



Københavns Universitet

Use of diagnostic coronary angiography in women and men presenting with acute myocardial infarction

Bjerking, Louise Hougesen; Hansen, Kim Wadt; Madsen, Mette; Jensen, Jan Skov; Madsen, Jan Kyst; Sørensen, Rikke; Galatius, Søren

Published in:

BMC Cardiovascular Disorders

DOI:

[10.1186/s12872-016-0248-9](https://doi.org/10.1186/s12872-016-0248-9)

Publication date:

2016

Document Version

Publisher's PDF, also known as Version of record

Citation for published version (APA):

Bjerking, L. H., Hansen, K. W., Madsen, M., Jensen, J. S., Madsen, J. K., Sørensen, R., & Galatius, S. (2016). Use of diagnostic coronary angiography in women and men presenting with acute myocardial infarction: a matched cohort study. *BMC Cardiovascular Disorders*, 16, [120]. <https://doi.org/10.1186/s12872-016-0248-9>

RESEARCH ARTICLE

Open Access



Use of diagnostic coronary angiography in women and men presenting with acute myocardial infarction: a matched cohort study

Louise Hougesen Bjerking^{1*}, Kim Wadt Hansen², Mette Madsen³, Jan Skov Jensen^{1,4}, Jan Kyst Madsen⁵, Rikke Sørensen¹ and Søren Galatius²

Abstract

Background: Based on evident sex-related differences in the invasive management of patients presenting with acute myocardial infarction (AMI), we sought to identify predictors of diagnostic coronary angiography (DCA) and to investigate reasons for opting out an invasive strategy in women and men.

Methods: The study was designed as a matched cohort study. We randomly selected 250 female cases from a source population of 4000 patients hospitalized with a first AMI in a geographically confined region of Denmark from January 2010 to November 2011. Each case was matched to a male control on age and availability of cardiac invasive facilities at the index hospital. We systematically reviewed medical records for risk factors, comorbid conditions, clinical presentation, and receipt of DCA. Clinical justifications, as stated by the treating physician, were noted for the subset of patients who did not receive a DCA.

Results: Overall, 187 women and 198 men received DCA within 60 days (75 % vs. 79 %, hazard ratio: 0.82 [0.67-1.00], $p = 0.047$). In the subset of patients who did not receive a DCA ($n = 114$), clinical justifications for opting out an invasive strategy was not documented for 21 patients (18.4 %). Type 2 myocardial infarction was noted in 11 patients (women versus men; 14.5 % vs. 3.8 %, $p = 0.06$) and identified as a potential confounder of the sex-DCA relationship. Receipt of DCA was predicted by traditional risk factors for ischaemic heart disease (family history of cardiovascular disease, hypercholesterolemia, and smoking) and clinical presentation (chest pain, ST-segment elevations). Although prevalent in both women and men, the presence of relative contraindications did not prohibit the use of DCA.

Conclusion: In this matched cohort of patients with a first AMI, women and men had different clinical presentations despite similar age. However, no differences in the distribution of relative contraindications for DCA were found between the sexes. Type 2 MI posed a potential confounder for the sex-related differences in the use of DCA. Importantly, clinical justification for opting out an invasive strategy was not documented in almost one fifth of patients not receiving a DCA.

Keywords: Acute myocardial infarction, Coronary angiography, Cardiac catheterization, Gender

* Correspondence: louise_bjerking@hotmail.com

¹Department of Cardiology, University Hospital Gentofte, Kildegårdsvej 28, 2900 Hellerup, Denmark

Full list of author information is available at the end of the article

Background

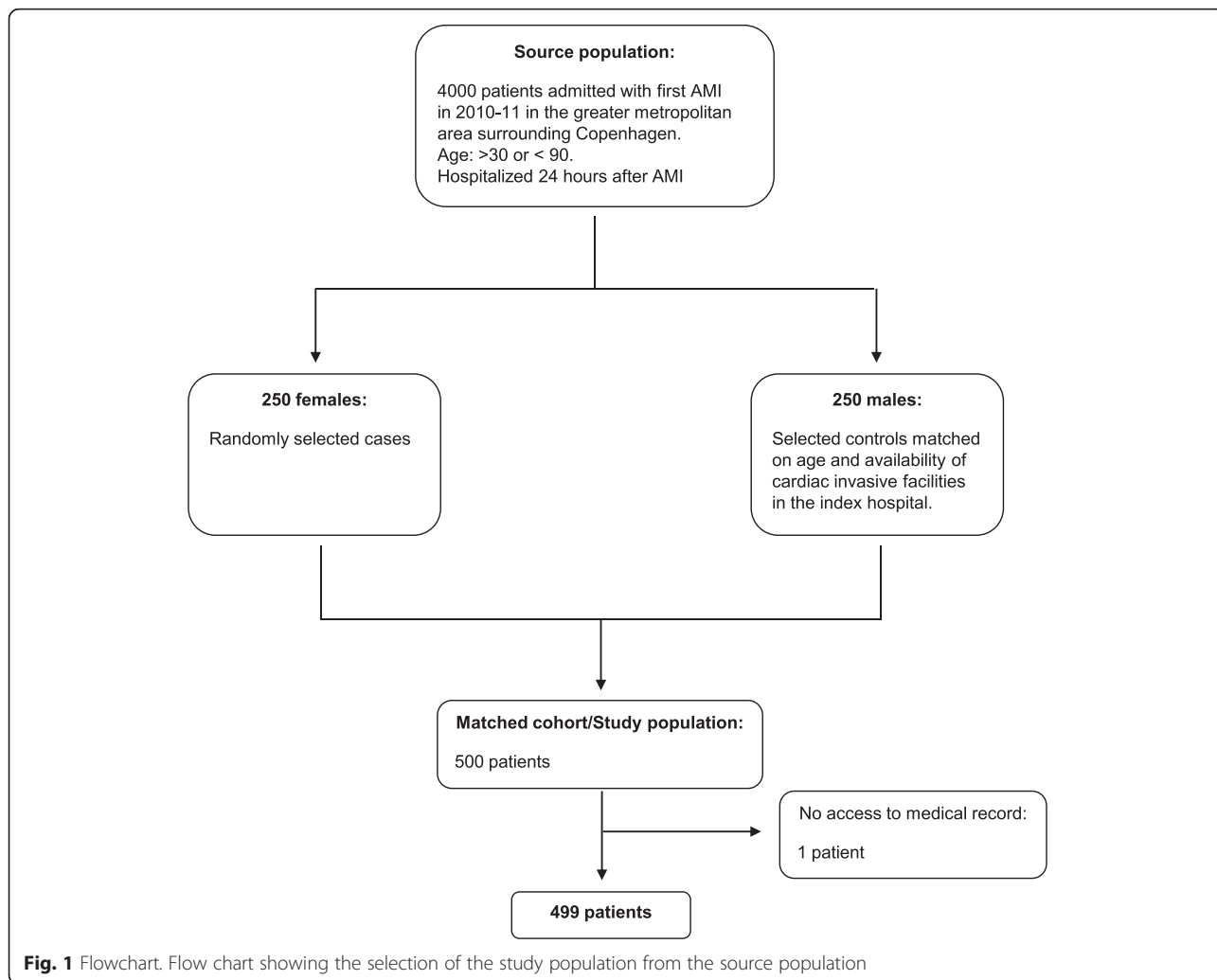
Ischemic heart disease (IHD) constitutes the leading cause of years of life lost worldwide and is one of the leading causes of death in both women and men [1]. Despite recommendations for similar treatment of women and men presenting with acute myocardial infarction (AMI) by the European Society of Cardiology and the Danish Society of Cardiology [2, 3], differences in invasive management of women and men have been widely reported [4–7]. The majority of studies have compared men and women with AMI at different ages prohibiting an appropriate comparison of baseline characteristics and comorbidities. Moreover, it has not been properly investigated whether clinical justifications for opting out an invasive strategy in patients presenting with AMI differ between women and men. The objective of this study was to characterize an age-matched cohort of women and men hospitalized with AMI, and to investigate reasons for

