

Sex differences in prescription patterns of secondary prevention pharmacotherapy in patients with acute myocardial infarction: a 20-year insight from the AMIS Plus registry

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Summary

AIMS: Recent studies have demonstrated sex-related differences in secondary prevention pharmacotherapy in patients with acute myocardial infarction, although guidelines recommend the same preventive approach in both women and men. This study builds upon previous research by examining temporal trends in prescribing patterns of secondary prevention medications using contemporary, long-term data from Switzerland, with particular focus on sex-related disparities.

METHODS: Acute myocardial infarction patients enrolled in the AMIS (Acute Myocardial Infarction in Switzerland) Plus project between 2003 and 2022 were included. For this retrospective analysis, optimal medical therapy was defined as the combination of all five guideline-recommended medications at discharge: aspirin; P2Y12 inhibitor; lipid-lowering drug; beta-blocker; angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Uni- and multivariable logistic regression analyses were performed.

RESULTS: Among 34,612 patients (75% men, n=25,913), women were older and had more comorbidities but were less frequently prescribed optimal medical therapy than men (51% vs 60%) across all age groups (all p < 0.001), with the greatest gap occurring in patients < 50 years of age. A marked increase in optimal medical therapy prescription (36% to 60%) was detected irrespective of age and sex, mainly due to greater prescription of dual antiplatelet therapy (71% to 91%) and lipid-lowering drugs (69% to 93%). The sex-related gap in optimal medical therapy prescription disfavoured women showed a fluctuating trend (0.7–14%) whereas there was a progressive and sustained reduction regarding the combination of dual antiplatelet therapy plus lipid-lowering drug, from 18% to 10% at the beginning and the end of the observation period, respectively. Multivariable analysis showed greater frequency of optimal medical therapy prescription in patients with STEMI (OR: 1.65, 95% CI: 1.57–1.73) and those treated with PCI (OR: 4.85, 95% CI: 4.49–5.24), whereas lower prescription frequencies were observed among female patients (OR: 0.90, 95% CI: 0.85–0.95) and older individuals (OR per additional year: 0.99, 95% CI: 0.98–0.99).

CONCLUSIONS: Although optimal medical therapy prescription increased gradually over time among both women and men, concerning sex disparities disfavoured women, particularly young women, remained. Targeted programmes to reduce sex-related differences in secondary prevention care are warranted.

Introduction

Over the past few decades, a strong trend towards a reduction in mortality attributable to coronary artery disease in general and acute myocardial infarction in particular has been observed in developed countries, owing to rapid progress in both prevention and treatment [1]. Ageing of the population largely offsets these benefits in terms of total number of deaths, and coronary artery disease remains one of the leading causes of morbidity and mortality [2]. Patients with a history of acute

Published
24 September 2026

doi
<https://doi.org/10.57187/4681>

Cite this as
Swiss Med Wkly. 2026;156:4681

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myocardial infarction, in particular, remain at considerable risk of recurrent acute myocardial infarction and death [3], and effective secondary pharmacological therapy is well known to counteract this progression [4]. But despite compelling agreement among experts about the efficacy of secondary prevention methods and the abundance of guidelines recommending their use, their implementation in real-world practice remains inconsistent [5]. This observation is particularly true for women, who are considerably less likely than men to be prescribed guideline-compliant pharmacotherapy upon hospital discharge [6, 7], even though guidelines issued by the European Society of Cardiology (ESC) and the American Heart Association (AHA) / American College of Cardiology (ACC) recommend the same preventive approach for both women and men [8-10]. The drivers behind sex inequity in treatment as well as the temporal trends of this treatment gap are not well understood.

The aim of this study was to assess long-term trends in prescribing patterns of secondary prevention pharmacotherapy following acute myocardial infarction, with particular regard to disparities based on sex.

Methods

Study design

The AMIS Plus project is an ongoing nationwide prospective registry of patients hospitalised with acute coronary syndrome in Swiss hospitals. It is an industry-sponsored project, launched in 1997 by the Swiss Societies of Cardiology, Internal Medicine and Intensive Care Medicine. Details on the registry are available online [11]. Of 106 acute cardiac care hospitals in Switzerland, 84 temporarily or continuously enrolled patients. Participating hospitals range from community facilities to large tertiary centres and voluntarily provide blinded data via dedicated web- or paper-based questionnaires including over 300 items. Collected information includes, but is not limited to, demographics, medical history, pre- and in-hospital assessment and management, as well as discharge medication and destination. The AMIS Plus Data Centre, based at the Institute of Epidemiology, Biostatistics and Prevention at the University of Zurich, verifies the data and queries participating institutions in case of ambiguity. The registry was established in accordance with the 1964 Declaration of Helsinki and its later amendments and has been approved by the National Ethics Committee for Clinical Trials, the Swiss Data Safety Board and all cantonal ethics committees.

