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# Statin use prior to first myocardial infarction in contemporary patients: Inefficient and not gender equitable

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ABSTRACT

*Objectives.* Guidelines recommend initiating primary prevention with statins to those at highest cardiovascular risk. We assessed the gender-specific implementation and effectiveness of this risk-guided approach.

*Methods.* We identified 1399 consecutive patients without known cardiovascular disease or diabetes hospitalized with a first myocardial infarction (MI) in Denmark. Statin use before MI was assessed, and cardiovascular risk was calculated using SCORE (Systematic COronary Risk Evaluation).

*Results.* Among patients with first MI, 36% were women. Compared with men, they were older (mean 72 vs. 65 years) but had a lower estimated risk (median 3.4% vs. 6.7%, SCORE high-risk model in the statin-naïve patients). Statin therapy had been initiated in 12% of women and 10% of men prior to MI. After adding 1.5 mmol/L to the total cholesterol concentration of those already on statins, the estimated pre-treatment risk was much lower in women than men (median 3.8% vs. 9.2%, SCORE high-risk model), and only 29% of women would have passed the risk-based treatment threshold defined by the European guidelines (SCORE ≥5%). Estimated risk and statin use correlated directly in men but not in women. Only ~5% of first MI are prevented by the current use of statins in people without diabetes.

*Conclusion.* In people destined for a first MI, statin therapy is uncommon and prevents few events. Lower-risk women receive as much statins as higher risk men. This gender disparity and inefficient targeting of statins to those at highest risk indicate that risk scoring is not widely used in routine clinical practice in Denmark.



## Introduction

Atherosclerotic cardiovascular disease (ASCVD) is caused by modifiable risk factors and thus preventable by timely identification and treatment of those who are at risk for the disease (Lim et al., 2012). In primary prevention, public health initiatives are important but so is personalized prevention for those at highest risk for ASCVD, called the high-risk strategy. In Denmark, the high-risk strategy has been implemented as an opportunistic screening strategy.

In current guidelines on primary prevention of ASCVD, the intensity of intervention is tailored to the predicted risk for ASCVD using multifactorial risk scores, such as SCORE (Systematic COronary Risk Evaluation) (Perk et al., 2012), QRISK (National Institute for Health andCare Excellence (NICE), 2014; JBS3 Board, 2014) and the Pooled Cohort Equations (Stone et al., 2014; Goff et al., 2013). These guidelines, including allocation of statin therapy to those at highest ASCVD risk, apply equally to men and women. However, because women in general are at lower risk for ASCVD than men, fewer women than men will pass the risk threshold above which primary prevention with statins should be considered. This should not be viewed as gender disparity since men and women with similar risk are recommended similar treatment (Paulus et al., 2015). Nevertheless, because fewer women than men qualify for risk-based statin therapy, this approach to statin allocation recommended by the guidelines (Perk et al., 2012; National Institute for Health andCare Excellence (NICE), 2014; JBS3 Board, 2014; Stone et al., 2014; Goff et al., 2013) has been perceived as gender disparity (Wenger, 2012). Consequently, alternative approaches have been suggested to ensure that lower risk women receive similar treatment as higher risk men, including use of more women-friendly risk scores (Mosca et al., 2011) and lower treatment thresholds for women (Mosca et al., 2011; Navar-Boggan et al., 2015). Although little is known about the actual gender-specific use of risk-guided statin therapy in real-world patients, an opinion leader in the field asserted recently that preventive strategies have been stunningly underutilized for women (Wenger, 2015).

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The aim of the present study was to assess the use and performance of the risk-based approach to statin therapy in nondiabetic men and women prior to a first ASCVD event, focusing on potential gender disparities in contemporary routine clinical practice.

## Material and method

We identified consecutive patients with a first myocardial infarction (MI) without knowledge of prior ASCVD (hereafter just called first MI) admitted to four hospitals in Denmark in 2010 to 2012 (Aarhus University Hospital and the Regional Hospitals in Randers, Herning and Horsens). Patients with lacking information about prior ASCVD were excluded. The universal definition of MI is implemented in Denmark, requiring clinical evidence of myocardial ischemia together with elevated biomarkers reflecting myocardial necrosis (Thygesen and Alpert, 2007). Patients with first MI were identified via hospital registers using the International Classification of Diseases 10 (ICD-10) codes I21.0 through I21.9. From the medical records we extracted information on traditional risk factors (age, sex, smoking status, cholesterol, systolic blood pressure (SBP) and diabetes) and use of risk-reducing medication as previously described (Mortensen and Falk, 2014 Oct 17). Plasma lipid values were obtained within 24 h after admission and/or available from a prior contact with the health care system. The blood pressure used for risk estimation was obtained prior to admission (if hospitalized previous year) or after recovery from MI (before hospital discharge or at first visit to the rehabilitation clinic). Hypertension was defined as SBP >140 mm Hg and/or use of antihypertensive agents at admission.

