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ORIGINAL PAPER

Gender-based prognostic value of pharmacological cardiac magnetic resonance stress testing: head-to-head comparison of adenosine perfusion and dobutamine wall motion imaging

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Abstract This study evaluated the gender related long-term prognostic value of adenosine perfusion and dobutamine wall motion imaging as assessed during a combined single-session stress cardiac magnetic resonance (CMR) examination. In 717 patients a combined CMR stress examination was performed. Inducible perfusion deficits and wall motion abnormalities were identified visually. Clinical parameters were assessed at the time of the CMR examination. All patients were contacted to determine the occurrence of hard cardiac events (cardiac death, myocardial infarction) during a median follow-up period of 5.3 years. A complete combined CMR examination and follow-up data were available in 679 patients (471 men). A total of 77 hard cardiac events (63 in men) occurred during follow-up. Multivariate analysis revealed the presence of inducible perfusion deficits or wall motion abnormalities as independent predictors of hard cardiac events for both gender with an incremental value over conventional cardiovascular risk factors. In case of a negative stress test result, event-free survival was 100% in women for 4 years and >99% in men for 2 years after the CMR examination. CMR perfusion and wall motion testing are equally suited for cardiac risk stratification in men and women. Stress CMR negative women exhibited very low event rates up to 4 years following the examination, while in men annual event rates increased after the second year. Consequently, the generally proposed 2-year warranty period of non-invasive stress testing may be prolonged to a 4 year level in CMR stress testing negative women.

Keywords Cardiac magnetic resonance imaging · Gender-based prognostic value · Adenosine · CMR perfusion imaging · Dobutamine · Wall motion analysis

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Introduction

Pharmacological stress cardiac imaging has been extensively investigated and widely employed for ischemia detection and prognostication of patients with known or suspected coronary artery disease (CAD). However, the diagnostic value and predictive power of stress tests differ according to sex, which still represents a clinical pitfall subsequently leading to gender-related differences in the delivery of care [1, 2]. In women clinical evaluation of CAD has

traditionally been more challenging mainly as a result of the lower disease prevalence in combination with the inherently variable performance of different imaging modalities and stress test protocols. The diagnostic quality of stress nuclear scintigraphy has been reported to suffer from gender-related technical difficulties including breast tissue attenuation artifacts and the generally smaller left-ventricular chamber size of women [3, 4]. Dobutamine stress echocardiography yielded an inferior diagnostic accuracy in women when compared to men especially with regard to sensitivity, though the existence of gender-related differences of dobutamine stress echocardiography remains controversial [5, 6]. Cardiac magnetic resonance (CMR) imaging has been demonstrated to overcome such limitations: both, adenosine perfusion and dobutamine wall motion imaging showed similar diagnostic results in men and women [7, 8]. In general, the gender-independent high diagnostic accuracy of CMR stress testing may translate into better prognostication of cardiovascular events resulting in improved risk assessment especially of the so called "difficult to diagnose–difficult to stratify" female patients complaining chest pain or dyspnea.

However, whether the similarly high diagnostic value of pharmacological CMR stress testing in men and women will result in a comparable prognostication of cardiac events has not been clarified. In addition, the preferable pharmacological agent for adequate risk stratification in women needs yet to be determined. For such purpose, CMR imaging offers the unique opportunity to directly compare dobutamine wall motion and vasodilator perfusion imaging during a single-session examination [9].

Thus, the present study sought to determine the long-term prognostic value of pharmacological stress CMR testing in men and women based on a head-to-head comparison of dobutamine wall motion and adenosine perfusion imaging.

Methods

Study population

The study was approved by the Charité Institutional Review Board. The study population consisted of 717 consecutive patients (500 men, 217 women) who had undergone a combined CMR stress protocol for the evaluation of chest pain or dyspnea between 2001 and 2008. Some of the patients were reported previously in a mixed gender study based on a short-term follow-up [10]. Written informed consent was obtained from all patients prior to the CMR examination. Patients with suspected or known coronary artery disease with or without prior percutaneous or surgical revascularization were included. Patients were not considered for study inclusion if they had typical contraindications for CMR imaging or the administration of dobutamine and adenosine. All patients were instructed to refrain from cigarette smoking, tea or coffee intake as well as beta-blockers and antianginal medication for at least 24 h prior to the CMR examination.