Secondary prevention medical therapy as recommended by the European and American clinical practice guidelines includes: aspirin and P2Y₁₂ inhibitors (their combination is defined as dual antiplatelet therapy), lipid-lowering agents, beta-adrenergic receptor blockers, and renin-angiotensin-aldosterone system blockers such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers [12, 13]. For the purpose of this study, optimal medical therapy was defined as the combination of all five guideline-recommended medication classes at discharge. Patients were classified as obese if their body mass index (BMI) was ≥ 30 kg/m² and their comorbidities were assessed using the Charlson Comorbidity Index (CCI) [14].

Patient selection

All patients with a final diagnosis of acute myocardial infarction enrolled in the AMIS Plus registry between January 2003 and December 2022 were eligible for inclusion. Acute myocardial infarction was defined in accordance with the universal definitions by characteristic clinical symptoms of acute myocardial ischaemia and/or serial ECG changes and elevated cardiac enzymes (either cardiac troponin above individual hospital cut-off levels, or creatine kinase MB fraction at least twice the upper limit of normal) [15]. Included patients were classified as either having STEMI or NSTEMI by means of the initial ECG findings. Classification of STEMI required any constellation compatible with acute ischaemia as defined above, together with ST segment elevation and/or new left bundle branch block (LBBB) on ECG. Conversely, depressed ST segments or T wave inversions went along with NSTEMI. Transferred patients (26%) and those with missing data on one or more optimal medical therapy drugs (7.5%) were excluded from analysis; see figure 1.

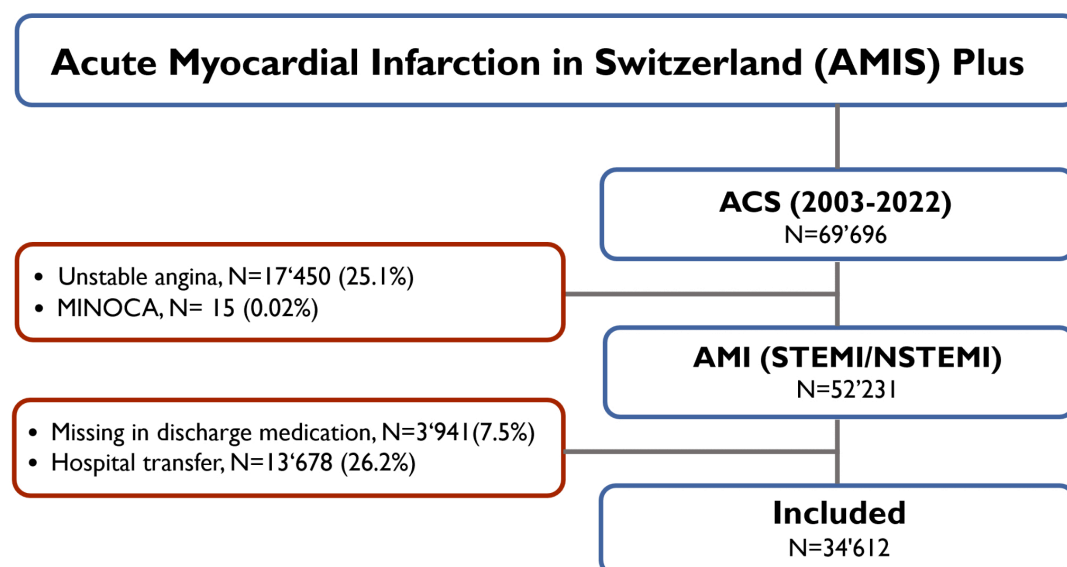


Figure 1: Inclusion and exclusion criteria for the population to be studied. Abbreviations: AMI: acute myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction.

Statistical analysis

Categorical variables are expressed as counts (%) and examined using the non-parametric Pearson χ^2 test. Continuous normally distributed variables are presented as mean ($\pm$ standard deviation) and analysed with the unpaired t-test; continuous variables with skewed distributions are presented as median (interquartile range) and compared using the Mann-Whitney U test. A two-tailed p-value <0.05 was considered significant. Univariable analyses were performed to assess clinical predictors of optimal medical therapy prescription at discharge. Multivariable logistic regression models were applied to evaluate optimal medical therapy prescribing with covariates selected a priori based on clinical expertise and expert knowledge, including sex, age, STEMI, comorbidities (CCI >1), atrial fibrillation, Killip class and percutaneous coronary intervention (PCI). Analyses were performed with SPSS software (version 28; SPSS, Chicago, IL, USA).