opting out an invasive treatment strategy in a real-world setting.

Methods

Design overview

This study was designed as a matched cohort study. Using all patients hospitalized between 1 January 2010 and 2 November 2011 with a first AMI in the Greater metropolitan area surrounding Copenhagen ($n = 4000$) as our source population, we randomly selected 250 female cases and matched them in a 1:1 ratio with 250 male controls based on age and availability of cardiac invasive facilities in the index hospital. This matched cohort of 500 patients constituted our *study population* (Fig. 1) for which we conducted a systematic, retrospective collection of patient data from medical records. Patients were followed for 60 days. We identified predictors of receiving a cardiac catheterization during follow-up, frequencies of relative contraindications



for coronary angiography, and documented reasons for opting out an invasive treatment strategy.

Settings

The greater metropolitan area surrounding Copenhagen included 10 hospitals with medical admission wards plus two high-volume hospitals with invasive heart centers performing diagnostic coronary angiography (DCA), percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG). The hospital catchment areas covered the greater northern capital area and a smaller remote island (Bornholm); a total of 1.68 million inhabitants in 2010 [8]. Pre-hospital triage ensured direct transport of patients presenting with ST-segment elevation myocardial infarction (STEMI) to treatment with primary PCI at an invasive heart center. Non-ST-segment elevation myocardial infarction (NSTEMI) patients were in general initially treated at the nearest hospital and subsequently referred to an invasive heart center for further invasive assessment. The guidelines for treatment of AMI issued by the Danish society of Cardiology follow those of European Society of Cardiology [9] and explicitly state that, unless contraindicated, all patients with AMI irrespective of sex should be offered a DCA.

Patients

We identified a source population of patients hospitalized with a first AMI from 1 January 2010 to 2 November 2011 from the Danish National Patient Register, which contains information on all hospital admissions in Denmark since 1978 [10]. The International Classification of Diseases (ICD) 10th revision codes for AMI (I21-I21.9) in the Danish National Patient Register have previously been validated showing a positive predictive value of 93.5 % [11]. We linked data on dates of index admission, index hospital, and cardiac procedures to information on dates of death from the Danish Register of Causes of Death and demographics from the Danish Civil Registration System using the unique personal civil registration number provided to all Danish citizens at birth or immigration. Further restrictions to the source population were applied; Patients discharged on the day of admission were excluded, as they were unlikely to have experienced an actual myocardial infarction. Similarly, death on the day of admission rendered patients ineligible for invasive treatment and thus were excluded. Finally, we excluded patients younger than 30 years, since AMI in this age group are rarely related to atherosclerosis, and patients older than 90 years, due to frailty in this elderly group [12–14].

From the source population a random draw of 250 female cases matched with 250 male controls of similar

age and similar access to invasive cardiac treatment at index hospital constituted the study population. The matching procedure was performed using the *MatchIt* package [15] of statistical software R, version 3.1.0 [16].

Data collection

Patient-level clinical data was collected from electronic medical records. The collection process was standardized using pretested extraction sheets (Additional file 1: Extraction sheet) in order to ensure consistent and comparable data. Each extraction sheet was divided into seven main topics: 1) index admission, 2) risk factors, 3) comorbidities, 4) electrocardiographic (ECG) findings, 5) clinical presentation, 6) in-hospital medications, and 7) blood test results. Only information available to the treating physicians prior to any cardiac catheterization was collected; in patients who did not receive a DCA all information from the hospital stay was collected. Data was entered in an electronic database and compiled with register-based data using the personal civil registration number as described above. Data collection, analysis and interpretation were performed by one specially trained individual (LHB) to ensure consistency and reproducibility. Upon completing the initial data collection process, the process was repeated for the initial 80 medical records and compared the obtained data in order to address potential intra-observer variability.

