Quantification of intrathoracic fat adds prognostic value in women undergoing myocardial perfusion imaging

Ahmed Haider [a,b], Mathias Possner [a], Michael Messerli [a], Susan Bengs [a,b], Elena Osto [b,c,d], Monika Maredziak [a,b], Angela Portmann [a,b], Michael Fiechter [a,b], Andreas A. Giannopoulos [a], Valerie Treyer [a], Thomas Gaisl [e], Elia von Felten [a], Dimitri Patriki [a], Dominik C. Benz [a], Tobias A. Fuchs [a], Christoph Gräni [a], Aju P. Pazhenkottil [a], Ronny R. Buechel [a], Philipp A. Kaufmann [a], Catherine Gebhard [a,b,*]

[a] *Department of Nuclear Medicine, University Hospital Zurich, Zurich, Switzerland*
[b] *Center for Molecular Cardiology, University of Zurich, Switzerland*
[c] *Laboratory of Translational Nutrition Biology, ETH, Zurich, Switzerland*
[d] *University Heart Center, Cardiology, University Hospital Zurich, Zurich, Switzerland*
[e] *Division of Pulmonology, University Hospital Zurich, Zurich, Switzerland*

A B S T R A C T

Aim: Amongst patients with coronary artery disease (CAD), women experience relatively worse outcomes as compared to men. Evidence to date has failed to explore unique female imaging targets as major determinants of cardiovascular risk. We sought to assess the prognostic value of epicardial (EFV) and intrathoracic fat volume (IFV) quantification in women and men with suspected and known CAD.
Methods and results: Intrathoracic fat volume and EFV were calculated from non-contrast CT and analyzed in a propensity-matched cohort of 190 patients (95 women, mean age 62.5 ± 11.3 years) undergoing myocardial perfusion imaging (MPI) and coronary computed tomography angiography (CCTA) for evaluation of CAD. IFV and EFV were significantly lower in women as compared to men (198.2 ± 78.4 vs 293.2 ± 114.7 cm^3 and 105.6 ± 48.9 vs 135.8 ± 60.9 cm^3, p < 0.001) and showed a strong association with coronary artery calcium score (CACS) and obstructive CAD in women (p < 0.05), but not in men. Fat volumes were not related to abnormal MPI in either population (p = NS). During a median follow-up of 2.8 years, high IFV was associated with reduced event free survival (log rank = 0.019 vs low IFV) in women, but not in men. Accordingly, a multivariate Cox regression model adjusted for cardiovascular risk factors, CACS, CCTA, and MPI findings selected IFV as a significant predictor of major adverse cardiovascular events (MACE) in women (HR 1.32, 95%CI 1.18–1.55, p = 0.001).
Conclusion: Quantification of IFV provides incremental prognostic value for MACE in women, beyond that provided by traditional risk factors and imaging findings.

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1. Introduction

An evolving knowledge regarding sex differences in prevalence, pathophysiology and symptom manifestation of coronary artery disease (CAD) has prompted calls to reconsider traditional cardiovascular risk stratification methods in women [1]. Indeed, conventional diagnostic approaches for cardiovascular risk assessment are derived from the concept that flow-limiting epicardial stenosis is the major risk determinant in ischemic heart disease (IHD) [2]. Although this concept has proven its reliability in men, it did not hold promise of dependably identifying women at risk for future cardiovascular events. Indeed, risk stratification in the latter population is particularly challenging, owing to the greater prevalence of non-obstructive CAD in women [3]. Despite a plethora of novel approaches introduced in the past decade with the aim to improve IHD risk assignment in women, recent annual population statistics consistently report higher mortality rates in women versus men [4]. State-of-the-art imaging strategies to characterize IHD in women are currently plagued by an insufficient diagnostic and prognostic accuracy, leading to unrecognized myocardial infarctions as well as undertreatment of female patients [5,6]. Thus, additional variables to improve risk-stratification in women are urgently needed.

Epicardial fat volume (EFV) has been associated with the presence of CAD and was identified as an independent predictor of future major adverse cardiac events (MACE) beyond traditional cardiovascular risk factors in the general population [7,8]. However, it is currently unknown whether quantification of intrathoracic fat volume (IFV) and EFV adds prognostic value in women. Thus, the aim of the present study was to explore the incremental prognostic value of epicardial and intrathoracic

* Corresponding author at: Department of Nuclear Medicine, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland.
E-mail address: Catherine.gebhard@usz.ch (C. Gebhard).

fat - quantified by non-contrast-enhanced computed tomography (CT) - as predictors of MACE in women and men with known or suspected CAD.