Results

Between 2003 and 2022, a total of 34,612 patients were enrolled (men: $n = 25,913$; 75%) in the AMIS Plus registry. Table 1 summarises exploratory comparisons of baseline and procedural characteristics according to sex. The mean population age was 66 ± 13 years and women were on average 7 years older than men. Around half of the women were >75 years of age, while only one in five men fell into this age category. As assessed by the CCI, women had more comorbidities (CCI >1 in 25% vs 21%; $p < 0.001$), including hypertension, diabetes, chronic kidney and lung disease, cerebrovascular disease, prior congestive heart failure and atrial fibrillation (for all, $p < 0.001$). Men were more likely to be current smokers, have dyslipidaemia and a history of prior acute myocardial infarction, while obesity was equally represented in both sexes. With respect to clinical presentation, STEMI was more common than NSTEMI in both women and men (56 vs 44%, $p < 0.001$), while female patients received PCI less often than male patients (78% vs 89%, $p < 0.001$).

Table 1: Baseline and procedural characteristics of patients with acute myocardial infarction according to sex.

Variable	n	Overall (n = 34,612)	Male (n = 25,913)	Female (n = 8699)	p-value
Age in years, mean (SD)	34,612	66 (13)	64 (13)	71(13)	<0.001
<50		4293 (12%)	3714 (14%)	579 (6.7%)	
50–75		21,039 (61%)	16,733 (65%)	4306 (50%)	
>75		9280 (27%)	5466 (21%)	3814 (44%)	
Diagnosis	34,612				<0.001
STEMI		19,227 (56%)	14,557 (56%)	4670 (54%)	
NSTEMI		15,385 (44%)	11,356 (44%)	4029 (46%)	
Medical history, n (%)					
Hypertension	32,963	20,649 (63%)	14,866 (60%)	5783 (70%)	<0.001
Dyslipidaemia	31,213	20,077 (64%)	15,403 (65%)	4674 (61%)	<0.001
Diabetes	33,045	6651 (20%)	4845 (20%)	1806 (22%)	<0.001
Obesity	31,354	6639 (21%)	5027 (21%)	1612 (21%)	0.6
Current smoker	31,277	12,013 (38%)	9703 (41%)	2310 (30%)	<0.001
Previous acute myocardial infarction	34,141	5557 (16%)	4421 (17%)	1136 (13%)	<0.001
Killip class	34,470				<0.001
I		29,896 (87%)	22,743 (88%)	7153 (83%)	
II		2940 (8.5%)	1913 (7.4%)	1027 (12%)	
III		791 (2.3%)	511 (2.0%)	280 (3.2%)	
IV		843 (2.4%)	641 (2.5%)	202 (2.3%)	
Cardiac insufficiency	32,473	884 (2.7%)	611 (2.5%)	273 (3.3%)	<0.001
Impaired LVEF*	30,615	2082 (6.8%)	1584 (6.8%)	498 (6.7%)	<0.001
Atrial fibrillation	32,842	1461 (4.4%)	998 (4.1%)	463 (5.5%)	<0.001
Peripheral vascular disease	34,117	1634 (4.8%)	1148 (4.5%)	486 (5.7%)	<0.001
Cerebrovascular disease	34,117	1701 (5.0%)	1184 (4.6%)	517 (6.0%)	<0.001
Chronic lung disease	34,116	1910 (5.6%)	1386 (5.4%)	524 (6.1%)	0.018
Moderate to severe renal disease	34,118	2244 (6.6%)	1470 (5.8%)	774 (9.0%)	<0.001
CCI >1	32,473	7114 (22%)	5020 (21%)	2094 (25%)	<0.001
Admission characteristics					
Pre-hospital resuscitation	34,611	1337 (3.9%)	1111 (4.3%)	226 (2.6%)	<0.001
Heart rate in bpm, median (IQR)	33,544	76 (65–88)	76 (65–88)	78 (67–90%)	<0.001
Systolic blood pressure in mm Hg, median (IQR)	33,542	138 (120–157)	137 (120–156)	140 (120–160)	<0.001
Diastolic blood pressure in mm Hg, median (IQR)	33,512	80 (70–90)	80 (70–92)	79 (68–90)	<0.001
Serum creatinine in $\mu\text{mol/l}$, median (IQR)	26,291	83 (71–99)	86 (75–101)	73 (62–90)	<0.001
Regular medication, n (%)					
Aspirin	31,704	10,903 (34%)	8060 (34%)	2843 (35%)	0.12
P2Y12 inhibitor	31,275	2438 (7.8%)	1872 (8.0%)	566 (7.1%)	0.008
Lipid-lowering drug	31,582	9496 (30%)	7349 (31%)	2147 (27%)	<0.001
Beta-blocker	31,468	8816 (28%)	6194 (26%)	2622 (33%)	<0.001
ACE-I or ARB	31,584	11,947 (38%)	8497 (36%)	3450 (43%)	<0.001
Oral anticoagulant	31,257	1370 (4.4%)	959 (4.1%)	411 (5.2%)	<0.001
Coronary revascularisation, n (%)					
PCI	33,984	29,233 (86%)	22,574 (89%)	6659 (78%)	<0.001
CABG	33,858	1108 (3.3%)	886 (3.5%)	222 (2.6%)	<0.001