Contextual variables

For each patient not receiving a coronary angiography we noted the clinical justification, as stated in the medical record by the treating physician, word-for-word and categorized them into 11 arbitrarily defined groups: DCA already performed, death before DCA, DCA declined by patient, DCA not possible to perform or not indicated, comorbidities/bad habitual conditions, lack of symptoms, type 2 MI, high age, DCA not mentioned in the medical record, no AMI, and other. The diagnosis of type 2 MI was assigned when one of two conditions was met: (1) the treating physician documented the qualifying AMI event as a type 2 myocardial infarction directly in the medical records, or (2) the reasons stated by the treating physician for opting out a DCA were consistent with criteria listed in the international definition of type 2 MI [17]. The definitions of relative contraindications for cardiac catheterization were based on guidelines developed by the Danish Society of Cardiology [18]. Uncontrolled hypertension, fever or active infection, malignant or terminal disease, risk of bleeding, ongoing bleeding, moderate to severe heart failure, previous allergy to contrast, digoxin intoxication, and electrolyte disturbances were all considered as individual relative contraindications for DCA. We used data collected from electronic medical

records for quantifying the distribution of these relative contraindications in the study population. We defined *uncontrolled hypertension* as an elevated systolic blood pressure (SBP) > [180 mmHg] or diastolic blood pressure (DBP) > [110 mmHg]. *Fever or active infection* was defined as a white blood cell count (WBC) above 8.8×10^9 /liter or temperature more than 38 degrees Celsius. *Malignant or terminal disease* was defined as severe anemia with hemoglobin below 6 mM or renal failure with serum-creatinine above 250 mM. *Risk of bleeding* was defined as a platelet count below 145 μ M or an International Normalized Ratio (INR) above 1.2, and *moderate to severe heart failure* as a history of heart failure, or clinical findings of neck vein distension, dependent edema, or pulmonary edema. *Electrolyte disturbances* were defined as potassium levels above 4.6 or below 3.5 mM.

All collected ECG findings and blood test results were those available to the treating physician as upon hospitalization; but always prior to the time of cardiac catheterization in patients receiving a DCA. The only exception was the second measurement of troponins ("troponin II") and the highest troponin value measured during hospitalization ("peak troponin") which was sometimes only available subsequent to a coronary angiography. As different troponin assays were used across hospitals we standardized all troponin-levels against the upper reference limit to enable comparisons.

Statistical methods

We present discrete data as counts and percentages, and continuous data as median and interquartile range (IQR). Categorical data were compared using a Chi-squared test or, if the expected number of observations in a group were less than five, using Fisher's exact test. Continuous data were analyzed using the non-parametric Mann-Whitney *U*-test. In order to identify predictors of DCA we constructed uni- and multivariable logistic regression models with receipt of coronary angiography within 60 days as the dependent variable and patient characteristics as independent variables. The multivariable logistic regression model was built using a backwards stepwise procedure using a *p*-value of 0.10 as cutoff for inclusion. The final model was tested for collinearity and interactions. Time-to-event analyses of all-cause death and receipt of DCA were conducted using proportional hazards Cox regressions. The assumption of proportional hazards was assessed with log-log curves and by testing the Schoenfeld residuals for time-dependency. Assumptions were found valid. All statistical tests had a two-sided significance level of 0.05. The analyses were conducted using Stata Statistics/Data analysis, MP 14.0 StataCorp, Texas, USA.

Results

The matching procedure successfully balanced the 250 women and 250 men on age and type of index hospital (Additional file 2: Table S1). The study population contained more elderly patients than the source population as expected from the use of female cases. Complete medical records were available for 499 patients (Fig. 1). Table 1 shows baseline characteristics of the study population. A higher proportion of women had heart failure and a family history of cardiovascular diseases (CVD) compared to men. In contrast, more men than women had known ischemic heart disease (IHD), prior PCI, and prior CABG. Numerically, men were more likely to have chest pain than women, whereas more women presented with atypical symptoms such as nausea and vomiting. The only significant difference in ECG patterns was a higher proportion of ST-depressions among men compared to women, although a tendency toward a higher rate of left bundle branch block (LBBB) among women was apparent. Women presented with higher systolic blood pressure, and heart rate but lower serum-creatinine levels than men. Coronary angiography was performed in 385 patients (77.2 %) within 60 days of index hospitalization; 198 men and 187 women. Thus, the cumulative incidence of DCA at 60 days was higher for men than women (79.2 % vs. 75.1 %, HR 0.82 [0.67-1.00], *p* = 0.047). There was no significant difference in all-cause mortality at 60 days between women and men (9.6 % vs. 10.4 %, HR 0.91 [0.52-1.59], *p* = 0.74), even when separated into age-quartiles (Additional file 3: Table S2).

In terms of relative contraindications for DCA women were more likely to have electrolyte-disturbances than men (Table 2). Compared to men, there was a trend towards more cases of uncontrolled hypertension among women, as well as a higher proportion of women with at least one relative contraindication. Among the two most common relative contraindications, uncontrolled hypertension, and risk of bleeding, no sex-related differences were found. The presence of relative contraindications did not preclude the use of DCA.

Table 3 displays univariable predictors of DCA at 60 days. Admission to a hospital with invasive cardiac facilities, known family history of CVD, hypertension, hypercholesterolemia, smoking, and chest pain were all associated with a higher use of DCA. On the other hand, previous CABG, valvular heart disease, atrial fibrillation, COPD, renal failure, stroke, dyspnea, and abdominal pain were associated with less use of DCA. After multivariable analysis arterial hypertension, hypercholesterolemia, smoking, known IHD, chest pain, and ST-elevation persisted as significant positive predictors of DCA. Age, prior CABG, COPD, renal failure, stroke, and Q-wave were negative predictors

