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Women are started on a lower daily dose of metoprolol than men irrespective of dose recommendations: *A potential source of confounding by contraindication in pharmacoepidemiology*

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Abstract

Purpose: Current guidelines have no sex-specific dosage advice for metoprolol. To evaluate whether women and men are prescribed the same dose a cohort analysis was performed in the population-based Rotterdam Study (RS). Results were replicated in the Integrated Primary Care Information (IPCI) database of automated general practice data.

Methods: The mean daily starting doses of metoprolol in both sexes were compared with independent-samples t-tests and a linear regression analysis was used to adjust in the RS for co-variables, notably, cardiovascular comorbidity, migraine, age, SBP, DBP, BMI, socioeconomic status, use of other antihypertensive drugs, smoking, and alcohol. In the IPCI-database, adjustment was for age only.

Results: The mean daily starting dose was statistically significantly lower in women than in men in both the RS and IPCI database, with a mean difference of 4.8 mg (95% CI −7.8, −1.8) and 4.6 mg (95%CI −5.3,-4.0), respectively. Statistical significance remained after adjustment in both databases.

Conclusions: Women received lower starting doses of metoprolol than men in two independent data collections despite non-sex specific cardiovascular guideline recommendations. This example of real-life pharmacotherapy can lead to a form of confounding by contraindication in pharmacoepidemiology.

KEYWORDS
drug utilization, evidence-based medicine, Pharmacoepidemiology, prescribing

1 | INTRODUCTION

Metoprolol is a widely used cardioselective beta-blocker without intrinsic sympathicomimetic activity and labeled for the treatment of hypertension, heart failure, atrial fibrillation, and for the secondary prevention of myocardial infarction. Research showed that metoprolol was among the most common cardiovascular drugs causing adverse drug reactions (ADRs).[1] In line with its pharmacological activity, the most frequent and severe ADRs caused by metoprolol are bradycardia, syncope and hypotension.[2-5]

Women are at greater risk of experiencing ADRs than men, and a 50%–70% higher risk in women was found in an analysis of multiple cohort studies.[6] In early trials on the use of beta-blockers for secondary prevention of myocardial infarction, only 20.5% of the study

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populations were women.[7] This underrepresentation resulted in scarce evidence on beta-blocker efficacy and safety in women.[8]

Nowadays there is more attention for sex differences in clinical trials but information on drugs marketed before the 1990s is still limited. However, an experimental study on the pharmacokinetics of metoprolol in healthy men and women showed a higher metoprolol plasma concentration in women, after taking 100 mg two times daily.[9] This was due to a lower distribution volume causing a higher maximum concentration, a greater "area under the curve" and a trend towards lower clearance. Based on these findings, the authors suggested that lowering the dose in women might be needed to avoid ADRs. Literature on patients with heart failure showed that women and elderly receive a lower daily dose of beta-blockers[10,11] and a recent publication showed that the optimal dose of metoprolol for heart failure, should be 50% lower in women than in men.[12]

Despite these published experimental pharmacokinetic data, product information, clinical pharmacological handbooks and current treatment guidelines make no distinction in recommended metoprolol dosage between men and women, neither in starting- nor in maintenance dosages.[13-25] Our hypothesis was that high metoprolol concentrations in women, might lead to a higher frequency of ADRs in women subsequently followed by an early discontinuation of metoprolol and/or a reduction of the daily dose. Therefore, our objective was to evaluate whether physicians prescribe the same starting dose of metoprolol for both women and men according to the formal dose recommendations. Furthermore, we investigated whether metoprolol would be titrated to a lower daily dose or lead to earlier discontinuation in women in community-dwelling middle/aged and elderly individuals under everyday circumstances.

Key Points

- Physicians prescribed statistically significantly lower metoprolol dosages to women than to men, irrespective of non-sex-specific dose recommendations and guidelines.
- Unrecognized prescriber's decisions in real-life may lead to confounding by contraindication in pharmacoepidemiology.