2. Methods

2.1. Study population

A total of 291 patients (33% women) who underwent clinically indicated adenosine stress/rest myocardial perfusion imaging by single-photon emission computed tomography (MPI-SPECT) protocol using ^{99m}Tc-tetrofosmin as well as a coronary computed tomography angiography (CCTA) exam, for the evaluation of known or suspected CAD were included in our retrospective analysis. The potential of cardiac hybrid imaging allowing a comprehensive evaluation of CAD through combination of both, morphological and functional information by fusing SPECT with CCTA has been demonstrated by previous reports [9]. Patients with incomplete datasets and patients who underwent early revascularization <30 days following MPI-SPECT/CCTA were excluded from our study. Patients were stratified by sex and propensity-matched models were applied to adjust for baseline differences between women and men. Following propensity matching, 190 patients (95 women) remained in the final analysis. Demographic factors and key elements of the patient's history were ascertained at the time of the study by patient interview and review of medical records. Information on follow-up was obtained by telephone interview. Patients were followed for the occurrence of major adverse cardiac events (MACE) including death, non-fatal myocardial infarction, unstable angina requiring hospitalization, and coronary artery revascularization The study conforms to the principles outlined in the Declaration of Helsinki and was evaluated and approved by the local ethics committee (KEK-ZH-Nr. 2014-0240). Informed consent was obtained from all individual participants included in the study. The study population was partly shared with an MPI-SPECT registry reported elsewhere [10].

2.2. ^{99m}Tc-tetrofosmin SPECT-myocardial perfusion imaging protocol

All patients underwent an electrocardiography (ECG)-gated 1-day stress/rest protocol (mean effective radiation dose 8.6 ± 0.9 millisievert [mSv]). MPI-SPECT acquisition was carried out using a dual-head camera (Infinia Hawkeye or Ventri, both GE Healthcare, Milwaukee, WI, USA) equipped with a low-energy, high-resolution collimator at 20% symmetric window and 140 keV; 64×64 matrix. The commercially available Cedars QGS/QPS software (Cedars-Sinai Medical Center, Los Angeles, CA, USA) was used for MPI-SPECT interpretation according to current guidelines [11]. A 20-segment model was applied where each segment was scored by consensus of two experienced readers using a 5-point scoring system: 0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction in tracer uptake and 4 = absence of detectable SPECT radioligand signal in the segment. Moreover, myocardial perfusion was considered abnormal if stress scores ≥2 were detected in two or more segments. Mismatches between stress and rest scores with either a rest score ≤1 or a stress score of 4 combined with a rest score of 2 were considered as reversible perfusion defect. For attenuation correction and coronary calcium scoring (CACS), a non-contrast CT exam was performed using a 64-slice CT scanner (LightSpeed VCT, GE Healthcare) with the following scanning parameters: 64×2.5 mm collimation, rotation time of 0.35 s, tube voltage of 120 kV and a tube current of 200 mA (mean effective radiation dose 0.6 ± 0.2 mSv). The semi-automatic software SmartScore (GE Healthcare) was used for quantification of CACS (Agatston units, AU). Segments with prior coronary artery stent implantation or bypass-vessels were not included in the CACS analysis. Quantification of IFV and EFV was performed on non-contrast CTs acquired for attenuation correction of MPI-SPECT using QFAT™ software (Cedars-Sinai Medical Center) [12]. IFV was defined as all fat volume within the thoracic cavity spatially restricted to the posterior limit of the heart as previously described [12]. EFV comprised the fat volume surrounding the myocardium with the visceral pericardium determining the outer boundary. Cranial as well as caudal boundaries were defined by the first CT slice illustrating the pulmonary trunk bifurcation and the most inferior CT slice of the pericardium, respectively. Eight to twelve control points were manually assigned to the pericardial contours in each slice. A representative non-contrast CT scan illustrating how IFV and EFV regions were defined is presented in Supplementary Fig. 1. IFV and EFV were calculated automatically and reported in cm^3 and three-dimensional fat voxels were defined based on thresholds of −190 HU and − 30 HU (identical thresholds for IFV and EFV) by an investigator experienced in cardiac CT [10]. IFV and EFV readers were blinded to patient's characteristics as well as to other imaging findings.