Table 1 Baseline characteristics and clinical presentations

| | Study Cohort <i>n</i> = 499 | Women <i>n</i> = 249 | Men <i>n</i> = 250 | <i>p</i> -value <i>n</i> = 499 |
|---|--------------------------------|-------------------------|-----------------------|-----------------------------------|
| Number | | | | |
| Age median(IQR) | | 74 (62-81) | 74 (62-81) | 0.96 |
| Admission to invasive heart center | | 89 (35.6) | 92 (36.8) | 0.78 |
| Risk factors | | | | |
| Family history of CVD | | 80 (32.1) | 61 (24.4) | 0.06 |
| Arterial hypertension | | 122 (49.0) | 119 (47.6) | 0.76 |
| Diabetes mellitus | | 36 (14.5) | 39 (15.6) | 0.72 |
| Hypercholesterolemia | | 80 (32.1) | 85 (34.0) | 0.7 |
| Smoking | | 69 (27.7) | 82 (32.8) | 0.08 |
| Prior PCI | | 6 (2.4) | 16 (6.4) | 0.047 |
| Prior CABG | | 6 (2.4) | 21 (8.4) | 0.005 |
| Previous MI | | 9 (3.6) | 9 (3.6) | 0.99 |
| Co-morbidities | | | | |
| Heart-related | | | | |
| Known IHD | | 20 (8.0) | 46 (18.4) | 0.001 |
| Heart failure | | 35 (14.1) | 19 (7.6) | 0.020 |
| Valvular heart disease | | 26 (10.4) | 19 (7.6) | 0.27 |
| Atrial fibrillation | | 39 (15.7) | 40 (16.0) | 0.92 |
| Other | | | | |
| COPD | | 23 (9.2) | 27 (10.8) | 0.56 |
| PAOD | | 14 (5.6) | 20 (8.0) | 0.29 |
| Renal failure | | 11 (4.4) | 9 (3.6) | 0.66 |
| Neoplasia | | 4 (1.6) | 12 (4.8) | 0.07 |
| Liver failure | | 0 (0.0) | 1 (0.4) | 1.00 |
| Stroke | | 25 (10.0) | 31 (12.4) | 0.40 |
| Symptoms | | | | |
| Chest pain | | 189 (75.9) | 203 (81.2) | 0.15 |
| Dyspnea | | 96 (38.6) | 81 (32.4) | 0.15 |
| Neck pain | | 25 (10.0) | 21 (8.4) | 0.53 |
| Diaphoresis | | 30 (12.1) | 36 (14.4) | 0.44 |
| Nausea/vomiting | | 47 (18.9) | 31 (12.4) | 0.046 |
| Fatigue | | 7 (2.8) | 8 (3.2) | 0.8 |
| Abdominal pain | | 14 (5.6) | 8 (3.2) | 0.19 |
| Back pain | | 27 (10.8) | 21 (8.4) | 0.36 |
| Cardiac arrest | | 15 (6.0) | 14 (5.6) | 0.84 |
| Other competing acute conditions at admission? ^a | | 42 (16.9) | 34 (13.6) | 0.31 |
| ECG | | | | |
| ST-elevations | | 104 (41.8) | 107 (42.8) | 0.82 |
| ST-depressions | | 59 (23.7) | 86 (34.4) | 0.008 |
| LBBB | | 24 (9.6) | 16 (6.4) | 0.18 |
| Q-wave | | 37 (14.9) | 38 (15.2) | 0.92 |
| Systolic blood pressure ^e | | 140 (126-160) | 137 (119.5-155) | 0.013 |
| Heart rate ^e | | 88 (70-105) | 81 (66-97) | 0.008 |

Table 1 Baseline characteristics and clinical presentations (Continued)

| | | | |
|------------------------------------|-----------------|-----------------|--------|
| Troponin level I ^{b,c,e} | 3.2 (1.4-9.2) | 2.5 (1.0-8.4) | 0.25 |
| Troponin level II ^{b,d,e} | 4.5 (2.1-12.5) | 6.1 (2.0-35) | 0.14 |
| Peak troponin level ^{b,e} | 12.4 (4.7-44.3) | 20.3 (4.1-73.6) | 0.23 |
| Creatinine level ^e | 70 (59-86.5) | 87 (74-100) | <0.001 |

Numbers are counts (%) unless otherwise stated. Numbers of missing values varied from 45 (Systolic blood pressure) to 269 (troponin concentration II).

IQR interquartile range, CVD cardiovascular disease, PCI percutaneous coronary intervention, CABG coronary artery bypass graft surgery, AMI acute myocardial infarction, IHD Ischemic heart disease, COPD chronic obstructive pulmonary disease, PAOD peripheral arterial occlusive Disease, LBBB left bundle branch block, INR International normalized ratio. ^aCompeting acute conditions include infections, dementia, ileus etc. ^bStandardized against upper limit. ^cThe first troponin value measured before CAG, ^dthe second troponin value measured before CAG. ^emedian (IQR)

of DCA (Table 4). In total 114 patients (22.9 %) did not receive a DCA; 52 men and 62 women. Clinical justifications for opting out an invasive treatment strategy, as stated by the treating physician, are summarized in Fig. 2. Most frequent reasons were multiple comorbidities or poor habitual condition (19.3 %), patients who declined invasive examination (16.7 %), or DCA not deemed feasible or indicated (16.7 %). Notably, in 21 (18.4 %) of the cases no reason at all for opting out a coronary angiography was documented in the medical record by the treating physician. There were no significant sex-related differences in any of the 11 groups, but a trend towards more cases of type 2 MI in women compared to men (14.5 % vs. 3.8 %, $p = 0.06$).

Discussion

Key findings

This study used detailed clinical information from 500 medical records of patients hospitalized with a first AMI to investigate the clinical basis for referring men

and women to DCA. Classical risk factors, symptoms and clinical findings predicted the receipt of DCA in this matched cohort. Women had an 18 % lower risk for receipt of DCA at 60 days than men, but a similar risk for all-cause mortality despite accounting for differences in age and type of index hospital. Surprisingly, no clinical justification for refraining from an invasive treatment strategy was documented in almost one fifth of the records of patients who did not receive a DCA.

Interpretations

The matched design of our study was intended to address two issues. First, it has been suggested that differences in patient characteristics, treatments and outcomes can largely be attributed to the differences in age between women and men presenting with ischemic heart disease [6]. Second, the use of cardiac catheterization is strongly associated with hospital-availability of this procedure [19]. By matching on age and hospital, these confounding effects were managed prior to our analyses. Despite the somewhat limited power of our analyses, we identified significant differences in patient characteristics between women and men of similar age; i.e. heart failure was more prevalent in women while more men presented with known IHD and prior revascularizations. Based on these findings a sex-related difference in the etiology of AMI seems more plausible than age in explaining previously observed differences in characteristics between women and men [20].