* Impaired LVEF defined as LVEF <35% on ventriculography and/or LVEF <30% on echocardiography.

Significant increases over time were observed in the prescription of all components of optimal medical therapy, except for beta-blockers ($p = 0.2$). Increases were particularly marked for dual antiplatelet therapy (71% to 91%) and lipid-lowering drugs (69% to 93%), but less pronounced for angiotensin-converting enzyme inhibitors / angiotensin receptor blockers (76% to 83%) (figure 2). This translated into an increase in the proportion of optimal medical therapy prescription over time (36% to 60%) as well as of the combination of dual antiplatelet therapy plus lipid-lowering drugs

(47% to 83%) irrespective of sex (p for trend <0.001 for both women and men). Furthermore, the rise in drug prescription was paralleled by the increasing proportion of patients undergoing PCI: from 69% in 2003 to 91% in 2022.

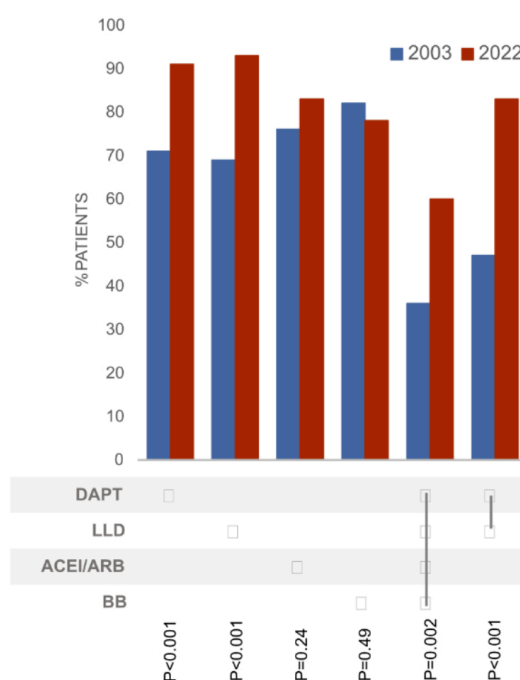


Figure 2: Prescription at discharge of each drug studied, and combinations thereof, in 2003 and 2022. ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BB: beta-blocker; DAPT: dual antiplatelet therapy (aspirin + P2Y12 inhibitor); LLD: lipid-lowering drug.

Sex-based analyses by drug class showed that, with the sole exception of beta-blockers ($p = 0.2$), women were significantly less exposed than men to evidence-based preventive treatments (for the remaining four components of optimal medical therapy, $p < 0.001$) (table 2). After making progress in narrowing and almost eliminating the sex-related gap in optimal medical therapy prescription in 2016, it started to widen again and ended up being similarly wide as at the beginning of the study period (ranging from 14% in 2003 to 0.7% in 2016 to 12% in 2022) (figure 3). The sex gap regarding the triple-drug regimen of dual antiplatelet therapy plus lipid-lowering drugs, on the other hand, narrowed continuously from 18% to 10% over the observation period. Comparing the periods of time before and after 2016 as binary variables, the sex gap changed from 8% to 9% for optimal medical therapy and from 12% to 8% for dual antiplatelet therapy plus lipid-lowering drugs.