CMR imaging

Cardiac magnetic resonance imaging was performed using a 1.5 Tesla MR scanner (Philips Intera CV, Best, The Netherlands) equipped with a Power-Trak6000 gradient system (23 mT/m; 219-μs rise time) and software package releases 9 and 10. A Vector-ECG was used for cardiac synchronization. As previously described, the combined single-session CMR examination consisted of adenosine perfusion (MRP) and high-dose dobutamine/atropine stress wall motion (DSMR) imaging [9]. First, standard cine sequences were acquired at rest (apical, mid and basal short axis views; 4-, 2- and 3-chamber views) using steady-state free-precession sequences with retrospective gating (repetition time, 2.7 ms; echo time, 1.4 ms; flip angle, 60°; >30 phases/cardiac cycle; spatial resolution, $1.8 \times 1.8 \times 8.0$ mm). Second, adenosine infusion was started (dosage, 140 μg/kg/min; maximal infusion duration, 6 min) and after at least 4 min first-pass vasodilatory perfusion imaging was performed (identical three short axis geometries) during the intravenous administration of a gadolinium-DTPA or -BOPTA bolus (dosage, 0.05 mmol/kg; infusion rate, 4 ml/s) using a turbo field echo-echo-planar imaging sequence (repetition time, 9.3 ms; echo time, 3.3 ms; flip angle, 30°) or a steady-state free precession sequence with one saturation prepulse per slice before data readout (repetition time, 2.8 ms; echo time, 1.4 ms; flip angle, 50°; prepulse delay, 100 ms; spatial resolution, $2.4 \times 2.4 \times 8.0$ mm). After a 10- to 15-min waiting period allowing for equilibration of the contrast agent

within the myocardium the identical perfusion sequence was repeated at rest. Third, dobutamine infusion was started and all standard cine views were repeated at each stress level (up to 40 μg/kg/min dobutamine; plus up to 2 mg atropine if necessary) until age-predicted target heart rate calculated as [220-age] * 0.85 was reached. Termination criteria were as previously published [9].

Dobutamine wall motion analysis

Cine images were viewed with the use of a software program (ViewForum Release 5.1, Philips Medical Systems, Best, The Netherlands) designed for display of dobutamine stress CMR images in a synchronized quadscreen format. Regional wall motion at rest and during each stress level was scored on a four-point scale as normal, hypokinetic, akinetic, or dyskinetic based on the standard 17-segment model [11]. An ischemic response was defined as new or worsening wall motion abnormalities during stress indicated by an increase of regional wall motion score $\geq$1 in $\geq$1 myocardial segment(s). A biphasic response was considered an ischemic response; if akinetic segments at rest became dyskinetic during stress this was not considered indicative of an ischemic reaction. Resting left-ventricular ejection fraction (LVEF) was determined by the use of a combined triplane model [12].

Adenosine perfusion analysis

For visual grading of perfusion deficits, perfusion scans during adenosine induced vasodilatation and at rest were magnified twofold and displayed simultaneously. Perfusion scans were analyzed per myocardial segment according to the standard 16-segment model (segment 17, the apex, was not visualized) [11]. On adenosine perfusion scans, myocardial segments showing a subendocardially arising hypoenhancement of $\geq$25% transmurality persisting for >3 consecutive dynamics were classified as ischemic (=inducible perfusion deficit). In case a regional hypoenhancement was noted on adenosine and rest perfusion images this was not considered an inducible perfusion deficit.

Follow-up

Patient's historical information, clinical risk factors and medical treatment were recorded at the time of CMR stress testing. Outcome was determined based on a standardized questionnaire from patients' interviews at the outpatient clinic, hospital chart reviews, and telephone interviews with the patient, a close relative or the referring physician. The date of last contact was recorded. All events were confirmed by contact with the general practitioner or the treating hospital. In addition, survival information was obtained from the Department of National Registration. Hard cardiac events were defined as cardiac death and non-fatal myocardial infarction. Cardiac death was defined as death related to acute coronary syndromes, significant arrhythmia, refractory congestive heart failure or sudden unexpected death; non-fatal myocardial infarction was defined by angina and concomitant development of new ECG changes ($\geq$1 mm ST-segment elevation in 2 contiguous electrocardiographic leads) or a significant increase in cardiac-specific enzymes. Other cardiac events (termed any event) included hard cardiac events and coronary arterial revascularization procedures (percutaneous or surgical). In case of simultaneous cardiac events, the worst event was used for follow-up analysis (cardiac death > myocardial infarction > revascularization).

Statistical analysis

All data analysis was performed using SPSS for Windows 17.0.0 (2008, Chicago, IL, USA). Continuous variables were expressed as mean and standard deviation; categorical variables were expressed as proportions. The unpaired Student's *t* test or repeated measures ANOVA was used to assess statistical significance of continuous variables. Group differences for categorical variables were tested with the χ^2—or Fisher's exact test. Univariate and multivariate Cox proportional Hazard regression models were used to identify independent predictors of cardiac events during follow-up. Univariate risk factors were selected based upon previous association with cardiovascular events. A significance level of 0.05 was required for a variable to be included into the multivariate model, whereas 0.1 was the cutoff value for exclusion. The increased or decreased risk of future cardiac events due to the presence or absence of a given variable was expressed by a hazard ratio (HR) with a corresponding 95% confidence interval (95% CI). In order to investigate the prognostic value

of CMR stress imaging incremental to clinical data, a stepwise modeling procedure was performed for comparison of the global χ^2-value. The probability of survival was calculated using the Kaplan–Meier method and survival curves were compared using the log-rank test. A P value <0.05 was considered statistically significant.

Results

Study population

The combined CMR stress examination was successfully completed in 696 out of 717 patients (97.1%; 487 men, 209 women). Reasons for a premature termination of the CMR examination were atrial fibrillation ($n = 7$), ventricular ectopy ($n = 8$), symptomatic hypotension ($n = 5$) and the occurrence of an AV-block ($n = 1$). Hence, the overall success rate of CMR stress testing in men and women was 98.8 and 97.7% for dobutamine ($P = 0.322$), and 98.2 and 96.8% for adenosine perfusion testing ($P = 0.272$), respectively.

