       | 0.89 (0.85-0.94)| 0.86 (0.81-0.91)|
| Emberson, 2001       | Mixed (CVD+DM)         | 60-79| NA           | NA         | 8%          | 7%        | 1.10 (0.95-1.29)| NA             |
| Forster, 2013        | High-risk, NHS health check | 40-74| NA           | NA         | 21%         | 18%       | 1.21 (1.14-1.29)| NA             |
| Gulliford, 2010      | CVD                    | 73   | NA           | NA         | 16%         | 19%       | 0.85 (0.79-0.92)| 0.83 (0.77-0.90)|
| Hendrix, 2005        | Mixed (CVD+HTN)        | 62   | NA           | NA         | 29%         | 41%       | 0.70 (0.69-0.72)| 0.94 (0.89-1.00)|
| Hyun, 2012           | Mixed (CVD+high risk defined by FRS) | 61   | NA           | NA         | 66%         | 68%       | 0.97 (0.95-0.99)| 0.95 (0.90-1.01)|
| Study, year     | CVD status                           | Age   | Age of Women | Age of men | % for women | % for men | Unadjusted PR       | Adjusted PR ¶ |
|-----------------|--------------------------------------|-------|--------------|------------|-------------|-----------|---------------------|----------------|
| Journath, 2005³⁸ | High-risk (HTN)                      | 66    | 67           | 65         | 28%         | 33%       | 0.85 (0.79-0.92)    | 0.90 (0.85-0.94) |
| Lahoz, 2008*¹²   | CVD                                  | 65    | 68           | 65         | 77%         | 80%       | 0.96 (0.93-0.98)    | 0.91 (0.86-0.95) |
| Majeed, 1996³⁹   | CVD                                  | NA    | NA           | NA         | 8%          | 13%       | 0.62 (0.59-0.65)    | NA             |
| Nilsson, 2009⁵²  | Mixed (CVD+HTN))                     | 65    | NA           | NA         | 96%         | 92%       | 1.04 (1.03-1.05)    | 0.91 (0.86-0.95) |
| Sheppard, 2009⁴¹ | Mixed (CVD+High-risk defined by FRS) | 54    | NA           | NA         | 92%         | 72%       | 1.27 (1.24-1.31)    | 1.03 (0.93-1.14) |
| Turnbull, 2008⁴² | Mixed (CVD+ high-risk defined by FRS)| 68    | 68           | 68         | 53%         | 59%       | 0.90 (0.85-0.95)    | 0.88 (0.83-0.93) |
| Virani, 2011⁴³   | CVD                                  | 71    | 66           | 71         | 58%         | 65%       | 0.89 (0.88-0.90)    | 0.85 (0.79-0.91) |
| Law, 2010⁴⁴     | High-risk, defined by FRS            | 58    | NA           | NA         | 91%         | 93%       | 0.97 (0.91-1.04)    | 0.98 (0.91-1.06) |
| Lee, 2018¹⁹     | CVD                                  | 67    | 65           | 68         | 56%         | 75%       | 0.74 (0.73, 0.74)   | 0.89 (0.84, 0.93) |
| Wandell, 2007⁴⁵  | CVD                                  | NA    | NA           | NA         | 33%         | 39%       | 0.84 (0.79, 0.89)   | NA             |
| Nanna, 2015⁴⁶   | Mixed (CVD+High-risk**)              | 68    | 68           | 68         | 67%         | 78%       | 0.85 (0.83, 0.88)   | 0.88 (0.83-0.93) |
| Pooled          |                                      | 65    | 71           | 68         | 60%         | 63%       | 0.90 (0.85, 0.95)   | 0.91 (0.87-0.95) |

CVD: cardiovascular disease; PR: prevalence ratio; NA: not available; %: percentage of using medication; mixed: patients at high-risks and with established CVD; FRS: Framingham risk score; HTN: hypertension; DM: diabetes

*Publication year

**No cardiovascular risk assessment tool is available

¶ Mean age of study population in each study was adjusted.
Table S7. Sex difference on beta-blockers prescription.