Our logistic and Cox proportional hazards regression analyses yielded differing results in terms of the association between sex and receipt of DCA. The reason for this lies in the poorer power of the logistic regression which only incorporates counts, as compared to the Cox regression modeling time-to-event data. We relied on the results of the latter, as the logistic regression attributes equal weights to early and late procedures and thus does not address the timing of DCAs, which we deemed of clinical relevance. Thus, despite women having a lower risk for DCA at 60 days than men, we were unable to demonstrate any significant differences in the most common

Table 2 Relative contraindications as defined by national guidelines

| | Female | Male | <i>p</i> -value |
|---|------------|------------|-----------------|
| Uncontrolled hypertension | 29 (13.1) | 18 (8.0) | 0.08 |
| Fever or active infection | 0 (0.0) | 1 (1.47) | 0.5 |
| Malignant or terminal disease | 11 (5.5) | 4 (2.2) | 0.12 |
| Risk of bleeding | 23 (14.7) | 26 (17.3) | 0.54 |
| Ongoing bleeding | 5 (2.0) | 9 (3.6) | 0.42 |
| Moderate/severe heart failure | 8 (3.2) | 5 (2.0) | 0.6 |
| Previous allergy to contrast | 0(0.0) | 0(0.0) | NA |
| Digoxin intoxication | 0 (0.0) | 0 (0.0) | NA |
| Electrolyte-disturbances (4.6 mM < potassium level < 3.5 mM) | 49 (24.6) | 29 (15.8) | 0.031 |
| At least one of the above mentioned relative contraindication (excluding heart failure) | 130 (52.0) | 120 (48.0) | 0.060 |

Numbers are counts (%) unless otherwise stated

We used clinical data to quantify the distribution of relative contraindications for men and women. The contraindications were not necessarily listed directly by the physicians in the medical records

Table 3 Univariable predictors of receipt of DCA at 60 days

| | OR | 95 % CI | p-value |
|--|-----------|------------|---------|
| Female | 0.79 | 0.52-1.20 | 0.28 |
| Age | | | |
| < 60 years | Reference | | |
| 60-69 years | 1.26 | 0.33-4.84 | 0.73 |
| 70-79 years | 0.26 | 0.1-0.72 | <0.001 |
| ≥ 80 years | 0.04 | 0.02-0.10 | <0.001 |
| Admission to a hospital with invasive cardiac facilities | 4.23 | 2.43-7.36 | <0.001 |
| Risk factors | | | |
| Family history of CVD | 6.99 | 3.31-14.79 | <0.001 |
| Arterial hypertension | 1.67 | 1.09-2.55 | 0.019 |
| Diabetes mellitus | 0.72 | 0.42-1.26 | 0.25 |
| Hypercholesteroleamia | 4.21 | 2.36-7.52 | <0.001 |
| Smoking | 1.91 | 1.45-2.52 | <0.001 |
| Prior PCI | 3.07 | 0.71-13.33 | 0.14 |
| Prior CABG | 0.41 | 0.18-0.90 | 0.027 |
| Previous AMI | 1.5 | 0.43-5.28 | 0.53 |
| Co-morbidities | | | |
| Heart-related | | | |
| Known IHD | 1.12 | 0.59-2.10 | 0.73 |
| Heart failure | 0.67 | 0.36-1.25 | 0.21 |
| Valvular heart disease | 0.40 | 0.21-0.76 | 0.005 |
| Atrial Fibrillation | 0.36 | 0.21-0.60 | <0.001 |
| Other | | | |
| COPD | 0.33 | 0.18-0.60 | <0.001 |
| PAOD | 0.81 | 0.37-1.79 | 0.60 |
| Renal failure | 0.11 | 0.04-0.30 | <0.001 |
| Neoplasia | 0.88 | 0.28-2.80 | 0.84 |
| Liver failure | - | - | - |
| Stroke | 0.19 | 0.10-0.33 | <0.001 |
| Symptoms | | | |
| Chest pain | 5.64 | 3.53-9.00 | <0.001 |
| Dyspnea | 0.47 | 0.31-0.72 | 0.001 |
| Neck pain | 0.94 | 0.46-1.91 | 0.86 |
| Diaphoresis | 1.01 | 0.54-1.87 | 0.98 |
| Nausea/vomiting | 0.71 | 0.41-1.23 | 0.22 |
| Fatigue | 0.81 | 0.25-2.59 | 0.72 |
| Abdominal pain | 0.19 | 0.08-0.45 | <0.001 |
| Back pain | 1.54 | 0.70-3.38 | 0.29 |
| Cardiac arrest | 0.76 | 0.33-1.78 | 0.53 |
| ECG | | | |
| ST-elevations | 5.36 | 3.12-9.21 | <0.001 |
| ST-depressions | 0.69 | 0.44-1.08 | 0.108 |
| LBBB | 0.52 | 0.26-1.03 | 0.06 |
| Q-wave | 0.62 | 0.36-1.06 | 0.08 |

Table 3 Univariable predictors of receipt of DCA at 60 days (Continued)

| Other | | | |
|----------------|------|-----------|--------|
| Systolic BP | 1.01 | 1.00-1.02 | 0.024 |
| Diastolic BP | 1.02 | 1.01-1.04 | 0.002 |
| HR | 0.99 | 0.98-1.00 | 0.010 |
| Troponine 1 | 0.99 | 0.99-1.00 | 0.028 |
| Troponine 2 | 1.00 | 1.00-1.00 | 0.34 |
| Peak troponine | 1.00 | 1.00-1.00 | 0.59 |
| Creatinine | 0.98 | 0.97-0.99 | <0.001 |

CVD cardiovascular disease, PCI percutaneous coronary intervention, CABG coronary artery bypass graft surgery, AMI acute myocardial infarction, IHD Ischemic heart disease, COPD Chronic obstructive pulmonary disease, PAOD Peripheral Arterial Occlusive Disease, LBBB left bundle branch block, ECG Electrocardiogram

relative contraindications. Interestingly, non of the defined relative contraindications were listed by the treating physician as reasons for not performing DCA in any patients. Of note, no patients with contrast allergy or pregnancy were found in our cohort; as these contraindications may be considered more severe. Classical risk factors such as family history of CVD, hypercholesterolemia, and smoking; symptoms of chest pain, and clinical findings of ST-segment elevations were significant predictors of an invasive strategy in our cohort. However, women were more likely than men to present with atypical symptoms of nausea and vomiting. Similar findings have been made in other studies [21, 22] and suggest that

increased vigilance is required when examining women in the emergency setting. Use of computed coronary tomography might be an option, as some trials suggest this method is effective for identification of patients in need of an invasive strategy [23].