2 | METHODS

2.1 | Design and setting

A cohort analysis was performed in the Rotterdam Study (RS), a prospective population-based follow-up study of men and women from the Ommoord municipality of Rotterdam, the Netherlands. The RS was designed as a prospective cohort study, initially comprising 7983 persons of 55 years or older living in the well-defined Ommoord district in the city of Rotterdam in The Netherlands (78% of 10 215 invitees). In 2000, 3011 participants (out of 4472 invitees) who had become 55 years of age or moved into the study district since the start of the study were added to the cohort. In 2006, a further extension of the cohort was initiated in which 3932 subjects were included. By the end of 2008, the RS therefore comprised 14 926 subjects.[26] The overall response number for all three cycles at baseline was 72.0% (14 926 out of 20 744). All participants were extensively examined at study entry (i.e. baseline) and subsequent follow-up visits that take place every 3 to 6 years. They were interviewed at home and then underwent an extensive set of examinations in a specially built research facility in the center of the district. The RS has an emphasis on possible causes of invalidating diseases in the elderly with information from imaging (of heart, blood vessels, eyes, skeleton and later brain) and collected biospecimens that enabled further in-depth molecular and genetic analyses. Participants are followed for a variety of frequent diseases, such as coronary heart disease, heart failure and stroke, Parkinson disease, dementias, depression and anxiety disorders, COPD, diabetes and cancer. For participants of the RS, medication records are available as of January 1st 1991 from all pharmacies serving the Ommoord region with details on the product- and international non-proprietary name, number of filled tablets/capsules, strength, prescribed daily dose and duration of use.[27]

2.2 | Study population

The study population consisted of all patients who filled at least one prescription of metoprolol within the time period between January 1, 1991 and June 1, 2018 at the community pharmacy. All patients had at least 180 days of database history prior to the date of this first metoprolol prescription. Patients were included and defined as incident users when no other prescription for metoprolol was prescribed in the 180 days prior to the first prescription. Patients were followed from the first metoprolol prescription until the 10th prescription, or until discontinuation defined by the end of the study period, or the last prescription if the 10th prescription was not reached.

2.3 | Outcome

The primary outcome was the mean daily starting dose in mg per prescription, of the first 10 prescriptions of metoprolol stratified by sex and prescription number. The secondary outcome was discontinuation of metoprolol use in men and women.

2.4 | Co-variables

Comorbidities as a proxy for indications for use of metoprolol were considered as co-variables, notably hypertension defined by systolic blood pressure (normal, high [≥140 mmHg], missing) and diastolic blood pressure (normal, high [≥90 mmHg], missing), atrial fibrillation, secondary prevention after myocardial infarction, chronic heart failure and migraine. Age was also considered as a co-variable. Patients were categorized according to their age at the first prescription in the following

age categories: 18–55, 56–65, 66–75, 76–85 and >85 years old. Other co-variables were body mass index (kg m^{-2}), diabetes, smoking (never, former, current), total cholesterol levels (mmol L^{-1}), socioeconomic status (level of education), use of blood pressure lowering drugs (yes/no), use of cholesterol lowering drugs (yes/no), glomerular filtration rate (ml min^{-1}) and alcohol consumption (grams per day).

2.5 | Data analysis

An independent t-test was used to compare the mean daily dose in mg of metoprolol for women and men for the first prescription. This was repeated for each of the prescriptions. With a linear regression model the mean daily dose of the prescriptions was compared for women and men per prescription and adjusted for the co-variables. Differences in discontinuation between women and men were presented with a Kaplan–Meier curve with the cumulative prescriptions over the first 10 prescriptions. Statistical analyses were performed using IBM SPSS Statistics (Version 25.0. Armonk, NY: IBM Corp.) and SAS Enterprise Guide (version 7.1. Cary, NC: SAS Institute Inc.).

2.6 | Replication cohort

Findings were replicated in the Dutch Integrated Primary Care Information (IPCI) database. IPCI is a longitudinal observational database which contains data from computer-based patient records retrieved from a selected group of GPs throughout the Netherlands, who voluntarily supply data to the database. It is a dynamic cohort because over time, people may enter the population as new patients, or leave because of removal or death. Details of the database have been described elsewhere.[28,29] From 1992 onwards, this database has expanded to now more than 2 500 000 patients. The database is representative of the Dutch population regarding age and sex. The electronic records of the IPCI database contain demographic information (date of birth, sex) as well as information about symptoms and diagnoses (coded according to the International Classification for Primary Care [ICPC] and/or free text), drug prescriptions with ICPC coded indications, ATC-codes and dosage regimens, laboratory results, measurements such as blood pressure and cholesterol levels, referrals to secondary care and hospitalizations.