2.3. CCTA scanning technique and image evaluation

CCTA was performed on a 64-slice CT scanner (LightSpeed VCT and Discovery HD 750, GE Healthcare, Waukesha, WI, USA) as previously described [13]. The mean effective radiation dose of CCTA in our study cohort was 11.4 ± 6.6 mSv. All coronary artery segments were assessed for the presence and severity of coronary stenosis.

2.4. Statistical analysis

The study population was stratified by sex and propensity score matching was used to balance both groups for baseline differences. The propensity score for each patient was estimated using a multivariable logistic regression model in which sex was modelled using age, body mass index (BMI), diabetes, smoking, hypertension, dyslipidaemia, family history of CAD, prior myocardial infarction (MI), and prior revascularisation as covariates in the model. The propensity score was then used to match women and men with similar estimated propensity to two decimal places. Baseline characteristics are reported as rates with percentages for categorical variables and mean with standard deviation for continuous variables. Prior to analyses, basic assumptions were checked. Comparative analysis of variables was performed by unpaired Student's *t*-test, Mann-Whitney *U* test, analysis of variance (ANOVA), Kruskal-Wallis test or Chi-square, as appropriate. For clinical convenience, IFV and EFV were displayed as dichotomous variables. As there are no current standardized quantitative categories available for IFV and EFV, cut-off values for IFV and EFV were determined by applying Youden's J statistics (Youden's index). The Youden's index (J) is widely used in combination with receiver operating characteristics (ROC), encompassing a curve that assigns diagnostic specificities and sensitivities to measured clinical values of a single parameter. J is the maximum vertical distance between the ROC curve and diagonal line (angle bisector), thereby indicating the values with the highest diagnostic accuracy to predict outcome. For an EFV of 100 cm^3 Youden's index was 0.23 (Sensitivity 84%, Specificity 39%, area under the curve [AUC] 0.62, p = 0.014) and for an IFV of 230 cm^3 Youden's index was 0.26 (Sensitivity 79%, Specificity 47%, AUC 0.62, p = 0.02) Time to MACE was estimated using a multivariable Cox proportional hazards survival model and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. Model covariates included: IFV (continuous variable), EFV (continuous variable), cardiovascular risk factors including hypertension, diabetes mellitus, dyslipidemia, positive family history of coronary artery disease, current smoking, and obesity, age, abnormal MPI-SPECT, CACS >400 AU, and obstructive CAD. This selection was made based on the well-described association of these variates with cardiac morbidity and mortality. Cumulative event-free survival curves were compared across dichotomous categories of IFV and EFV by use of the Kaplan-Meier methodology and log-rank test. A two-tailed *p*-value of 0.05 was considered statistically significant. SPSS version 25.0 (SPSS Inc., Armonk, NY) was used for all statistical analyses.

3. Results

3.1. Study population

Following propensity score matching, a total of 190 subjects (95 [50.0%] women, mean age 62.2 ± 11.3 years, Table 1) were analyzed and followed for a median of 2.8 years (interquartile range 2.0–3.5 years). Before matching, men were more often diabetic than women (18.4% vs 7.4%, p = 0.013) and had more often undergone coronary artery bypass graft (CABG) surgery (8.7% vs 0%, p = 0.003, Table 1). IFV and EFV were significantly lower in women as compared to men (198.2 ± 78.4 vs 293.2 ± 114.7 cm^3 and 105.6 ± 48.9 vs 135.8 ± 60.9 cm^3, after propensity score matching, p < 0.001, Table 1). High CACS and obstructive CAD were detected more frequently in men as compared to women (p < 0.001, Table 1). Patient's characteristics of both, unmatched and matched cohorts, stratified by sex are depicted in Table 1.

3.2. Association between intrathoracic/epicardial fat volume and imaging findings

Intrathoracic fat volume and EFV showed a graded and positive relation with CACS in women, but not in men (p = 0.005 in women, Fig. 1A and p = 0.194 in men, Fig. 1B and p = 0.001 in women, Fig. 1C and p = 0.016 in men, Fig. 1D). Accordingly, significantly more women with high IFV (cut-off value 230 cm^3) had a CACS >400 Agatston Units (AU) as compared to women with low IFV (≤230cm^3, p = 0.01, Supplementary Table 1), while this difference was not observed in men (p = 0.49, Supplementary Table 1). Similarly, obstructive (≥50% stenosis) CAD was associated with an increased IFV in women (p = 0.002, Fig. 2A), but not in men (p = 0.14, Fig. 2B). Further, EFV was significantly higher in women with obstructive CAD as compared to women with non-obstructive CAD (Fig. 2C, p = 0.001), while this difference was absent in men (p = 0.13, Fig. 2D). Notably, no associations were found between abnormal MPI-SPECT and both, IFV (Fig. 2E and F, Supplementary Table 1) and EFV (Fig. 2G and H, Supplementary Table 1) in both sexes.