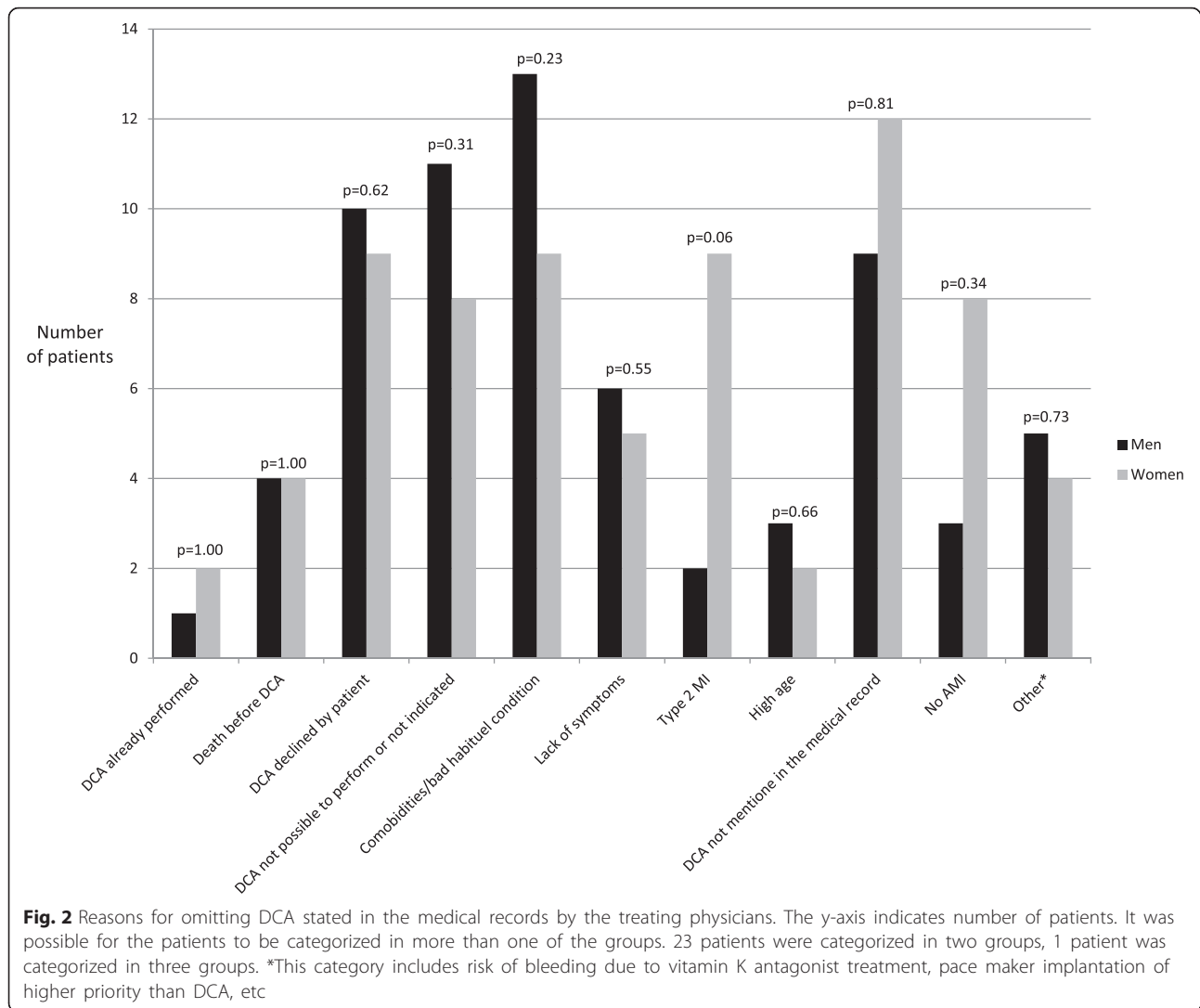
By reviewing medical records containing the treating physicians' reflections and rationale for opting out an invasive treatment strategy in some patients, we got a unique insight into the actual treating process of patients with AMI. Noticeably, we found a trend towards more cases of type 2 MI in women and a potential confounding effect on the sex-DCA relationship. This is in accordance with the findings of Saaby et al. who showed a higher prevalence of type 2 MI in women compared to men, and less cardiac catheterizations in type 2 MI [24]. It is possible that type 2 MI plays a larger role in the sex-related differences in treatment of AMI, than previously known.

Prior studies have proposed several hypotheses as to why sex-related differences in the management of AMI exist. It has been discussed if women were more likely to refuse DCA than men. Golden et al. showed that fewer women preferred DCA in the emergency room and in-hospital [25]. Heidenreich et al. found that elderly women were more likely to refuse DCA than men, but the rate of refusals was low (5.1 %) [26]. In another study, Mumma et al. found that female patients were less likely to receive a cardiac catheterization recommended by the physician, yet this could not explain the gender gap [27]. In our study 17 % of those who were not invasively investigated had refused DCA, without any sex-related differences. Physicians' reasons for not adopting an invasive strategy in women compared to men has previously been investigated [28], but no study examining this issue based on medical records in a real life setting is known by us. Although evidence and guidelines supports that all patients with AMI should undergo DCA, perhaps with the exception of low risk biomarker positive women [29], cases where lack of evidence drives to omitting DCA in patients with AMI exist. According to Poon et al.