Seventeen patients (2.4%; 16 men, 1 woman) were lost to follow-up. Consequently, the final study population consisted of 679 patients (471 men, 208 women).

Patient characteristics

Clinical characteristics by gender are shown in Table 1. Men showed a higher body mass index and a higher prevalence of general cardiovascular risk factors (i.e. hyperlipoproteinemia, smoking). In addition, men more often had a history of coronary artery disease including a higher proportion of prior myocardial infarctions and revascularization procedures.

For both gender, patients with hard cardiac events were of advanced age and had more frequently a history of CAD or prior myocardial infarction. A higher proportion of an impaired ejection fraction $<40\%$ was seen in women sustaining hard cardiac events while in men hard cardiac events more often occurred in diabetic patients (Table 2).

During CMR testing, patients with and without hard cardiac events did not demonstrate any differences in heart rate and blood pressure at rest. During dobutamine stress, the age-predicted heart rate response was equally distributed among patients with and without events. Similarly, during adenosine induced vasodilatation no differences were found for the heart rate pressure product (Table 3). No gender-related differences with regard to hemodynamic parameters during dobutamine or adenosine testing were detected (i.e. age-predicted heart rate response and heart rate pressure product, respectively).

Table 1 Baseline characteristics of men and women

	Men ($n = 471$)	Women ($n = 208$)	P
Patient characteristics			
Age (years)	60.8 ± 9.5	61.6 ± 9.7	0.344
Range	27–82	35–86	NA
BMI (kg/m^2)	27.6 ± 3.4	26.5 ± 4.4	0.001
Range	18.5–38.6	16.4–41.0	NA
LVEF (%)	56.1 ± 8.5	58.1 ± 8.0	0.004
LVEF <40%, *n* (%)	25 (5.3)	10 (4.8)	0.853
Historical information			
Known CAD, *n* (%)	282 (59.9)	86 (41.3)	<0.001
Prior revascularization, *n* (%)	251 (53.3)	75 (36.1%)	<0.001
Prior myocardial infarction, *n* (%)	129 (27.4)	34 (16.3)	0.002
Hypertension, *n* (%)	372 (79.0)	156 (75.0)	0.271
Diabetes mellitus, *n* (%)	114 (24.2)	40 (19.2)	0.165
Hyperlipoproteinemia, *n* (%)	360 (76.4)	140 (67.3)	0.014
Cigarette smoking, *n* (%)	191 (40.6)	50 (24.0)	<0.001
Medications			
Beta-Blockers, *n* (%)	338 (71.8)	138 (66.3)	0.173
ACE inhibitors, *n* (%)	296 (62.8)	107 (51.4)	0.007
Sartans, *n* (%)	58 (12.3)	30 (14.4)	0.459
Nitrates, *n* (%)	72 (15.3)	36 (17.3)	0.497
Statins, *n* (%)	324 (68.8)	108 (51.9)	<0.001

BMI body mass index, *LVEF* left-ventricular ejection fraction, *CAD* coronary artery disease

Outcomes

During a median follow-up of 5.32 years (mean, 4.73 ± 2.13) a total of 77 hard cardiac events occurred. For the male population 63 hard cardiac events (41 cardiac deaths, 22 nonfatal myocardial

Table 2 Baseline characteristics of men and women with and without hard cardiac events

	Men			Women		
	Without events ($n = 408$)	With events ($n = 63$)	P	Without events ($n = 194$)	With events ($n = 14$)	P
Patient characteristics						
Age (years)	60.1 ± 9.5	65.4 ± 8.1	<0.001	61.2 ± 9.4	67.1 ± 12.2	0.028
Range	27–82	42–80	NA	35–86	38–81	NA
BMI (kg/m^2)	27.6 ± 3.4	27.8 ± 3.3	0.655	26.5 ± 4.4	26.7 ± 4.5	0.880
Range	18.5–37.8	21.5–38.6	NA	16.4–41.0	20.9–37.1	NA
LVEF (%)	56.6 ± 7.9	53.2 ± 11.0	0.004	58.7 ± 7.0	51.0 ± 14.8	<0.001
LVEF <40%, *n* (%)	18 (4.4)	7 (11.1)	0.062	6 (3.1)	4 (28.6)	0.002
Historical information, *n* (%)						
Known CAD	233 (57.1)	49 (77.8)	0.002	76 (39.2)	10 (71.4)	0.024
Prior revascularization	209 (51.2)	42 (66.7)	0.029	68 (35.1)	7 (50.0)	0.265
Prior myocardial infarction	103 (25.2)	26 (41.3)	0.010	27 (13.9)	7 (50.0)	0.003
Hypertension	320 (78.4)	52 (82.5)	0.511	147 (75.8)	9 (64.3)	0.346
Diabetes mellitus	89 (21.8)	25 (39.7)	0.004	35 (18.0)	5 (35.7)	0.151
Hyperlipoproteinemia	309 (75.7)	51 (81.0)	0.427	128 (66.0)	12 (85.7)	0.152
Cigarette smoking	163 (40.0)	28 (44.4)	0.495	47 (24.2)	3 (21.4)	0.813
Medications, *n* (%)						
Beta-blockers	287 (70.3)	51 (81.0)	0.098	130 (67.0)	8 (57.1)	0.559
ACE inhibitors	255 (62.5)	41 (65.1)	0.780	96 (49.5)	11 (78.6)	0.051
Sartans	49 (12.0)	9 (14.3)	0.680	28 (14.4)	2 (14.3)	0.988
Nitrates	53 (13.0)	19 (30.2)	0.001	33 (17.0)	3 (21.4)	0.714
Statins	282 (69.1)	42 (66.7)	0.770	98 (50.5)	10 (71.4)	0.169