The cardiovascular risk was estimated using the SCORE model introduced in 2003 (Conroy et al., 2003). SCORE was developed to predict the absolute 10-year risk for fatal CVD in people free of CVD and diabetes based on an individual's sex, smoking status, total cholesterol level and SBP. Thus, SCORE is not applicable in patients with diabetes who, by definition, are considered to be at high or very high risk for ASCVD. Two standard SCORE models are available, one for countries with a high incidence of fatal CVD (high-risk SCORE, range 0–47%), the other for countries with a low incidence (low-risk SCORE, range 0–26%). Denmark, together with many other mostly non-Eastern European countries, was reclassified from "high-risk" to "low-risk" in 2012 and recommended to use the SCORE low-risk model instead of the high-risk model (Perk et al., 2012). The SCORE risk was calculated using the risk equations published by Conroy et al (Conroy et al., 2003), and we used both the high-risk and the low-risk SCORE equations to clarify the consequences of replacing the former with the latter. The age-related risk was capped at age 65 to comply with clinical practice (Perk et al., 2012; Conroy et al., 2003), which means that the default age was set to 65 in people older than 65. SCORE was created for use in people 40 to 65 years of age, risk charts are available only for people without diabetes 40 to 65 years of age, and the age-related risk is capped at age 65 in the online risk calculator, *HeartScore* (ESC HeartScore risk calculator). In general, initiation of statin therapy is recommended or should be considered in individuals with SCORE ≥5%, defined as high or very-high risk (Perk et al., 2012). Statins are rarely indicated if SCORE is <5%.

In patients treated with statins prior to MI, we tried to estimate the SCORE risk before statin therapy was initiated. Guided by Naci et al's meta-analysis of randomized statin trials (Naci et al., 2013), we added 1.5 mmol/L to the on-treatment total cholesterol concentration (nearly all statin treated took simvastatin 40 mg) to get an estimate of SCORE before treatment. Furthermore, as a sensitivity analysis, we instead of adding 1.5 mmol/L increased the on-treatment total cholesterol concentration by 40%.

The study was approved by the Danish Data Protection Agency (Reference: 2007-58-0010, int. ref: 1-16-02-46-12). Registry studies do not require ethical approval in Denmark.

## Statistical analysis

All statistical analysis was performed using Stata version 13.1 SE (StataCorp LP, College Station, TX, USA). The 10-year risk of fatal CVD was calculated for each patient using both the high-risk and low-risk SCORE algorithms (Conroy et al., 2003). Baseline characteristics were compared with Student's t-test, Mann–Whitney test, Fishers exact test (categorical variables) or binormial probability test. We used logistic regression analyses to assess the association between risk factors and SCORE risk with use of statins before MI. These results are presented as odds ratio (OR) with 95% confidence intervals (CI).

## Results

We identified 1632 consecutive patients with first MI, 233 of whom had diabetes (n = 228) or missing information on diabetes (n = 5). The 1399 nondiabetic patients with first MI constitute the study population (Table 1). About 1/3 (36%) were women, and they had their first MI 7 years later than men (mean age in women: 72.1 years). Compared with men, fewer women smoked (32% vs. 43%), and they had a less atherogenic lipid profile with higher high-density lipoprotein cholesterol concentration (HDL-C), lower triglycerides, and similar low-density lipoprotein cholesterol concentration (LDL-C) (Table 1).

Information about statin use prior to first MI was available in all but 5 patients (Table 2). Statin therapy had been initiated in 12% of women and 10% of men prior to MI. Men treated with statins were older than those not on statins (difference 3.5 years, p = 0.02), but this was not the case in women (difference 0.3 year, p = 0.89).

On average, women with first MI had a substantially lower predicted risk than men. In statin-naïve patients, the median high-risk SCORE was 3.4% in women and 6.7% in men (low-risk SCORE: 2.3% in women, 3.7% in men; p < 0.0001), and only 30% of women versus 68% of men had a high-risk SCORE ≥5% (low-risk SCORE ≥5%: 12% vs. 33%; p < 0.0001) (Table 2 and Fig. 1). In patients on statins prior to MI (simvastatin 40 mg in nearly all), we added 1.5 mmol/L to the on-treatment total cholesterol concentration (Naci et al., 2013) and then calculated the SCORE risk as recommended for people not on statins. Before statin therapy, the median high-risk SCORE would have been approximately 3.8% in women and 9.2% in men (low-risk SCORE: 2.6% in women, 5.2% in men), and only 29% of women versus 84% of men would have passed the 5% high-risk threshold (low-risk SCORE: 13% vs. 52%; p < 0.0001) (Table 2 and Fig. 1). In statin-treated women, the estimated pre-treatment SCORE risk (3.8%) was nearly similar to that calculated for women not on statins prior to MI (3.4%). In men, the SCORE risk was higher in those using statins prior to MI (9.2% vs. 6.7%) (Table 2 and Fig. 1). Similar results were obtained by increasing the on-treatment total cholesterol concentration by 40% instead of adding 1.5 mmol/L (Supplementary Table 1).

The association of risk factors and use of statin prior to MI are shown in Table 3. In men, age, total cholesterol and hypertension were strongly associated with taking statins. In women, only total cholesterol was significantly associated with taking statins. Using the measured total cholesterol concentrations in the statin-naïve patients and the estimated pre-treatment concentrations in those on statins, there was a highly significant relationship between the SCORE risk and statin therapy in men but not in women (Fig. 2). Further, in men, but not in women, those at high-risk were more often using statins than those at lower-risk (Fig. 3). Similar results were obtained regardless of method used to estimate the pre-treatment cholesterol concentration (adding 1.5 mmol/L to the on-treatment total cholesterol concentration or increasing it by 40%; Supplementary data).

## Discussion

In the present study, approximately one third of consecutive, nondiabetic patients hospitalized with a first MI were women. They were older, and both among the untreated and statin treated patients had women a lower ASCVD risk estimated by SCORE than men. Statin therapy prior to first MI (primary prevention) was uncommon but, unexpectedly, it was more common in lower-risk women than in higher-risk men. There was a direct relationship between estimated risk and statin use in men, but not in women.

Denmark belongs to one of the 24 European countries classified as low-risk countries (Perk et al., 2012). In Denmark, with a population of ~5,650,000, statins are widely used (n ~ 650,000), nearly 1/3 of statin