| Study, year | CVD status | Age | Age of women | Age of men | % for women | % for men | Unadjusted PR | Adjusted PR |
|-------------|------------|-----|--------------|------------|-------------|-----------|---------------|-------------|
| Brady, 1998¹¹ | CVD        | 69  | NA           | NA         | 19%         | 23%       | 0.86 (0.81-0.90) | 0.91 (0.85-0.97) |
| Al-Lawati, 2007¹⁰ | Mixed [CVD+DM] | 54  | 54           | 54         | 7%          | 7%        | 1.08 (0.73-1.59) | 1.00 (0.88-1.14) |
| Brady, 2002²⁰ | CVD        | 67  | NA           | NA         | 38%         | 42%       | 0.91 (0.87-0.95) | 0.92 (0.87-0.98) |
| Carlsson, 2013²¹ | CVD        | 76  | 75           | 74         | 59%         | 55%       | 1.07 (1.03-1.11) | 0.87 (0.77-0.98) |
| Catalan-Ramos, 2009²² | High-risks, defined by FRS | 51  | NA           | NA         | 40%         | 36%       | 1.09 (1.08-1.10) | 1.02 (0.87-1.19) |
| Dreyer, 2001³⁴ | CVD        | 70  | 71           | 67         | 28%         | 38%       | 0.74 (0.63-0.88) | 0.91 (0.85-0.97) |
| Emberson, 2001²⁵ | Mixed [CVD+DM] | 60-79 | NA           | NA         | 25%         | 17%       | 1.49 (1.37-1.62) | NA         |
| Grevin, 2000⁴⁹ | High-risks [HTN] | 63  | NA           | NA         | 41%         | 41%       | 1.01 (0.95-1.07) | 0.94 (0.89-1.00) |
| Hawkins, 2007⁵⁰ | CVD        | 68  | NA           | NA         | 24%         | 28%       | 0.86 (0.82-0.89) | 0.92 (0.86-0.97) |
| Hendrix, 2005²⁶ | Mixed [CVD+HTN] | 62  | NA           | NA         | 28%         | 32%       | 0.86 (0.84-0.88) | 0.95 (0.89-1.01) |
| Hippisley-Cox, 2001²⁷ | CVD        | 62  | NA           | NA         | 49%         | 51%       | 0.96 (0.91=1.01) | 0.95 (0.89-1.01) |
| Journath, 2005²⁸ | High-risks [HTN] | 66  | 67           | 65         | 54%         | 51%       | 1.05 (1.01-1.11) | 0.93 (0.88-0.98) |
| Lahoz, 2008²¹² | CVD        | 65  | 68           | 65         | 41%         | 49%       | 0.83 (0.78-0.87) | 0.93 (0.88-0.99) |
| Murphy, 2004⁵¹ | High-risks [HTN] | NA  | NA           | NA         | 20%         | 23%       | 0.86 (0.68-1.09) | NA         |
| Owen, 2009⁴⁷ | High-risks [HTN] | 63  | 63           | 62         | 19%         | 19%       | 0.99 (0.92-1.06) | 0.94 (0.89-1.00) |
| Paulsen, 2011⁴⁸ | High-risks [HTN] | 66  | 66           | 66         | 29%         | 28%       | 1.04 (0.96-1.13) | 0.98 (0.90-1.06) |
| Lee, 2018¹⁹ | CVD        | 67  | 65           | 68         | 38%         | 50%       | 0.76 (0.75-0.77) | 0.93 (0.88, 0.98) |
| Wandell, 2007⁴⁵ | CVD        | NA  | NA           | NA         | 79%         | 75%       | 1.05 (1.02, 1.07) | NA         |
| Pooled       |            | 65  | 69           | 66         | 38%         | 38%       | 0.95 (0.89, 1.02) | 0.93 (0.88, 0.99) |
CVD: cardiovascular disease; PR: prevalence ratio; NA: not available; %: percentage of using medication; DM: diabetes; FRS: Framingham risk score; HTN: hypertension