3.3. Patients characteristics according to IFV and EFV

When the study population was stratified by sex and IFV (cut-off 230 cm^3) or EFV (cut-off 100 cm^3), women with high IFV or high EFV

were significantly older (69.1 ± 9.1 vs 59.1 ± 10.8 years, p < 0.001 and 67.1 ± 9.6 vs 58.4 ± 11.2 years, respectively, p < 0.001) and had a higher BMI (29.8 ± 6.0 vs 25.5 ± 4.7, p < 0.001 and 28.9 ± 5.9 vs 25.2 ± 4.6, p = 0.001, respectively) than women with low IFV or EFV (Supplementary Table 1 and 2), while no differences in other demographic parameters were observed in women. Men with high IFV or EFV were more often obese (BMI 28.2 ± 4.1 vs 25.3 ± 4.3 kg/m^2, p = 0.017 and 28.0 ± 4.1 vs 24.9 ± 4.4 kg/m^2, p = 0.002) than men with low IFV (Supplementary Table 1 and 2), and older age was associated with increased IFV (64.0 ± 10.7 vs 58.2 ± 11.7 years, p = 0.002), but not EFV in men (Supplementary Table 1 and 2). In addition, a higher prevalence of diabetes (19.7% vs 2.9%, p = 0.023) was observed in men with high IFV as compared to men with low IFV (Supplementary Table 1).

3.4. Clinical endpoints by intrathoracic fat volume and sex

During a median follow-up of 2.8 years, 11.6% of women and 11.6% of men experienced a MACE (p = 1.0 for women vs men, Table 1). Mean IFV was significantly greater in women who experienced a MACE as compared to those without event (p = 0.04, Fig. 3A), while this difference was less pronounced for EFV (p = 0.08, Fig. 3C). No significant increase in fat volumes was observed in men with clinical events (p = NS, Fig. 3B and D). Accordingly, high IFV > 230 cm^3 was associated with an increased event rate in women (log rank = 0.019 for high vs low IFV, Fig. 3E), while no differences were found in men (log rank p = 0.16 for high vs low IFV, Fig. 3F). Conversely, high EFV was not associated with reduced event free survival, regardless of sex.

3.5. Prognostic value of intrathoracic fat volume in women and men

Univariate Cox regression analysis identified IFV (HR 1.33, 95%CI 1.1–1.72, p < 0.001, Supplementary Table 3), but not EFV (HR 1.00, 95%CI 0.99–1.01, p = 0.18, Supplementary Table 3), as a significant predictor of MACE in women, while neither IFV nor EFV were associated with future clinical events in men (IFV: HR 1.00, 95%CI 0.99–1.03, p = 0.65 and EFV: HR 1.00, 95%CI 0.99–1.01, p = 0.61, Supplementary Table 3). In addition, a stepwise Cox regression model adjusted for cardiovascular risk factors (including hypertension, diabetes mellitus, dyslipidemia, positive family history of coronary artery disease, current smoking, and obesity), age, CACS, abnormal MPI-SPECT, and severity of CAD as assessed by CCTA selected IFV (continuous variable), but not EFV (continuous variable) as an independent predictor of MACE in women (HR 1.32, 95%CI 1.18–1.55, p = 0.001), but not in men

(Supplementary Table 4). Accordingly, a first order interaction term of female sex and IFV was significant when the total cohort was analyzed (HR 1.33, 95% CI 1.10–1.62, p = 0.006).