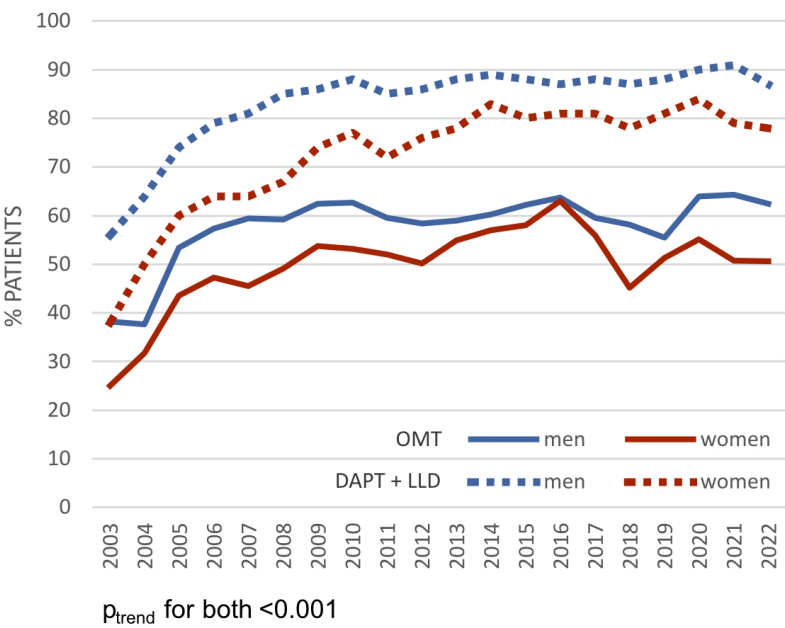


Figure 3: Temporal development of optimal medical therapy and dual antiplatelet therapy plus lipid-lowering drug prescribing, according to sex. Examined using the non-parametric Pearson χ^2 test.

Table 2: Discharge medication for patients with acute myocardial infarction according to sex.

Variable, n (%)	Overall (n = 34,612)	Male (n = 25,913)	Female (n = 8699)	p-value
Aspirin	33,292 (96%)	25,107 (97%)	8185 (94%)	<0.001
P2Y12 inhibitor	30,864 (89%)	23,676 (91%)	7188 (83%)	<0.001
Lipid-lowering drug	31,779 (92%)	24,212 (93%)	7567 (87%)	<0.001
Beta-blocker	27,483 (79%)	20,621 (80%)	6862 (79%)	0.2
ACE-I or ARB	28,650 (83%)	21,583 (83%)	7067 (81%)	<0.001
Optimal medical therapy*	19,880 (57%)	15,408 (60%)	4472 (51%)	<0.001

ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker.

Figure 4 illustrates that optimal medical therapy prescribing was lowest in the >75 age group for both sexes (44% of women vs 47% of men). It also shows that initiation of appropriate secondary prevention medical therapy was notably lower in women across all ages (all $p < 0.001$). However, the greatest sex discrepancy in optimal medical therapy prescribing is depicted in the <50 age group with rates of 55% for female patients and 65% for male patients.

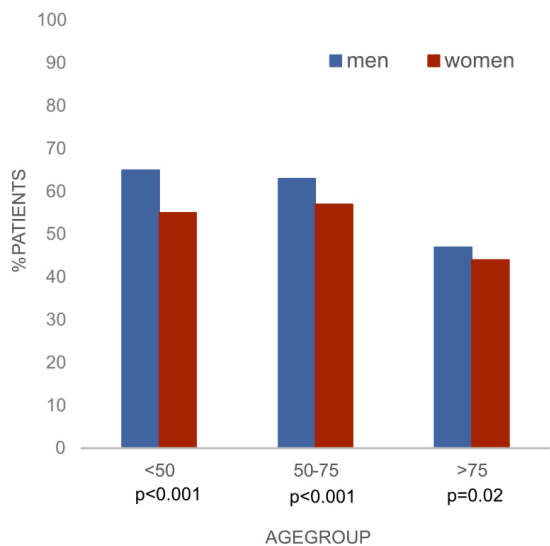


Figure 4: Optimal medical therapy prescription at discharge, by sex and age group.

Multivariable logistic regression analysis showed greater frequency of optimal medical therapy prescription in patients with STEMI (OR: 1.65, 95% CI: 1.57–1.73) and those treated with PCI (OR: 4.85, 95% CI: 4.49–5.24), whereas lower prescription frequencies were observed among female patients (OR: 0.90, 95% CI: 0.85–0.95), older individuals (OR per additional year: 0.99, 95% CI: 0.98–0.99) and patients with comorbidities defined as CCI >1 (table 3).