infarctions) were registered; in addition, 173 revascularization procedures were performed (percutaneous coronary intervention in 155 and coronary artery bypass grafting in 18 men). For the female population 14 hard cardiac events (8 cardiac deaths, 6 nonfatal myocardial infarctions) were recorded and 56 revascularization procedures were performed (percutaneous coronary intervention in 48 and coronary artery bypass grafting in 8 women).

Outcome prediction

Univariate predictors of hard cardiac events in men and women are summarized in Table 4. In men, multivariate analysis revealed age (hazard ratio, 1.99; 95% CI, 1.20–3.29; $P = 0.014$), diabetes (hazard ratio, 1.77; 95% CI, 1.06–2.97; $P = 0.019$) and the presence of inducible wall motion abnormalities (hazard ratio, 2.30; 95% CI, 1.37–3.85; $P = 0.004$) or inducible perfusion deficits (hazard ratio, 3.02; 95% CI, 1.69–5.40; $P < 0.001$) as significant independent predictors of hard cardiac events. In women, the only independent predictors of hard cardiac events were an impaired left-ventricular ejection fraction <40% (hazard ratio, 6.91; 95% CI, 2.13–22.34; $P = 0.006$) and the presence of inducible wall motion abnormalities (hazard ratio, 3.12; 95% CI, 1.06–10.06; $P = 0.039$) or inducible perfusion deficits (hazard ratio, 4.08; 95% CI, 1.12–14.83; $P = 0.011$).

Stepwise Cox proportional hazards analysis demonstrated a significant increase of the global Chi-square value when adding the results of stress testing to the independent clinical variables as determined by multivariate analysis (i.e. age and diabetes in men or LVEF <40% in women; see Fig. 1). Consequently, in male and female patients both CMR stress tests—dobutamine wall motion and adenosine perfusion

Table 3 Hemodynamic parameters during dobutamine and adenosine stress testing in men and women with and without hard cardiac events

	Men			Women		
	Without events ($n = 408$)	With events ($n = 63$)	*P*	Without events ($n = 194$)	With events ($n = 14$)	*P*
Dobutamine						
Dobutamine dose, μg/kg/min	35.8 ± 6.7	35.1 ± 7.2	0.430	33.6 ± 8.0	31.1 ± 10.0	0.261
Atropine dose, mg	0.3 ± 0.4	0.3 ± 0.5	0.836	0.2 ± 0.3	0.2 ± 0.3	0.836
Baseline						
Heart rate, bpm	71 ± 12	70 ± 13	0.671	71 ± 12	76 ± 16	0.133
Systolic blood pressure, mmHg	134 ± 20	130 ± 19	0.105	132 ± 22	128 ± 22	0.469
Heart rate pressure product, bpm mmHg	9,471 ± 2,202	9,080 ± 2,265	0.192	9,475 ± 2,540	9,808 ± 2,877	0.640
Peak stress						
Heart rate, bpm	138 ± 17	133 ± 23	0.022	138 ± 14	132 ± 16	0.148
Systolic blood pressure, mmHg	151 ± 33	146 ± 36	0.209	142 ± 30	135 ± 29	0.401
Heart rate pressure product, bpm mmHg	20,927 ± 5,344	19,017 ± 4,931	0.008	19,580 ± 4,391	17,955 ± 4,813	0.185
Maximum predicted heart rate response for age, %	86.6 ± 10.5	85.9 ± 15.2	0.672	86.9 ± 8.6	86.6 ± 10.5	0.898
Adenosine						
Baseline						
Heart rate, bpm	71 ± 12	71 ± 14	0.868	72 ± 12	77 ± 12	0.113
Systolic blood pressure, mmHg	135 ± 21	132 ± 21	0.284	132 ± 22	127 ± 23	0.386
Heart rate pressure product, bpm mmHg	9,580 ± 2,411	9,328 ± 2,244	0.436	9,583 ± 2,681	9,847 ± 2,437	0.720
Peak stress						
Heart rate, bpm	88 ± 16	87 ± 14	0.450	92 ± 16	91 ± 13	0.766
Systolic blood pressure, mmHg	135 ± 23	130 ± 20	0.119	129 ± 23	124 ± 18	0.350
Heart rate pressure product, bpm mmHg	11,927 ± 3,147	11,237 ± 2,528	0.098	11,961 ± 3,035	11,248 ± 2,279	0.391

imaging—demonstrated an incremental value over conventional clinical risk factors with regard to the prediction of hard cardiac events.