*Publication year
¶ Mean age of study population in each study was adjusted.
Table S8. Sex difference on calcium channel blockers prescription.

| Study, year          | CVD status        | Age   | Age of women | Age of men | % for women | % for men | Unadjusted PR         | Adjusted PR ¶  |
|----------------------|-------------------|-------|--------------|------------|-------------|-----------|-----------------------|----------------|
| Brady, 1998          | CVD               | 69    | NA           | NA         | 12%         | 14%       | 0.85 (0.80-0.91)       | 0.98 (0.87-1.13) |
| Al-Lawati, 2007       | High-risks (DM)   | 54    | 54           | 54         | 2%          | 1%        | 1.38 (0.58-3.27)       | 0.87 (0.72-1.04) |
| Carlsson, 2013        | CVD               | 75    | 75           | 74         | 7%          | 6%        | 1.17 (0.97-1.40)       | 1.04 (0.85-1.29) |
| Catalan-Ramos, 2009   | High-risks (HTN)  | 51    | NA           | NA         | 25%         | 27%       | 0.94 (0.93-0.95)       | 0.85 (0.67-1.05) |
| Dreyer, 2007          | CVD               | 70    | NA           | NA         | 39%         | 31%       | 1.26 (1.11-1.42)       | 1.00 (0.86-1.16) |
| Greving, 2000         | High-risks (HTN)  | 63    | NA           | NA         | 18%         | 24%       | 0.74 (0.68-0.81)       | 0.94 (0.85-1.04) |
| Hendrix, 2005         | Mixed (CVD+HTN)   | 62    | NA           | NA         | 30%         | 28%       | 1.08 (1.05-1.10)       | 0.93 (0.84-1.03) |
| Journath, 2005        | High-risks (HTN)  | 66    | 67           | 65         | 26%         | 34%       | 0.78 (0.72-0.84)       | 0.96 (0.86-1.07) |
| Lahoz, 2008           | CVD               | 65    | 68           | 65         | 27%         | 24%       | 1.13 (1.04-1.23)       | 1.18 (1.06-1.31) |
| Nilsson, 2007         | High-risks (HTN)  | 52    | 53           | 51         | 26%         | 34%       | 0.77 (0.64-0.92)       | 0.68 (0.53-0.89) |
| Owen, 2009            | High-risks (DM+HTN)| 63   | 63           | 62         | 26%         | 27%       | 0.96 (0.90-1.02)       | 0.94 (0.87-1.02) |
| Paulsen, 2011         | High-risks (HTN)  | 66    | 66           | 66         | 32%         | 38%       | 0.84 (0.78-0.90)       | 0.61 (0.55-0.69) |
| Wandell, 2007         | CVD               | NA    | NA           | NA         | 37%         | 34%       | 1.07 (1.01, 1.14)      | NA             |
| Pooled               |                   | 63    | 65           | 64         | 25%         | 26%       | 0.95 (0.87-1.05)       | 0.94 (0.85-1.04) |

CVD: cardiovascular disease; PR: prevalence ratio; NA: not available; %: percentage of using medication; HTN: hypertension; DM: diabetes

*Publication year

¶ Mean age of study population in each study was adjusted.
Table S9. Sex difference on ACE-inhibitors prescription.