Table 3: Univariate and multivariate regression analyses for optimal medical therapy prescription in patients with acute myocardial infarction.

OR	Univariate		Multivariate			
	95% CI	p-value	OR	95% CI	p-value	
Female sex	0.72	0.69–0.76	<0.001	0.90	0.85–0.95	<0.001
Age per additional year	0.98	0.98–0.98	<0.001	0.99	0.98–0.99	<0.001
STEMI	2.02	1.93–2.11	<0.001	0.89	0.83–0.94	<0.001
Killip >2	0.94	0.85–1.04	0.241	1.09	0.97–1.22	0.161
CCI >1	0.89	0.83–0.94	<0.001	0.60	0.57–0.63	<0.001
Atrial fibrillation	0.71	0.58–0.87	<0.001	0.76	0.61–0.94	0.012
PCI	6.29	5.85–6.77	<0.001	4.85	4.49–5.24	<0.001

CCI: Charlson Comorbidity Index; PCI: percutaneous coronary intervention; STEMI: ST-elevation myocardial infarction.

Discussion

While secondary prevention medications improve long-term outcomes in patients with acute myocardial infarction, previous studies have suggested deficient guideline adherence, sex-based inequities disfavouring women and lack of improvement over time [16–19]. The results of our nationwide cohort study revealed suboptimal prescribing practices in Switzerland throughout the study period, with 57.1% post-acute myocardial infarction patients being discharged on full-scale optimal medical therapy (i.e. with all five cardiac medications: aspirin, P2Y12 inhibitor, lipid-lowering agent, beta-blocker and renin-angiotensin-aldosterone system blocker). The proportions presented here perform better than the latest research on secondary prevention pharmacotherapy conducted all over the world (39.8% in China [20], 45.2% in Sudan [21], 42.6% in Thailand [22]), but worse in comparison with investigations among 14 European countries with a similar healthcare system to Switzerland conducted by Zeymar et al. (2013) [23]. The latter is further supported by recent findings from a nationwide cohort study conducted over an 8-year period in Germany, which reported prescription rates of 68.4% [24].

This finding notwithstanding, there was a major improvement within the 20-year study period in the prescription of all five drug classes examined, except for beta-blockers, for which no increase in prescription rates was observed. Several factors may explain this finding, including the fact that the evidence supporting beta-blocker therapy is largely derived from the pre-reperfusion era. Moreover, several recent registry-based studies have questioned the continued efficacy of long-term beta-blocker use in patients without heart failure or left ventricular dysfunction[25]. Moreover, improvements in prescribing practices over time correlated strongly with the proportion of patients undergoing primary PCI in both STEMI and NSTEMI patients. Higher frequencies of optimal medical therapy prescription were observed among patients treated with PCI compared with those managed non-invasively. This association reflects both system-level factors such as the availability of institutional resources, as well as individual behaviours regarding diagnostic uncertainty and treatment inertia among clinicians and patients [26, 27].

But despite encouraging trends in prescribing medical therapies for secondary prevention, serious sex disparities disfavouring women continue to exist as has been repeatedly described [6, 20, 28]. A prospective observational cohort study from the Melbourne Interventional Group registry, for example, evaluated sex differences in secondary prevention pharmacotherapy and outcome between 2005 and 2017 and found reduced mortality but an unchanged sex gap over time [7]. This finding differs from results reported in contemporary data from the Korean acute myocardial infarction registry, demonstrating a continuous narrowing of the sex gap year by year [29]. Regarding the five-drug optimal medical therapy regimen, we identified the sex gap registered at the end of the study period to be nearly as wide as at the beginning, albeit with a surprising absence of significant sex inequity for a short period in-between. On the other hand, there was a steady narrowing of the sex gap when considering the triple-drug regimen, antiplatelet plus lipid-lowering therapies, suggesting that the shifting trend in evidence-based optimal medical therapy prescription may not be universal, but rather limited to angiotensin-converting enzyme inhibitors / angiotensin receptor blockers and beta-blockers. This daring hypothesis requires further investigation, as the available data and analyses are in fact not sufficient to explain this finding.