Table 4 Multivariable predictors of receipt of DCA at 60 days

| | OR | 95 % CI | p-value |
|-----------------------|------|------------|---------|
| Age | 0.90 | 0.87-0.94 | <0.001 |
| Admission to center | 2.8 | 1.27-6.21 | 0.011 |
| Family history of CVD | 2.35 | 0.92-5.97 | 0.072 |
| Arterial hypertension | 2.38 | 1.23-4.62 | 0.010 |
| Hypercholesterolemia | 3.00 | 1.38-6.48 | 0.005 |
| Smoking | 2.03 | 1.39-2.97 | <0.001 |
| Prior CABG | 0.25 | 0.06-0.98 | 0.047 |
| Co-morbidities | | | |
| Heart-related | | | |
| Known IHD | 3.85 | 1.27-11.63 | 0.017 |
| Other | | | |
| COPD | 0.37 | 0.15-0.87 | 0.023 |
| Renal failure | 0.20 | 0.05-0.83 | 0.027 |
| Stroke | 0.31 | 0.13-0.70 | 0.005 |
| Symptoms | | | |
| Chest pain | 2.99 | 1.58-5.67 | 0.001 |
| ECG | | | |
| ST-elevations | 4.44 | 2.05-9.60 | 0.000 |
| Q-wave | 0.35 | 0.15-0.78 | 0.011 |

CABG coronary artery bypass graft surgery, COPD Chronic obstructive pulmonary disease, CVD cardiovascular disease, ECG Electrocardiogram, IHD Ischemic heart disease



significantly more women than men were not referred for DCA because the physician found that it was not supported by evidence [28]. In our study the decision not to refer to a coronary angiography was justified in more than 80 % of the cases, but in the remainder of patients an assessment of indications for cardiac catheterization was not provided. Interestingly, women were more prevalent in this subset of patients. This finding emphasizes the importance of considering and documenting clinical decisions; especially when deviating from guideline-recommended treatments.

Strengths and limitations

Our study included detailed data from medical records representing the actual information available to the treating physicians. This provided unique insights

to the clinical decision underlying referral to cardiac catheterization in a real world-setting.

Our study has some important limitations. First, this was an observational study prohibiting any conclusion regarding causality. Second, given the retrospective data collection process some degree of misclassification cannot be ruled out. Hence, contradictory or inconsistent descriptions in the medical records may have resulted in misinterpretation or missing. We addressed this issue by checking reproducibility through standardized extraction sheets, a specially trained data collector and extensive rereading of the first 80 patients medical records. Third, we did not have information on the level of training or specialization of the treating physicians; particularly the physician who decided whether or not the patient should receive an invasive treatment strategy. Finally, the sample size

was small and the study thus underpowered to detect significant differences in the subset analyses of clinical justifications. However, logistic and practical constraints made it impossible to include more than 500 patients.

Conclusion

In this contemporary matched cohort of patients hospitalized with a first AMI we found that patient characteristics differed between women and men despite similar age. Although women had a lower risk for DCA at 60 days than men, we were unable to detect any differences in the distribution of relative contraindications for coronary angiography between the sexes. In patients not referred for DCA, physicians did not document any reasons for opting out this procedure in one fifth of patients. Thus, physicians should focus on managing both women and men in accordance with current guidelines and only refrain from using DCA when evidence-driven. Finally, type 2 MI poses a potential confounder for the sex-DCA relationship and merits further investigations.

Ethics approval and consent to participate

This project was carried out in accordance with current rules of ethics and legislature. It was approved by The Danish Data Protection Agency [record number 2007-58-0015] and the Danish Health and Medicines Authority [record number 3-3013-376/1/]. The approval from the Danish Health and Medicines Authority provided statutory authority for collecting patient information from all 500 medical records without obtaining written informed consent. All personal information was anonymized upon database closure using a positive integer ranging from 1 to 500 as unique patient identifiers and stored on a secure encrypted hard drive. The conversion key was kept on a separate encrypted hard drive. Register-based studies do not require approval from an Ethics Committee in Denmark.

Additional files

Additional file 1: Extraction sheet. (PDF 86 kb)

Additional file 2: Table S1. (PDF 96 kb)

Additional file 3: Table S2. (PDF 330 kb)

Abbreviations

AMI: acute myocardial infarction; CABG: coronary artery bypass graft; CVD: cardiovascular disease; DBP: diastolic blood pressure; DCA: diagnostic coronary angiography; ECG: electrocardiogram; HR: hazard ratio; ICD: the international classification of diseases; IHD: ischemic heart disease; INR: international ratio; IQR: interquartile range; LBBB: left bundle branch block; NSTEMI: non ST-elevation myocardial infarction; PCI: percutaneous intervention; SBP: systolic blood pressure; STEMI: ST-elevation myocardial infarction; WBC: white blood cell count.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

LBH, KWH, RS, MM, JKM, JSJ and SG participated in study design. LBH, KWH and SG obtained funding. LBH performed data analysis and wrote the report. All authors interpreted the results, revised the report, and approved the final version. The corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgement

The authors wish to thank the hospitals in the Greater metropolitan area surrounding Copenhagen for cooperating in the collection of data.

Financial and equipment support

The project was financed by Department of Cardiology, University Hospital Gentofte, Denmark.

Author details

¹Department of Cardiology, University Hospital Gentofte, Kildegårdsvej 28, 2900 Hellerup, Denmark. ²Department of Cardiology, University Hospital Bispebjerg, Copenhagen, Denmark. ³Department of Public Health, University of Copenhagen, Copenhagen, Denmark. ⁴Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark. ⁵Emergency Department, Holbaek Hospital, University of Copenhagen, Holbaek, Denmark.