| Author, year | CVD status             | Age | Age of women | Age of men | % for women | % for men | Unadjusted PR | Adjusted PR |
|--------------|------------------------|-----|--------------|------------|-------------|-----------|---------------|-------------|
| Brady, 1998  | CVD                    | 69  | NA           | NA         | 12%         | 14%       | 0.85 (0.80-0.91) | 0.84 (0.79-0.89) |
| Macchina, 2011 | CVD                | 68  | 74           | 65         | 79%         | 79%       | 1.00 (0.98-1.01) | 0.81 (0.66-0.99) |
| Al-Lawati, 2007 | High-risks (DM)     | 54  | 54           | 54         | 37%         | 46%       | 0.80 (0.71-0.92) | 0.74 (0.57-0.96) |
| Brady, 2002 | CVD                    | 67  | NA           | NA         | 25%         | 28%       | 0.89 (0.84-0.95) | 0.81 (0.67-0.97) |
| Catalan-Ramos, 2009 | High-risks (HTN) | 51  | NA           | NA         | 53%         | 59%       | 0.90 (0.89, 0.90) | 0.73 (0.52-1.01) |
| Dreyer, 2007 | CVD                    | 70  | NA           | NA         | 44%         | 52%       | 0.85 (0.77-0.93) | 0.82 (0.65-1.05) |
| Emberson, 2001 | Mixed (CVD+DM)     | 60-79 | NA           | NA         | 26%         | 23%       | 1.11 (1.03-1.20) | NA         |
| Greving, 2000 | High-risks (HTN)     | 63  | NA           | NA         | 28%         | 37%       | 0.76 (0.71-0.82) | 0.78 (0.67-0.91) |
| Hawkins, 2007 | CVD                    | 68  | NA           | NA         | 52%         | 56%       | 0.92 (0.90-0.94) | 0.81 (0.66-0.99) |
| Hendrix, 2005 | Mixed (CVD+HTN)      | 62  | NA           | NA         | 44%         | 52%       | 0.85 (0.84-0.87) | 0.78 (0.67-0.91) |
| Journath, 2005 | High-risks (HTN)    | 66  | 67           | 65         | 18%         | 27%       | 0.67 (0.61-0.73) | 0.80 (0.67-0.95) |
| Lahoz, 2008 | CVD                    | 65  | 68           | 65         | 40%         | 39%       | 1.01 (0.95-1.07) | 0.80 (0.68-0.94) |
| Majeed, 2002 | CVD                    | NA  | NA           | NA         | 68%         | 76%       | 0.89 (0.85-0.94) | NA         |
| Murphy, 2004 | CVD                    | NA  | NA           | NA         | 34%         | 46%       | 0.74 (0.64-0.87) | NA         |
| Nilsson, 2007 | High-risks (HTN)     | 52  | 53           | 51         | 18%         | 27%       | 0.67 (0.53-0.83) | 0.73 (0.54-0.99) |
| Nilsson, 2004 | Mixed (CVD+DM)       | 65  | NA           | NA         | 27%         | 33%       | 0.80 (0.76-0.86) | 0.80 (0.68-0.94) |
| Owen, 2009   | High-risks (DM+HTN)  | 62  | 63           | 62         | 45%         | 51%       | 0.87 (0.84-0.91) | 0.78 (0.67-0.91) |
| Paulsen, 2011 | High-risks (HTN)    | 66  | 66           | 66         | 37%         | 48%       | 0.77 (0.72-0.82) | 0.80 (0.67-0.95) |
| Tabenkin, 2004 | High-risks (HTN)    | 53  | 52           | 53         | 41%         | 52%       | 0.79 (0.64-0.98) | 0.73 (0.55-0.98) |
| Lee, 2018   | CVD                    | 67  | 65           | 68         | 55%         | 69%       | 0.80 (0.80, 0.81) | 0.80 (0.68, 0.95) |
| Wandell, 2007 | CVD                   | NA  | NA           | NA         | 33%         | 40%       | 0.83 (0.78, 0.88) | NA         |
| Pooled      |                        | 63  | 65           | 61         | 51%         | 57%       | 0.85 (0.81, 0.89) | 0.84 (0.79, 0.89) |
CVD: cardiovascular disease; PR: prevalence ratio; NA: not available; %: percentage of using medication; mixed: patients at high-risks and with established CVD; DM: diabetes; HTN: hypertension