The scientific and ethical advisory board of the IPCI project approved the study (Project number: 6/2017). Incident metoprolol users were included and the same design and methodology was used to replicate findings from the RS within the time period of January 1, 1996 and December 31, 2016. Also, the duration of the first prescription in days was compared between women and men to evaluate the physicians prescribing behavior.

3 | RESULTS

The RS consists of 8823 women and 6103 men of 55 years or older, of whom 1263 women (14.3%) and 870 men (14.3%) were dispensed metoprolol at least once during the study period. Table 1 shows an overview of the baseline characteristics of the patients. Women had more often hypertension than men (77.3% and 66.9%, respectively) and men had more often a history of myocardial infarction than women (36.8% and 19.6%, respectively) before start of metoprolol. The mean daily starting dose of metoprolol was significantly lower in women (61.1 mg, SD = 31.4) than in men (65.9 mg, SD = 36.3) (Figure 1A). The difference between the starting dose in women and men was 4.8 mg daily (95% CI −7.8, −1.8). Although the dosages increased over time for both sexes, the difference in daily dose became smaller during subsequent prescriptions. The dosage was still significantly lower in women up to and including the third prescription (−4.3 mg, 95% CI −7.9, −0.7). The percentage of starting prescriptions per daily dosage are shown in Figure 2 for both women and men. Linear regression was used to adjust for all co-variables (Figure 3). After adjustment the difference in starting dose between women and men remained statistically significant (−5.2 mg, 95% CI −8.5, −1.9). The proportion of women and men discontinuing treatment with metoprolol during the study period was similar (Figure 4).

Analysis was replicated in the IPCI database. From the IPCI database, 23 074 women (1.8%), and 19 562 men (1.6%) were included. In the IPCI database, the mean daily starting dose of metoprolol was significantly lower in women (57.3 mg, SD = 31.6) than in men (62.0 mg, SD = 35.6) (Figure 1B). The difference between the starting dose in women and men was 4.6 mg (95% CI −5.3, −4.0). The difference in dosage remained statistically significant until the 10th prescription (−3.7 mg, 95% CI −5.1, −2.2). The difference in dose between men and women was statically significant after adjustment for age. As information on indication was only available in approximately 10% of the patients, it was decided not to adjust for indications. To evaluate if physicians tend to prescribe more carefully to women than to men, we compared the duration of the first prescription for women and men. The duration of the first prescription was shorter in women than in men. The percentage of patients who received a prescription for 2 weeks was 36.9% for women and 28.7% for men, for the prescriptions with a duration of 1 month it was 29.6% and 27.7% respectively. The percentage for prescriptions with a duration of 3 months were 20.2% and 30.7%, for women and men, respectively.

4 | DISCUSSION

We showed a statistically significantly lower starting dosage of metoprolol in women than in men in both the RS and IPCI database. Literature showed that women have higher plasma concentration levels of metoprolol, probably due to higher absorption, a lower distribution volume, and lower clearance.[9] In addition, metabolism of metoprolol primarily involves CYP2D6 which is less active in women.[30,31] Furthermore, it has been described that healthy women have a greater reduction in exercise heart rate and systolic blood pressure than men.[9] Despite this, we are unaware of any guideline, pharmacotherapeutic handbook, or approved product information which advises to start at a lower dose of metoprolol in women than in