Extending research on equitable treatment delivery in acute myocardial infarction patients from the early 2000s [30], our results showed that sex inequity in initiation of appropriate pharmacotherapy after acute myocardial infarction was most pronounced in young women aged <50 years. Considering that it is already known that younger female acute myocardial infarction patients had a worse in-hospital prognosis compared with males [31], it is difficult to explain this finding. Weizman et al. (2023) proposed that the increased proportion of myocardial infarction with non-obstructive coronary arteries (MINOCA) among young women may contribute to the marked differences [32]. Our results, however, showed that even among patients who underwent PCI, women were still prescribed less secondary prevention pharmacotherapy. This is particularly concerning as the annual incidence of acute myocardial infarction hospitalisations attributable to young women has increased markedly over the past two decades [33].

The factors underlying sex differences in treatment patterns remain incompletely understood. As stated by Smolina et al. (2015), it is believed to be the result of numerous factors, including divergent clinical presentation, concerns about deficient evidence on efficacy and safety of corresponding drugs in women, skewed risk perception for adverse outcomes and recurrent events as well as physician biases [34]. Comparable to earlier studies, women in this study were nearly a decade older, accounted for more comorbidities and were less likely to receive timely reperfusion therapy than men, which is consistent with our findings [21, 33]. The observed sex differences in secondary prevention pharmacotherapy also persisted after adjustment for baseline characteristics and acute management.

Our findings are consistent with those of Fox et al., who reported that patients aged >75 years were less likely to receive optimal medical therapy at discharge than younger patients [35]. Advanced age coincided with an increased comorbid burden, but nonetheless, there is emerging evidence supporting the age-independent guideline recommendations that there is no difference in safety and efficacy as a function of age [36]. It is likely that improved prescribing practices among older adults would reduce the ongoing sex gap, as in our study population proportionately more than twice as many women as men are aged >75 years. However, possible risks need to be considered carefully in the harm-benefit assessment before prescribing.

Several strengths and limitations to our study merit consideration. A key advantage of this study lies in the use of an unselected database of women and men of all ages admitted with acute myocardial infarction to nationwide healthcare facilities, reflecting common practice in Switzerland. Moreover, this study adds to the literature as, to our knowledge, no study group evaluated decades-long trends in prescribing patterns of a five-drug regimen for secondary prevention at discharge with the sole exception of Dagan et al. (2022) [7]. In accordance with prior literature [7, 20, 22], optimal medical therapy was defined as the combination of all five guideline-recommended medication classes at hospital discharge. The most recent 2023 ESC guidelines for the management of acute coronary syndromes reaffirm the central role of dual antiplatelet therapy and intensive lipid-lowering treatment as class I recommendations for all post-acute myocardial infarction patients, whereas they introduce a more selective framework for beta-blockers and angiotensin-converting enzyme inhibitors / angiotensin receptor blockers [8]. These agents retain a class I indication only for patients with reduced left ventricular ejection fraction or specific comorbidities such as diabetes mellitus, chronic kidney disease or hypertension, and are considered class IIa otherwise. Therapeutic decisions must be tailored to specific clinical circumstances, and the evidential basis for the rigid one-size-fits-all approach is progressively weakening. While the dataset did not contain specific physician-reported reasons for withholding prescriptions, the large sample size allows for precise estimates after adjustment for age and comorbidities with appropriate caution. Further limitations include the absence of dosage information and the reliance on discharge prescriptions rather than verified medication adherence. Finally, we were not able to assess long-term medication patterns or outcome data and relate them to prescribing patterns at hospital discharge.

The results of our nationwide investigation show suboptimal guideline adherence despite improving prescribing practices of recommended secondary prevention medications in post-acute myocardial infarction patients over time. However, sex disparities in secondary prevention care disfavoured women, and particularly young women, persist. Targeted programmes to ensure appropriate treatment delivery among both sexes are warranted.

Data sharing statement

Individual data used for the construction of the AMIS Plus registry is the property of the hospitals participating in the AMIS registry and may only be made available by each hospital's principal investigator and steering committee. Due to data protection regulations related to the different hospitals involved in this study, the authors do not have authorisation to provide unrestricted data access. However, after approval of the AMIS Plus Steering Committee and subsequent negotiation of an individual AMIS Plus module contract with the AMIS Plus Steering Committee, analysis files can be handed over to other researchers. Requests must be submitted to Prof. Dr Hans Rickli, President of the AMIS Plus Steering Committee (hans.rickli[at]kssg.ch) and Dr Dragana Radovanovic, Head of Data Center AMIS Plus (dragana.radovanovic[at]juzh.ch).