*Publication year
¶ Mean age of study population in each study was adjusted.
| Author, year     | CVD status           | Age | Age of women | Age of men | % for women | % for men | Unadjusted PR       | Adjusted PR ¶       |
|------------------|----------------------|-----|--------------|------------|-------------|-----------|---------------------|---------------------|
| Brady, 1998¹¹    | CVD                  | 69  | NA           | NA         | 29%         | 19%       | 1.51 (1.42-1.61)    | 1.32 (1.20-1.44)    |
| Al-Lawati, 2012¹⁰| High-risks (DM)      | 54  | 54           | 54         | 4%          | 4%        | 1.16 (0.68-2.01)    | 1.33 (1.17-1.53)    |
| Carlsson, 2013²¹ | CVD                  | 76  | 76           | 75         | 56%         | 42%       | 1.33 (1.27-1.40)    | 1.30 (1.10-1.55)    |
| Catalan-Ramos, 2009³² | High-risks (HTN)  | 51  | NA           | NA         | 68%         | 48%       | 1.43 (1.42-1.44)    | 1.34 (1.14-1.58)    |
| Greving, 2009⁴⁹  | High-risks (HTN)     | 63  | NA           | NA         | 47%         | 32%       | 1.48 (1.39, 1.58)   | 1.32 (1.22-1.43)    |
| Hendrix, 2005*²⁶ | Mixed (CVD+HTN)      | 62  | NA           | NA         | 58%         | 50%       | 1.14 (1.13-1.16)    | 1.32 (1.22-1.44)    |
| Journath, 2005³⁸ | High-risks (HTN)     | 66  | 67           | 65         | 64%         | 48%       | 1.35 (1.29-1.41)    | 1.32 (1.21-1.44)    |
| Lahoz, 2008*¹²   | CVD                  | 65  | 68           | 65         | 46%         | 32%       | 1.43 (1.35-1.52)    | 1.31 (1.21-1.43)    |
| Majeed, 2002¹⁴   | CVD                  | NA  | NA           | NA         | 81%         | 79%       | 1.02 (0.98-1.07)    | NA                  |
| Murphy, 2004⁵¹   | CVD                  | NA  | NA           | NA         | 81%         | 80%       | 1.01 (0.95-1.07)    | NA                  |
| Nilsson, 2007*⁵² | High-risks (HTN)     | 52  | 53           | 51         | 59%         | 45%       | 1.31 (1.16-1.48)    | 1.37 (1.15-1.56)    |
| Owen, 2009⁴⁷     | High-risks (DM+HTN)  | 63  | 63           | 62         | 23%         | 17%       | 1.34 (1.25-1.44)    | 1.32 (1.22-1.43)    |
| Paulsen, 2011⁴⁸  | High-risks (HTN)     | 66  | 66           | 66         | 66%         | 57%       | 1.01 (0.97-1.05)    | 1.32 (1.20-1.44)    |
| Wandell, 2007⁴⁵  | CVD                  | NA  | NA           | NA         | 69%         | 54%       | 1.28 (1.23, 1.32)   | NA                  |
| Pooled           |                      | 63  | 65           | 64         | 47%         | 39%       | 1.26 (1.17, 1.37)   | 1.32 (1.22-1.43)    |

CVD: cardiovascular disease; PR: prevalence ratio; NA: not available; %: percentage of using medication; Mixed: patients at high-risks and with established CVD; HTN: hypertension; DM: diabetes

*Publication year

¶ Mean age of study population in each study was adjusted.
Table S11. Inclusion information, stratified by CVD status.