TABLE 1 Patient characteristics of the Rotterdam Study (RS) at baseline

		Women (n = 1263)	Men (n = 870)
Age (years), mean (SD)		64.8 (8.3)	63.6 (7.1)
Age categories, years, n (%)	18–55	36 (2.9)	13 (1.5)
	56–65	246 (19.5)	204 (23.4)
	66–75	477 (37.8)	394 (45.3)
	76–85	383 (30.3)	228 (26.2)
	>85	121 (9.6)	31 (3.6)
Hypertension, n (%)		976 (77.3)	582 (66.9)
Systolic blood pressure (mmHg), mean (SD)		142.5 (22.3)	143.9 (21.9)
SBP categories, (mmHg), n (%)	<140	539 (42.7)	367 (42.2)
	≥140	619 (49.0)	454 (52.2)
	Missing	105 (8.3)	49 (5.6)
Diastolic blood pressure (mmHg), mean (SD)		77.6 (11.4)	80.8 (12.4)
DBP categories, (mmHg), n (%)	<90	982 (77.8)	641 (73.7)
	≥90	176 (13.9)	180 (20.7)
	Missing	105 (8.3)	49 (5.6)
Myocardial infarction, n (%)		247 (19.6)	320 (36.8)
Heart failure, n (%)		194 (15.4)	170 (19.5)
Atrial fibrillation, n (%)		234 (18.5)	181 (20.8)
Migraine, n (%)		122 (9.7)	26 (3.0)
Diabetes mellitus, n (%)		16 (1.3)	11 (1.3)
BMI (kg m^{-2}), mean (SD)		27.3 (4.3)	26.9 (3.4)
BMI categories, (kg m^{-2}), n (%)	<18.5	7 (0.6)	1 (0.1)
	18.5–24.9	361 (28.6)	240 (27.6)
	25.0–29.9	527 (41.7)	455 (52.3)
	30.0–34.9	209 (16.5)	114 (13.1)
	≥35	61 (4.8)	17 (2.0)
	Missing	98 (7.8)	43 (4.9)
GFR (ml min^{-1}), mean (SD)		76.5 (14.4)	80.4 (13.3)
GFR categories (ml min^{-1}), n (%)	<10	-	-
	10.0–29.9	1 (0.1)	-
	30.0–59.9	138 (10.9)	47 (5.4)
	60–89.9	634 (50.2)	450 (51.7)
	≥90	73 (5.8)	188 (21.6)
	Missing	298 (23.6)	185 (21.2)
Smoker	Never	409 (32.4)	113 (13.0)
	Former	444 (35.2)	477 (54.8)
	Current	145 (11.5)	96 (11.0)
Total cholesterol (mmol L^{-1}), mean (SD)		6.0 (0.9)	5.5 (1.0)
Total cholesterol Categories (mmol L^{-1}), n (%)	<5	141 (11.2)	194 (22.3)
	5.0–6.4	580 (45.9)	407 (46.8)
	6.5–7.9	239 (18.9)	111 (12.8)
	≥8.0	25 (2.0)	5 (0.6)
	Missing	278 (22.0)	153 (17.6)
Alcohol consumption (grams per day), mean (SD)		6,2 (9.2)	14.9 (17.1)
Alcohol Categories, (grams per day), n (%)	<0.25	242 (19.2)	76 (8.7)
	0.25–4.99	284 (22.5)	119 (13.7)
	5.00–24.99	255 (20.2)	238 (27.4)
	≥25.00	50 (4.0	117 (13.4)
	Missing	432 (34.2)	320 (36.8)
Antihypertensive drugs, n (%)		398 (31.5%)	252 (29.0%)
Cholesterol lowering drugs, n (%)		94 (7.4%)	68 (7.8%)
SES, n (%)	No or unknown education	26 (2.1%)	7 (0.8%)
	Primary	407 (32.2%)	162 (18.6%)
	Junior general secondary education	485 (38.4%)	199 (22.9%)
	Senior vocational training	222 (17.6%)	283 (32.5%)
	Senior general secondary education	29 (2.3%)	41 (4.7%)
	Vocational college	83 (6.6%)	147 (16.9%)
	Doctoral degree	11 (0.9%)	31 (3.6%)

Abbreviations: BMI, body mass index; GFR, glomerular filtration rate; SD, standard deviation; SES, socioeconomic status based on highest completed level of education.

men. Nevertheless, physicians prescribed metoprolol at a lower dose in women and although the reasoning for this could not be derived from the two datasets, it might be based on clinical intuition and