Event-free survival

Kaplan–Meier analyses of hard cardiac event rates in men and women with and without inducible wall motion abnormalities or inducible perfusion deficits, respectively, are given in Fig. 2. In men and women no differences were found between DSMR and MRP imaging regarding the occurrence of hard cardiac events (Fig. 3). Comparison of event-free survival in men and women in case of a negative stress test result is illustrated in Fig. 4a. In addition, Kaplan–Meier analysis for any cardiac events revealed a significantly decreased event rate in stress test negative-women versus -men (Fig. 4b). Cumulative annual event rates of men and women with negative stress test results are supplied in Table 5.

Discussion

The present study has been conducted to determine long-term prognostic data on CMR stress testing for both routinely performed pharmacological stress protocols (i.e. adenosine perfusion and dobutamine wall motion imaging) with special emphasis on gender-related differences. In addition, the study was designed to utilize the unique capability of CMR imaging to perform combined stress test protocols:

Table 4 Univariate Predictors for Hard Cardiac Events in Men and Women

	Men			Women		
	HR	95% CI	*P*	HR	95% CI	*P*
Clinical parameters						
Age >65 years	2.02	1.23–3.31	0.006	2.85	0.95–8.55	0.061
Hypertension	1.39	0.72–2.66	0.326	0.49	0.16–1.47	0.201
Diabetes mellitus	2.16	1.31–3.59	0.003	2.44	0.81–7.23	0.111
Hyperlipoproteinemia	1.42	0.76–2.67	0.273	2.18	0.49–9.82	0.309
Cigarette smoking	1.11	0.68–1.83	0.681	0.83	0.23–2.96	0.768
Known CAD	2.25	1.24–4.08	0.008	2.38	0.73–7.71	0.150
Prior revascularization	1.63	0.96–2.75	0.069	1.20	0.42–3.49	0.733
Prior myocardial infarction	1.89	1.14–3.12	0.013	4.01	1.40–11.49	0.010
CMR imaging parameters						
LVEF <40%	3.11	1.41–6.82	0.005	8.32	2.60–26.62	<0.001
WMA at rest	1.70	1.04–2.79	0.035	6.24	2.09–18.66	0.001
Inducible WMA	2.32	1.39–3.87	0.001	3.62	1.12–11.64	0.031
Inducible perfusion deficit	3.12	1.74–5.57	<0.001	4.57	1.27–16.51	0.020

CAD coronary artery disease, *LVEF* left-ventricular ejection fraction, *WMA* wall motion abnormalities

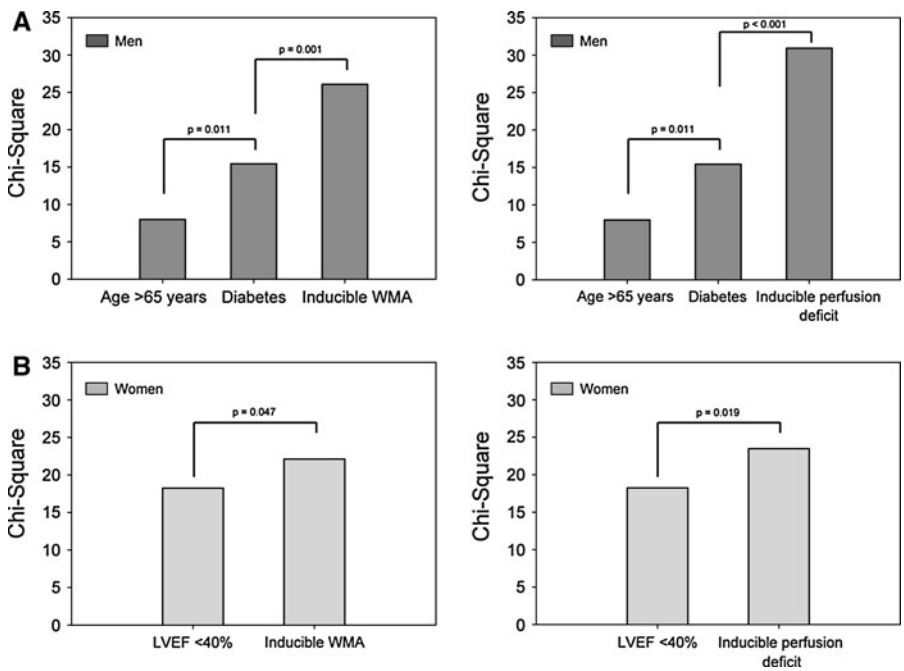

Fig. 1 Comparison of the global Chi-square values (stepwise Cox model) of all independent predictors of hard cardiac events. **a** Incremental prognostic value of inducible wall motion abnormalities (*WMA*, *left*) and inducible perfusion deficits (*right*) over clinical risk factors (age, diabetes) in men. **b** Incremental prognostic value of inducible wall motion abnormalities (*left*) and inducible perfusion deficits (*right*) over left-ventricular ejection fraction (*LVEF*) in women

during a single-session examination both, adenosine and dobutamine stress testing were applied in the same patient thereby leading to a paired assessment of the prognostication achievable with either test in a "head-to-head" comparative fashion.