|               | Aspirin | Statin         | BB   | CCB | ACE-Inhibitor | Diuretics |
|---------------|---------|----------------|------|-----|---------------|-----------|
| **High-risk** | No. Paper | NA 7 7 7 8 7 |      |     |               |           |
| No. Women     | NA      | 399,002 343,724 343,866 344,046 343,866 |      |     |               |           |
| No. Men       | NA      | 406,962 344,523 344,504 344,726 344,204 |      |     |               |           |
| PP. women     | NA      | 67% 39% 25% 52% 70% |      |     |               |           |
| PP. men       | NA      | 64% 36% 27% 58% 47% |      |     |               |           |
| Pooled PR     | NA      | 0.93(0.82,1.07) 1.04(0.96,1.12) 0.85(0.61,1.18) 0.79(0.49,1.26) 1.31(0.77,2.20) |      |     |               |           |
| **CVD**       | No. Paper | 11 19 12 5 10 | 6    |     |               |           |
| No. Women     | 98,294 170,702 111,640 19,733 104,151 15,364 |      |     |               |           |
| No. Men       | 130,704 1,177,332 140,974 30,903 130,772 24,027 |      |     |               |           |
| PP. women     | 48% 44% 38% 18% 50% 52% |      |     |               |           |
| PP. men       | 62% 63% 47% 19% 58% 36% |      |     |               |           |
| Pooled PR     | 0.89(0.84,0.94) 0.85(0.80,0.90) 0.90(0.85,0.96) 1.08(0.94,1.23) 0.88(0.84,0.93) 1.25(1.09,1.43) |      |     |               |           |
| **Mixed**     | No. Paper | 7 5 2 NA 3 | NA   |     |               |           |
| No. Women     | 42,025 18,552 33,494 NA 37,787 NA |      |     |               |           |
| No. Men       | 55,855 21,018 47,552 NA 52,634 NA |      |     |               |           |
| PP. women     | 24% 61% 28% NA 40% NA |      |     |               |           |
| PP. men       | 42% 61% 31% NA 47% NA |      |     |               |           |
| Pooled PR     | 0.71(0.54,0.93) 1.05(0.93,1.18) 1.13(0.66,1.94) NA 0.91(0.75,1.10) NA |      |     |               |           |

PP: Pooled prevalence; PR: prevalence ratio; CCB: calcium channel blocker; NA: not available.
Figure S1. Women-to-men prevalence ratio from 10 studies reporting all four antihypertensive medications.

| Author, year | Women % | Men % | Prevalence ratio [95% CI] |
|--------------|---------|-------|--------------------------|
| Brady1998\textsuperscript{11} | 19 | 23 | 0.86 [0.81, 0.90] |
| Al Lawati2007\textsuperscript{10} | 7 | 7 | 1.08 [0.73, 1.59] |
| Catalan Ramos2009\textsuperscript{32} | 40 | 36 | 1.09 [0.99, 1.07] |
| Greeving2000\textsuperscript{26} | 41 | 41 | 0.86 [0.84, 0.88] |
| Journath2005\textsuperscript{38} | 54 | 51 | 1.05 [1.01, 1.11] |
| Lahoz2008\textsuperscript{13} | 41 | 49 | 0.83 [0.78, 0.87] |
| Owen2009\textsuperscript{17} | 19 | 19 | 0.99 [0.92, 1.06] |
| Paulsen2011\textsuperscript{46} | 29 | 28 | 1.04 [0.96, 1.13] |
| Wandell2007\textsuperscript{45} | 79 | 75 | 1.05 [1.02, 1.07] |

Pooled prevalence ratio for beta blockers: 0.97 [0.91, 1.04]

| Author, year | Women % | Men % | Prevalence ratio [95% CI] |
|--------------|---------|-------|--------------------------|
| Brady1998\textsuperscript{11} | 12 | 14 | 0.85 [0.80, 0.91] |
| Al Lawati2007\textsuperscript{10} | 2 | 1 | 1.35 [1.05, 1.10] |
| Catalan Ramos2009\textsuperscript{32} | 25 | 27 | 0.94 [0.93, 0.95] |
| Greeving2000\textsuperscript{26} | 18 | 24 | 0.74 [0.68, 0.81] |
| Journath2005\textsuperscript{38} | 26 | 34 | 0.97 [0.92, 1.06] |
| Lahoz2008\textsuperscript{12} | 27 | 24 | 1.13 [1.04, 1.23] |
| Owen2009\textsuperscript{47} | 26 | 27 | 0.96 [0.90, 1.02] |
| Paulsen2011\textsuperscript{46} | 32 | 38 | 0.84 [0.78, 0.90] |
| Wandell2007\textsuperscript{45} | 37 | 34 | 1.07 [1.01, 1.14] |