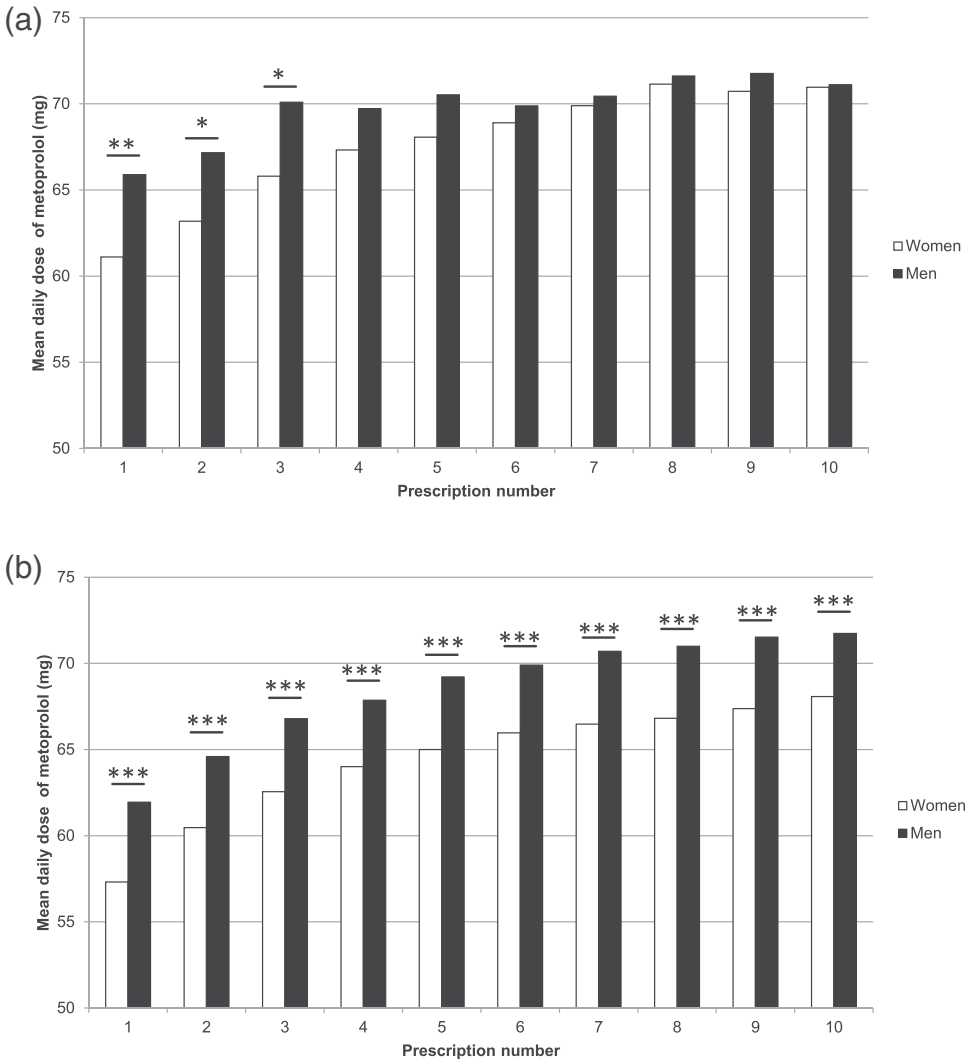

FIGURE 1 (A) The mean daily dose of metoprolol in milligrams for women and men during the first 10 prescriptions in the Rotterdam Study (RS). (B) The mean daily dose of metoprolol in milligrams for women and men during the first 10 prescriptions in the IPCI database

experience. This may be a source of unmeasured confounding in a pharmacoepidemiological study, but we could not verify this because we did not know whether physicians prescribing lower doses knew this literature or had more female patients with metoprolol-attributed adverse reactions in the past. If so, this might be an incentive for prescribing lower doses in women or to prescribe another antihypertensive drug, and this might lead to a type of confounding by contraindication which would require adjustment for sex and dose. Although the term "confounding by indication" is a hallmark phenomenon in non-randomized interventions in observational research, "confounding by contraindication" is less well-known. Whereas confounding by indication usually leads to an overestimation of the true risk, confounding by contraindication may underestimate the true risk. That confounding by contraindication really occurs, was demonstrated earlier.[32]

The first 10 prescriptions were evaluated because we expected patients to be up-titrated during this period. In our study, women had a larger increase in daily dose which might indicate that metoprolol dosages in women are up-titrated towards a tolerated dose. Men were also up-titrated during the first 10 prescriptions but to a lesser extent, as they were already started on a higher daily dose.

In our study, the lower dosage in women remains after adjustment for age and indication for use, that is, heart failure, atrial fibrillation, hypertension, myocardial infarction and other co-variables. Also, the lower dosage in women could not be explained by the different salt forms of metoprolol, tartrate and succinate. Under prescribing and underuse of beta-blockers in elderly and women with heart failure have been described earlier in the literature.[10,11] Physicians seem to take also other considerations into account than the recommendations in guidelines.