The main findings of the study were: (1) in men and women, the presence of inducible wall motion abnormalities or inducible perfusion deficits forecasted a high rate of cardiovascular events, including future myocardial infarction and cardiac death, (2) the predictive power of positive stress test results was equally high for adenosine perfusion and dobutamine wall motion imaging, (3) in men and women, both stress tests exhibited an incremental prognostic value over conventionally assessed cardiovascular risk factors, (4) a negative stress test

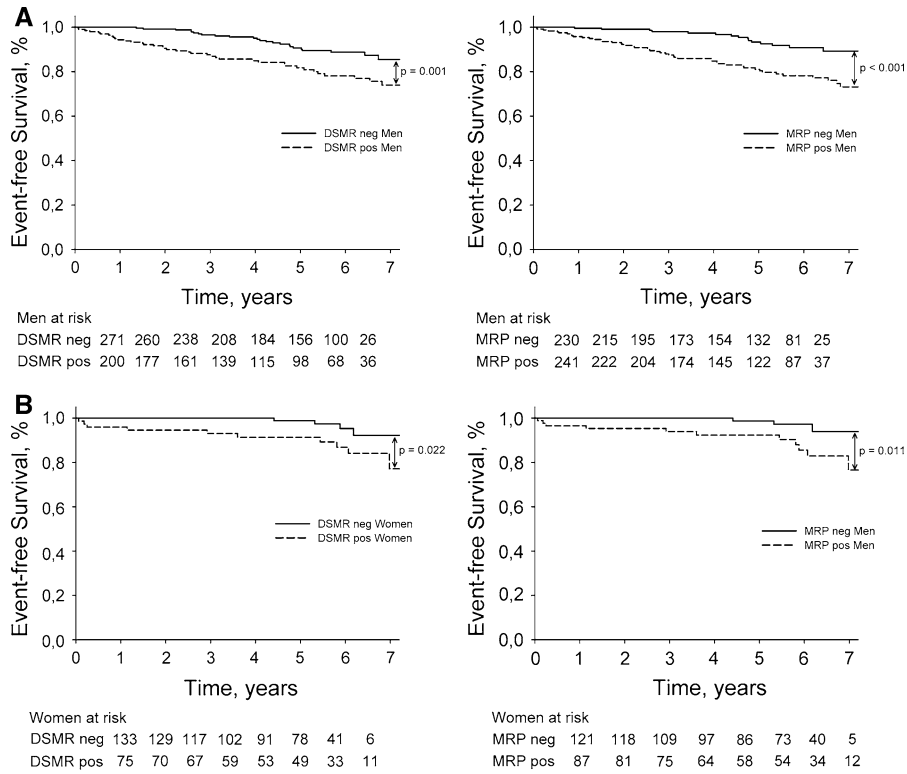

Fig. 2 Kaplan–Meier survival plots indicating the proportion of men and women free from hard cardiac events over time. **a** Event-free survival of men according to the results of dobutamine wall motion (DSMR, *left*) and adenosine perfusion imaging (MRP, *right*). **b** Event-free survival of women according to the results of dobutamine wall motion (*left*) and adenosine perfusion imaging (*right*). Differences between *curves* are statistically significant (log-rank test)

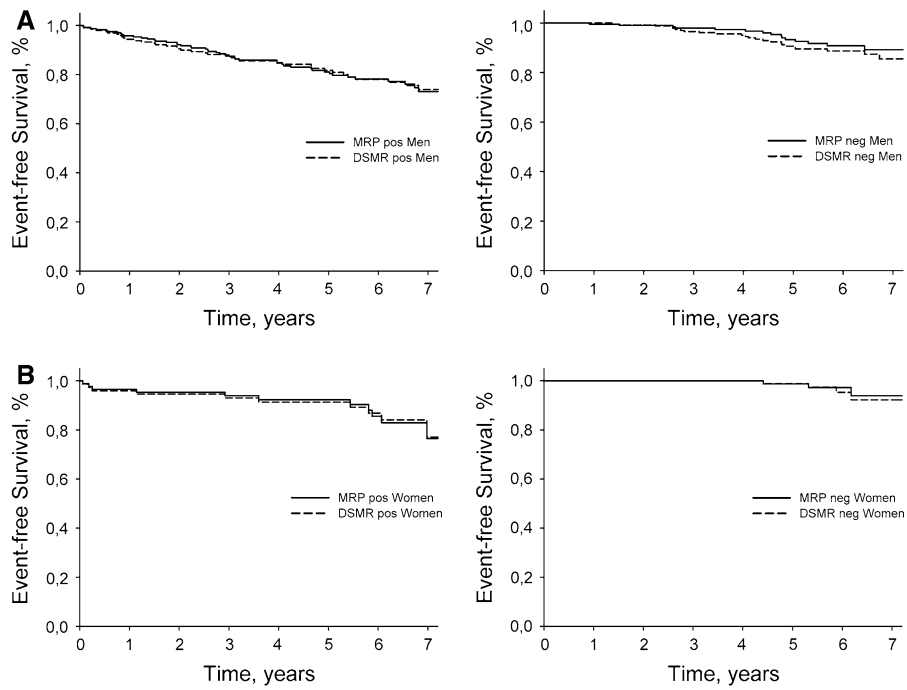

Fig. 3 Kaplan–Meier survival plots for the comparison of dobutamine wall motion (DSMR) with adenosine perfusion imaging (MRP) regarding the event-free survival of men (**a**) and women (**b**) with positive (*left*) or negative (*right*) results of CMR stress testing