Pooled prevalence ratio for calcium channel blockers: 0.93 [0.84, 1.02]

| Author, year | Women % | Men % | Prevalence ratio [95% CI] |
|--------------|---------|-------|--------------------------|
| Brady1998\textsuperscript{11} | 12 | 14 | 0.85 [0.80, 0.91] |
| Al Lawati2007\textsuperscript{10} | 2 | 1 | 1.35 [1.05, 1.10] |
| Catalan Ramos2009\textsuperscript{32} | 25 | 27 | 0.94 [0.93, 0.95] |
| Greeving2000\textsuperscript{26} | 18 | 24 | 0.74 [0.68, 0.81] |
| Journath2005\textsuperscript{38} | 26 | 34 | 0.97 [0.92, 1.06] |
| Lahoz2008\textsuperscript{12} | 27 | 24 | 1.13 [1.04, 1.23] |
| Owen2009\textsuperscript{47} | 26 | 27 | 0.96 [0.90, 1.02] |
| Paulsen2011\textsuperscript{46} | 32 | 38 | 0.84 [0.78, 0.90] |
| Wandell2007\textsuperscript{45} | 37 | 34 | 1.07 [1.01, 1.14] |

Pooled prevalence ratio for ACE-inhibitors: 0.83 [0.78, 0.89]

| Author, year | Women % | Men % | Prevalence ratio [95% CI] |
|--------------|---------|-------|--------------------------|
| Brady1998\textsuperscript{11} | 12 | 14 | 0.85 [0.80, 0.91] |
| Al Lawati2007\textsuperscript{10} | 2 | 1 | 1.35 [1.05, 1.10] |
| Catalan Ramos2009\textsuperscript{32} | 25 | 27 | 0.94 [0.93, 0.95] |
| Greeving2000\textsuperscript{26} | 18 | 24 | 0.74 [0.68, 0.81] |
| Journath2005\textsuperscript{38} | 26 | 34 | 0.97 [0.92, 1.06] |
| Lahoz2008\textsuperscript{12} | 27 | 24 | 1.13 [1.04, 1.23] |
| Owen2009\textsuperscript{47} | 26 | 27 | 0.96 [0.90, 1.02] |
| Paulsen2011\textsuperscript{46} | 32 | 38 | 0.84 [0.78, 0.90] |
| Wandell2007\textsuperscript{45} | 37 | 34 | 1.07 [1.01, 1.14] |

Pooled prevalence ratio for diuretics: 1.32 [1.21, 1.43]
For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.
Figure S2. Association between age and sex differences in the prescription of cardiovascular medication.

Bubbles are individual studies; diameters of the bubbles are proportional to studies weight for analysis.
Figure S3. Association between age difference between the sexes and sex differences in the prescription of cardiovascular medication.

Bubbles are individual studies; diameters of the bubbles are proportional to studies weight for analysis.
Figure S4. Yearly trend of sex differences in the prescription of cardiovascular medication.

Bubbles are individual studies; diameters of the bubbles are proportional to studies weight for analysis.
Figure S5. Women-to-men prevalence ratio of cardiovascular medication prescription, stratified by CVD status.

For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.
Figure 56. Women-to-men prevalence ratio of aspirin prescription, stratified by CVD status.

For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.
Figure S7. Women-to-men prevalence ratio of statin prescription, stratified by CVD status.

For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.
Figure S8. Women-to-men prevalence ratio of beta blocker prescription, stratified by CVD status.

For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.
Figure 59. Women-to-men prevalence ratio of calcium channel blocker prescription, stratified by CVD status.

For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.
Figure S10. Women-to-men prevalence ratio of ACE-inhibitor prescription, stratified by CVD status.

For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.
Figure S11. Women-to-men prevalence ratio of diuretics prescription, stratified by CVD status.

For each study, the square is centered on the women-to-men prevalence ratio and the horizontal lines show the associated 95% confidence interval. The diamond indicates the pooled summary and its 95% confidence interval.