Notes

Acknowledgements: The authors would like to express their gratitude to the teams of the following hospitals (listed in alphabetical order with the names of the local principal investigators): Aarau, Kantonsspital (L Haegeli); Affoltern am Albis, Bezirksspital (F Hess); Altdorf, Kantonsspital Uri (R Simon/S Gisler); Altstätten, Spital (PJ Hangartner); Baden, Kantonsspital (U Hufschmid); Basel, Universitätsspital (R Jeger); Basel, St. Claraspital (L Altwegg); Bern, Beau-Site Klinik (A Schönfelder); Bern, Inselspital (S Windecker); Bern, Tiefenau Spital (P Loretan); Biel, Spitalzentrum (H Schläpfer/C Roethlisberger); Büsingen, Spital (G Mang); Burgdorf, Regionalspital Emmental (D Ryser); Davos, Spital (G Niedermaier/W Kistler); Dornach, Spital (A Droll/T Hongler); Einsiedeln, Regionalspital (S Stäubli); Flawil, Spital (G Freiwald); Frauenfeld, Kantonsspital (HP Schmid); Fribourg, Hôpital cantonal (JC Stauffer/S Cook); Frutigen, Spital (K Bietenhard); Genève, Hôpitaux universitaires (M Roffi); Grenchen, Spital (B Oertli/R Schönenberger); Herisau, Kantonales Spital (M Bötschi/W Lakner); Horgen, See Spital (B Federspiel/B Kälin); Interlaken, Spital (EM Weiss); Kreuzlingen, Herzzentrum Bodensee (K Weber); La Chaux-de-Fonds, Hôpital (H Zender); Lachen, Regionalspital (C Steffen/I Poepping); Langnau im Emmental, Regionalspital (A Hugli); Laufenburg, Gesundheitszentrum Fricktal (J Frei/E Koltai); Lausanne, Centre hospitalier universitaire vaudois (O Muller); Lugano, Cardiocentro Ticino (G Pedrazzini); Luzern, Kantonsspital (P Erne/F Cuculi); Männedorf, Kreisspital (T Heimes); Mendrisio, Ospedale regionale (A Pagnamenta); Meyrin, Hôpital de la Tour (A Fassa); Moutier, Hôpital du Jura bernois (C Stettler); Münsingen, Regionales Spital Zentrum (F Repond); Münsterlingen, Kantonsspital (F Widmer); Muri, Kreisspital für das Freiamt (C Heimgartner); Nyon, Group. Hosp. Ouest lémanique (R Polikar); Olten, Kantonsspital (S Bassetti/S Ernst); Rheinfelden,

Gesundheitszentrum Fricktal (HU Iselin); Rorschach, Kantonales Spital (M Giger); Samedan, Spital Oberengadin (P Egger); Sarnen, Kantonsspital Obwalden (T Kaeslin); Schaffhausen, Kantonsspital (R Frey/A Fischer); Schlieren, Spital Limmattal (T Herren/B Caduff); Scuol, Ospidal d'Engiadina Bassa (G Flury/C Neumeier); Sion, Hôpital du Valais (G Girod); Solothurn, Bürgerspital Solothurn (R Vogel); Stans, Kantonsspital Nidwalden (B Niggli); St. Gallen, Kantonsspital (H Rickli); Sursee, Luzerner Kantonsspital (S Yoon/J Nossen); Thun, Spital (U Stoller); Uster, Spital (E Bächli); Wetzikon, GZO Spital (U Eriksson); Winterthur, Kantonsspital (T Fischer); Wolhusen, Luzerner Kantonsspital (M Peter); Zofingen, Spital (S Gasser); Zollikerberg, Spital (R Fatio); Zürich, Klinik Hirslanden (C Wyss); Zürich, Klinik im Park (O Bertel); Zürich, Universitätsspital Zürich (M Maggiorini); Universitätsspital Zürich, Kardiologie (B Stähli); Zürich, Stadtsipital Triemli (F Eberli/R Jeger); Zürich, Stadtsipital Waid (S Christen).

Funding

The AMIS Plus registry is funded by unrestricted grants from Abbott Medical (Schweiz) AG, Amgen AG, AstraZeneca AG, Bayer (Schweiz) AG, Biotronik (Schweiz) AG, Boston Scientific AG, B. Braun Medical AG, Cordis-Cardinal Health GmbH, Daiichi-Sankyo (Schweiz) AG, Medtronic AG, Novartis Pharma Schweiz AG, Pfizer/BMS (Schweiz), SIS Medical AG, Terumo (Schweiz) AG, Vascular Medical GmbH. The sponsors did not play any role in the design, data collection, analysis or interpretation of the registry.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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