result in men and women—be it perfusion or wall motion imaging—was associated with a very low cardiac event rate during the following years with (5) a warranty period of 2 years in men and a prolonged warranty period of up to 4 years in women.

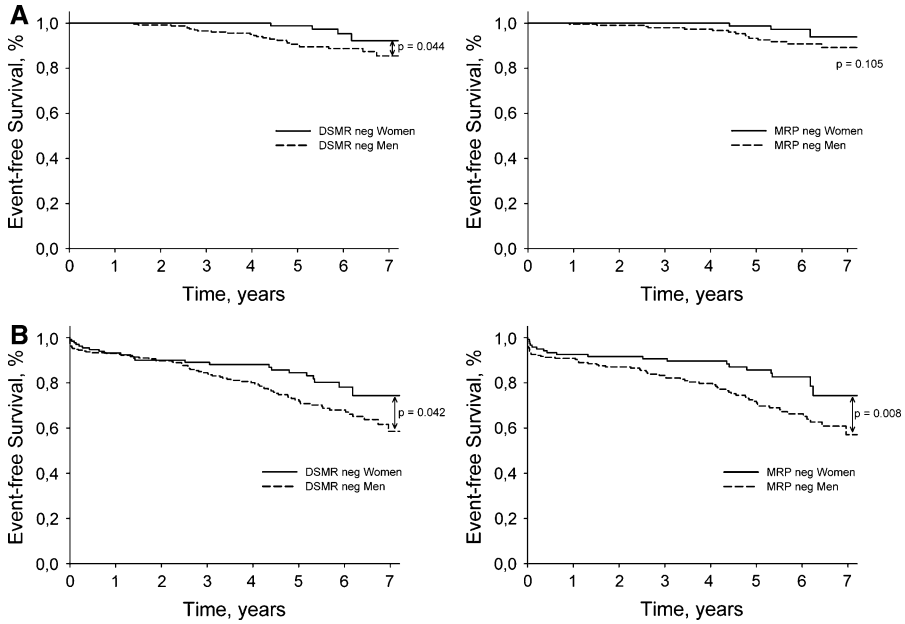

Fig. 4 Kaplan–Meier survival plots for the comparison of men and women with negative results of CMR stress testing. A: Proportion of men and women with negative CMR stress testing (dobutamine wall motion, DSMR, *left*; adenosine perfusion, MRP, *right*) being free from hard cardiac events (cardiac death, myocardial infarction). **b** Proportion of men and women with negative CMR stress testing (dobutamine wall motion, DSMR, *left*; adenosine perfusion, MRP, *right*) being free from any cardiac events (cardiac death, myocardial infarction, revascularization). Statistical differences between *curves* were tested by log-rank test

Table 5 Cumulative annual event rates in men and women in case of negative CMR stress test results

	Cumulative event rates during follow-up intervals (%)						
	1 year	2 years	3 years	4 years	5 years	6 years	7 years
Hard cardiac events							
DSMR negative men	0.0	0.8	3.4	4.9	9.3	11.4	14.1
MRP negative men	0.4	0.9	2.0	2.6	6.6	9.2	10.9
DSMR negative women	0.0	0.0	0.0	0.0	1.2	4.4	8.4
MRP negative women	0.0	0.0	0.0	0.0	1.3	3.0	7.2
Any cardiac events							
DSMR negative men	1.6	5.0	10.6	15.2	23.1	28.2	36.9
MRP negative men	1.5	5.6	9.7	13.6	22.1	28.5	37.7
DSMR negative women	3.2	6.5	7.5	8.6	12.3	19.3	23.9
MRP negative women	2.6	3.6	4.6	5.8	9.8	13.6	23.5

DSMR indicates dobutamine stress CMR wall motion imaging; MRP, adenosine CMR perfusion imaging

The diagnosis of CAD in women has been recognized to be challenging for a number of reasons. Knowingly, the diagnostic results of exercise electrocardiography may be equivocal in women due to gender-specific limitations including pre-existing resting ST-T-wave changes, lower ECG voltage, and hormonal factors such as endogenous oestrogen and hormone replacement therapy in postmenopausal women [13, 14]. In addition, women are diagnosed of having coronary artery disease at an advanced age and, thus, are less capable to perform adequately during exercise testing. Consequently, pharmacological stress testing is increasingly gaining importance for non-invasive detection of myocardial ischemia and cardiac prognostication in the female population presenting with chest pain or dyspnea [15].