A strength of the study is the use of information from a prospective population-based study in middle-aged and elderly persons. This limits the chance of selection and information bias. Another strength is the fact that we found similar results in the completely independent and much larger IPCI database with information of the indication for use per prescription. This increased the precision and possibly also the generalizability of the results because the IPCI database covers all geographical areas and is representative of the Dutch population.[33] The RS is a population based prospective cohort study, collecting detailed information on patients at regular time intervals, but the sample size in the RS is smaller than in the IPCI database which could explain why the mean dose was slightly higher

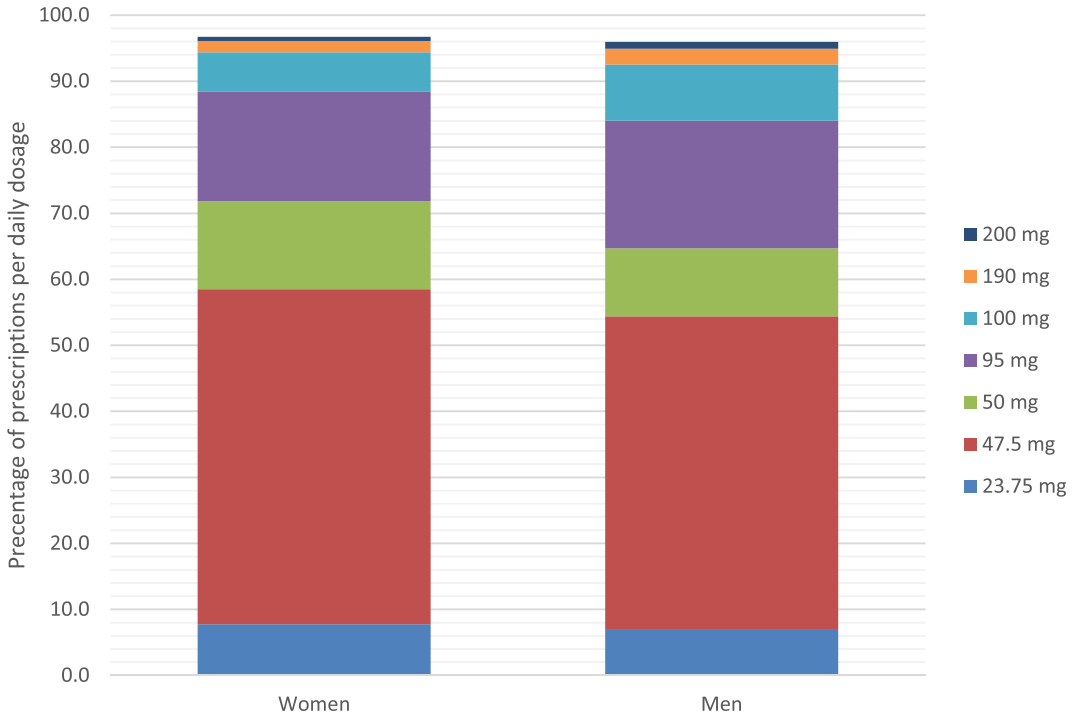

FIGURE 2 The percentage of the first prescriptions per daily dosage for women and men in the Rotterdam Study (RS) [Colour figure can be viewed at wileyonlinelibrary.com]