Received: 6 February 2016 Accepted: 15 April 2016

Published online: 01 June 2016

References

- Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2095–128.
- Authors/Task Force Members, Hamm CW, Bassand J-P, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D, ESC Committee for Practice Guidelines, Bax JJ, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2999–3054.
- Authors/Task Force Members, Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D, ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *Eur Heart J*. 2012;33:2569–619.
- Vaccarino V, Rathore SS, Wenger NK, Frederick PD, Abramson JL, Barron HV, Manhapra A, Mallik S, Krumholz HM, National Registry of Myocardial Infarction Investigators. Sex and racial differences in the management of acute myocardial infarction, 1994 through 2002. *N Engl J Med*. 2005;353:671–82.
- Nguyen JT, Berger AK, Duval S, Luepker RV. Gender disparity in cardiac procedures and medication use for acute myocardial infarction. *Am Heart J*. 2008;155:862–8.
- Hvelplund A, Galatius S, Madsen M, Rasmussen JN, Rasmussen S, Madsen JK, Sand NPR, Tilsted H-H, Thyssen P, Sindby E, Højbjerg S, Abildstrøm SZ. Women with acute coronary syndrome are less invasively examined and subsequently less treated than men. *Eur Heart J*. 2010;31:684–90.

7. Hansen KW, Soerensen R, Madsen M, Madsen JK, Jensen JS, Kappelgaard LM von, Mortensen PE, Galatius S. Developments in the invasive diagnostic–therapeutic cascade of women and men with acute coronary syndromes from 2005 to 2011: a nationwide cohort study. *BMJ Open*. 2015;5:e007785.
8. Statistikbanken. <http://www.statistikbanken.dk/statbank5a/default.asp?w=1366>. Accessed 20 Jan 2016.
9. Guidelines of the Danish society of Cardiology. <http://nbv.cardio.dk>. Accessed 20 Jan 2016.
10. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register: A valuable source of data for modern health sciences. *Dan Med Bull*. 1999;46:263–8.
11. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol*. 2003;56:124–30.
12. Bach RG, Cannon CP, Weintraub WS, DiBattiste PM, Demopoulos LA, Anderson HV, DeLucca PT, Mahoney EM, Murphy SA, Braunwald E. The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. *Ann Intern Med*. 2004;141:186–95.
13. Rosengren A, Wallentin L, Simoons M, Gitt AK, Behar S, Battler A, Hasdai D. Age, clinical presentation, and outcome of acute coronary syndromes in the Euroheart acute coronary syndrome survey. *Eur Heart J*. 2006;27:789–95.
14. Malkin CJ, Prakash R, Chew DP. The impact of increased age on outcome from a strategy of early invasive management and revascularisation in patients with acute coronary syndromes: retrospective analysis study from the ACACIA registry. *BMJ Open*. 2012;2:e000540.
15. Matchit: Nonparametric Preprocessing for Parametric Causal Inference. <http://gking.harvard.edu/matchit>. Accessed 20 Jan 2016.
16. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2014.
17. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol*. 2012;60:1581–98.
18. Rasmussen K, Abildgaard U, Dalsgaard D, Kastrup J, Markenvard J, Pedersen KE, Svendsen TL, Thuesen L. KAG, Hjerterkateterisation Og PCI Hos Voksne. Retningslinier Udarbejdet Af En Arbejdsgruppe Nedsat Af Dansk Cardiologisk Selskab. Dansk Cardiologisk Selskab; 2002. http://www.cardio.dk/docman/cat_view/48-rapporter/49-kliniske-rapporter?limit=5&order=name&dir=DESC&start=10. Accessed 21 Apr 2016.
19. Ko DT, Wang Y, Alter DA, Curtis JP, Rathore SS, Stukel TA, Masoudi FA, Ross JS, Foody JM, Krumholz HM. Regional variation in cardiac catheterization appropriateness and baseline risk after acute myocardial infarction. *J Am Coll Cardiol*. 2008;51:716–23.
20. Shaw LJ, Bugiardini R, Merz CNB. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol*. 2009;54:1561–75.
21. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, Fitzgerald G, Jackson EA, Eagle KA, Global Registry of Acute Coronary Events investigators. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. *Heart Br Card Soc*. 2009;95:20–6.
22. Čulić V, Eterović D, Mirić D, Silić N. Symptom presentation of acute myocardial infarction: Influence of sex, age, and risk factors. *Am Heart J*. 2002;144:1012–7.
23. D'Ascenzo F, Cerrato E, Biondi-Zoccai G, Omedè P, Sciuto F, Presutti DG, et al. Coronary computed tomographic angiography for detection of coronary artery disease in patients presenting to the emergency department with chest pain: a meta-analysis of randomized clinical trials. *Eur Heart J Cardiovasc Imaging*. 2013;14:782–9.
24. Saaby L, Poulsen TS, Hosbond S, Larsen TB, Pyndt Diederichsen AC, Hallas J, Thygesen K, Mickleth H. Classification of myocardial infarction: frequency and features of type 2 myocardial infarction. *Am J Med*. 2013;126:789–97.
25. Golden KE, Chang AM, Hollander JE. Sex preferences in cardiovascular testing: the contribution of the patient-physician discussion. *Acad Emerg Med Off J Soc Acad Emerg Med*. 2013;20:680–8.
26. Heidenreich PA, Shlipak MG, Geppert J, McClellan M. Racial and sex differences in refusal of coronary angiography. *Am J Med*. 2002;113:200–7.
27. Mumma BE, Baumann BM, Diercks DB, Takakuwa KM, Campbell CF, Shofer FS, Chang AM, Jones MK, Hollander JE. Sex bias in cardiovascular testing: the contribution of patient preference. *Ann Emerg Med*. 2011;57:551–560.e4.
28. Poon S, Goodman SG, Yan RT, Bugiardini R, Bierman AS, Eagle KA, Johnston N, Huynh T, Grondin FR, Schenck-Gustafsson K, Yan AT. Bridging the gender gap: Insights from a contemporary analysis of sex-related differences in the treatment and outcomes of patients with acute coronary syndromes. *Am Heart J*. 2012;163:66–73.
29. O'Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, de Winter RJ, Fox KAA, Lagerqvist B, McCullough PA, Murphy SA, Spacek R, Swahn E, Wallentin L, Windhausen F, Sabatine MS. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *JAMA*. 2008;300:71–80.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at
www.biomedcentral.com/submit