Two different pharmacological approaches are widely employed in clinical practice using different

imaging modalities: first, myocardial perfusion assessment using nuclear or CMR imaging during coronary vasodilatation (e.g. adenosine induced coronary hyperaemia); second, wall motion analysis using echocardiography or CMR imaging during inotropic stimulation (e.g. dobutamine induced adrenergic myocyte stimulation). However, since the preferable stress test for risk stratification in women has not been determined yet, a head-to-head comparison of wall motion and perfusion imaging is of particular interest and clinically relevant. CMR imaging allows for a direct comparison of both stress test approaches during a single-session examination in the same patient thereby excluding any potential bias resulting from inherent limitations of different imaging modalities with examinations performed on different days.

In the present study, inducible myocardial ischemic reactions were the strongest independent predictors of hard cardiac events in men and women and had an incremental value over clinical parameters and cardiovascular risk factors. In case of a positive stress test result a significantly increased number of hard cardiac events occurred in men and women without any differences in the event-free survival between DSMR positive and MRP positive men or women. Thus, dobutamine wall motion and adenosine perfusion imaging were equally effective in identifying in a gender-independent manner those patients being at a high risk of cardiac events. Our results corroborate previous findings from dobutamine stress echocardiographic and nuclear perfusion studies identifying inducible myocardial ischemic reactions as strong and independent predictors of cardiac events for men and women [16–19]. Consequently, women with inducible myocardial ischemic reactions on non-invasive stress testing should be treated as aggressively as men.

Ideally, a non-invasive stress test should not only identify those patients at high risk for future cardiac events, but discriminate those with a low cardiac event rate either. The prognostic value of negative dobutamine stress echocardiographic testing in women has been established in several studies reporting an annual event rate of 1–2% for the following 3–5 years [16, 17, 20]. A first dobutamine stress CMR study examined the prognostic value in women and found in case of test negativity an annual event rate of 1.2% during the 5 years after stress testing [21]. Our results yielded equally low cardiac event rates in women with a negative dobutamine stress CMR test: during the initial 4 years following stress testing, no hard cardiac events occurred and revascularization procedures were performed in less than 9% of DSMR negative women.

With regard to myocardial perfusion imaging, nuclear techniques are well established for the prognostication of subsequent cardiac death or myocardial infarction. Pooled myocardial perfusion data of >7,500 women demonstrated an annual cardiac event rate of <1% in case of a normal nuclear scan [19]. Our findings indicate that CMR adenosine perfusion imaging offers similarly favourable results during the initial 4 years following testing: no hard cardiac events were recorded and revascularization procedures were carried out in less than 6% of MRP negative women. Importantly, no significant differences in the event-free survival of DSMR and MRP negative women were found. Thus, both pharmacological CMR approaches can be used interchangeably for the identification of women being at low risk for future cardiac events.

The current data demonstrated that for stress test negative men both CMR approaches yielded a similarly low cardiac event rate in comparison to women during the initial 2 years after the examination [10]. However, in men overall event rates including cardiac death, myocardial infarction and revascularization procedures increased earlier (i.e. during the third year after stress testing) resulting in an overall significantly higher cardiac event rate of stress test negative men compared to women. Hypothetically, the higher cardiac event rate among men with negative stress test results may be due to male-gender related differences in the progression of non-obstructive coronary artery lesions which were not severe enough to induce myocardial ischemic reactions at the time of testing. Consequently, for the male population the warranty period of non-invasive stress testing should be set at a 2 year level while prognostication for the female population can be considered valid up to 4 years following CMR stress testing.

Study limitations

At the time the present study was initiated, delayed enhancement CMR imaging did not constitute a routinely performed component of a CMR stress examination and would have prolonged the total

examination duration of a combined stress protocol with two different pharmacological agents. Consequently, delayed enhancement CMR imaging was not part of the present study protocol. Recent studies reported on the relative merit and incremental predictive value of a multicomponent CMR approach using a single pharmacological agent (mean follow-up of 2.6 ± 1.2 years) [22]. The investigators demonstrated that the presence of abnormalities in adenosine perfusion, delayed enhancement imaging, LV ejection fraction, and aortic flow each conferred incremental prognostic power for the prediction of adverse cardiovascular events, and were additive, not redundant. Most notably, the head-to-head comparison of the predictive value of delayed enhancement and adenosine perfusion imaging was found to be challenging because of collinearity of both CMR domains. Hence, additional large scale studies are needed to adequately separate and quantify the relative predictive merit of these CMR components.

Conclusion

In men and women with known or suspected coronary artery disease dobutamine wall motion and adenosine perfusion imaging demonstrated a similarly high predictive value regarding the occurrence of subsequent cardiac death or myocardial infarction. Both approaches had a significant incremental value over conventional cardiovascular risk factors for the prognostication of cardiac events. Since women with evidence of myocardial ischemic reactions exhibited equally high cardiac event rates compared to men, their treatment should be forcefully pursued either. While women without evidence of myocardial ischemia proved to have very low event rates during the 4 years after stress testing, the annual event rates in men increased earlier (i.e. 2 years after stress testing). Thus, the generally proposed 2-year warranty period of non-invasive stress testing may be prolonged to a 4 year level in CMR stress testing negative women.

Conflict of interest None.

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