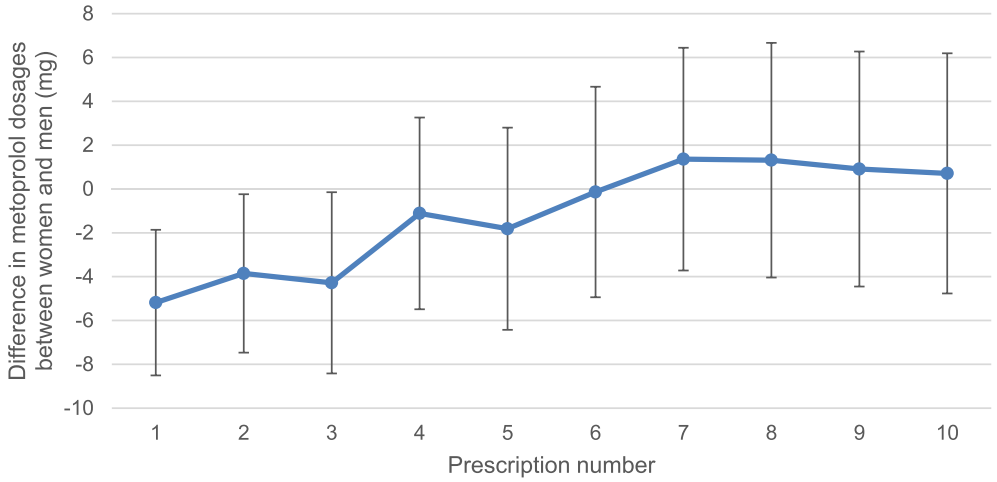

FIGURE 3 The differences in dosages in mg (95% CI) between women and men adjusted for hypertension (defined by systolic blood pressure (normal, high [≥140 mmHg], missing) and diastolic blood pressure (normal, high [≥90 mmHg], missing), atrial fibrillation, myocardial infarction, chronic heart failure, age (categories: 18–55, 56–65, 66–75, 76–85, and >85 years old), body mass index (kg m^{-2}), diabetes, smoking (never, former, current), total cholesterol levels (mmol L^{-1}), socioeconomic status (level of education), use of blood pressure lowering drugs (yes/no), use of cholesterol lowering drugs (yes/no), glomerular filtration rate (ml min^{-1}) and alcohol consumption (grams per day) in the Rotterdam Study (RS) [Colour figure can be viewed at wileyonlinelibrary.com]

in the RS study than in the IPCI database. Also, the IPCI database consists of prescriptions of general practitioners and a younger study population what could contribute to the difference to the RS. Therefore, the analysis on duration of the first prescription could only be performed in the IPCI database because IPCI contains prescription data. The RS database comprises pharmacy dispensing data. When a patient is started on a new drug for chronic use, pharmacies in the Netherlands will dispense the amount for 2 weeks irrespective of the duration of the prescription.[34]

Higher plasma concentration levels could cause more ADRs in women which might result into discontinuation of treatment. However, we saw no difference in discontinuation between women and men. In men, the lowest hazards of death or hospitalization for heart failure occurred at 100% of the recommended dose of β-blockers, but

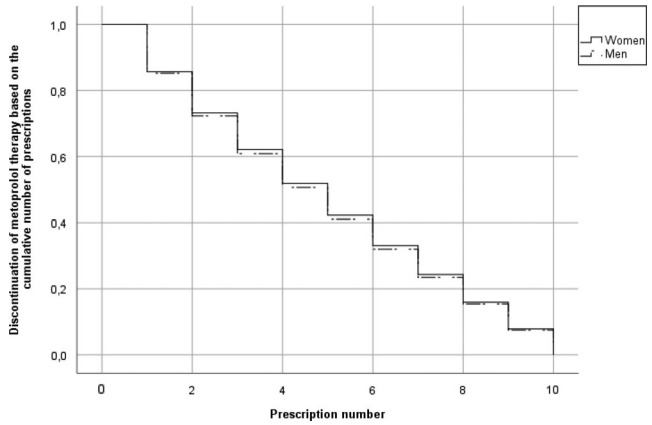

FIGURE 4 Kaplan–Meier curve of the cumulative prescriptions for women and men showing the discontinuation of metoprolol therapy over the first 10 prescriptions in the Rotterdam Study (RS)

women showed approximately 30% lower risk at only 50% of the recommended doses, with no further decrease in risk at higher dose levels.[12] Strikingly; it seems that physicians already incorporate this into daily practice.

In conclusion, we demonstrated in two independent community-dwelling populations that women were started on a lower dosage of metoprolol than men. Although this lower starting dose cannot be found back as recommendations in handbooks or guidelines, the lower starting dose makes sense as it was demonstrated that women have a higher maximum concentration than men. The clinical consequence of starting with a lower than the recommended dose in women is probably minimal as upwards dose-titration seems to occur. Hence, our data do not suggest that women are continuously undertreated.

This example of real-life pharmacotherapy might lead to confounding by contraindication in a pharmacoepidemiological study on the association between metoprolol and clinical endpoints which can be adjusted for by sex, dose, or the use of propensity scores.

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CONFLICT OF INTEREST

KV works for a research group who in the past received unconditional research grants from Yamanouchi, Pfizer/Boehringer Ingelheim, Novartis, GSK. None of which are related to the content of this work.

ETHICS STATEMENT

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregis ter.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp /netwo rk/prima ry/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

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