4. Discussion

Our study is the first reporting sex differences in the prognostic value of EFV and IFV in patients undergoing MPI-SPECT, CACS and CCTA. We demonstrate that both, EFV and IFV, show strong associations with CACS and obstructive coronary stenosis in women, but not in men. Intrathoracic fat volumes, but not EFV, were significantly higher in women who experienced a MACE during follow-up as compared to women without events, while no significant increase in fat volumes was observed in men with clinical events. Accordingly, in our study, IFV provided significant complementary information for the prediction of MACE in women, even when CACS, MPI-SPECT and CCTA findings were known. Considering that non-contrast cardiac CT for attenuation correction is of importance in women undergoing MPI-SPECT as it reduces the number of false-positive exams caused by breast attenuation artifacts, our study stresses the value of examining and reporting IFV in female patients. Importantly, a recent report has demonstrated that women with larger sized and more prevalent calcium lesions, as detected by non-contrast CT, had a 2.2-fold higher cardiovascular mortality risk as compared to men [14]. Taken together with these previous data, our study emphasizes the prognostic importance of variables derived from non-contrast CT in women, as the latter may further refine risk detection and promote preventive strategies of cardiovascular care in female patients.

Despite a large number of studies investigating the association between epicardial fat quantification and atherosclerosis [15], there is currently no consensus as to whether visceral adipose tissue surrounding the heart provides incremental clinical value as an imaging biomarker of cardiovascular risk. Indeed, while some studies report that EFV is independently associated with adverse outcomes but risk models were not further improved when CACS was added, others suggest that EFV remains an independent predictor of MACE irrespective of CACS and other imaging findings [7,8]. A comparative analysis of previous data is further complicated by the lack of agreement regarding binary cut-off values for visceral fat volumes, the use of non-contrast vs contrast-enhanced CT or different software solutions for visceral fat quantification as well as a wide variety of study populations assessed. Indeed, two recent meta-analyses indicate that specific subpopulations such as patients with CACS>400, asymptomatic individuals, and patients with low-to-intermediate pre-test probability of CAD might

Table 1

Characteristics of study population by sex. Unmatched (left) and matched (right) cohort following propensity score (PS) matching. BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; IFV, intrathoracic fat volumes; EFV, epicardial fat volumes; MPI, myocardial perfusion imaging; MACE, major adverse cardiovascular events. Data are presented as mean ± SD. Two-sided p-values are indicated.

| Baseline characteristics	Unmatched cohort				PS Matched cohort			
	Total n = 291	Women n = 95	Men n = 196	p-value	Total n = 190	Women n = 95	Men n = 95	p-value
Age (years), mean ± SD	61.5 ± 11.0	62.5 ± 11.3	61.0 ± 10.8	0.29	62.2 ± 11.3	62.5 ± 11.3	61.9 ± 11.4	0.72
BMI (kg/m^2), mean ± SD	27.0 ± 4.7	27.0 ± 5.5	27.0 ± 4.3	0.99	27.0 ± 5.0	27.0 ± 5.5	27.1 ± 4.4	0.81
Hypertension, n(%)	162(55.7)	58(61.1)	104(53.1)	0.20	112(58.9)	58(61.1)	54(56.8)	0.56
Smoking, n(%)	82(28.2)	21(22.1)	61(31.1)	0.11	43(22.6)	21(22.1)	22(23.3)	0.86
Diabetes, n(%)	43(14.8)	7(7.4)	36(18.4)	0.013	20(10.5)	7(7.4)	13(13.7)	0.16
Dyslipidemia, n(%)	130(44.7)	43(45.3)	87(44.4)	0.89	81(42.6)	43(45.3)	38(40.0)	0.46
Family history of CAD, n(%)	80(27.5)	32(33.7)	48(24.5)	0.10	58(30.5)	32(33.7)	26(27.4)	0.35
Previous MI, n(%)	16(5.5)	4(4.2)	12(6.1)	0.50	10(5.3)	4(4.2)	6(6.3)	0.52
Previous PCI, n(%)	33(11.3)	10(10.5)	23(11.7)	0.76	24(12.6)	10(10.5)	14(14.7)	0.38
Previous CABG, n(%)	17(5.8)	0(0)	17(8.7)	0.003	0(0)	0(0)	0(0)	–
IFV (cm^3), mean ± SD	257.4 ± 104.5	198.2 ± 78.4	286.0 ± 103.6	<0.001	254.7 ± 108.9	198.2 ± 78.4	293.2 ± 114.7	<0.001
EFV (cm^3), mean ± SD	124.5 ± 53.7	105.6 ± 48.9	133.6 ± 53.6	<0.001	120.7 ± 57.1	105.6 ± 48.9	135.8 ± 60.9	<0.001
Abnormal MPI, n(%)	54(18.6)	11(11.6)	43(21.9)	0.033	27(14.2)	11(11.6)	16(16.8)	0.30
CACS>400 AU, n(%)	87(30.4)	12(12.6)	75(39.3)	<0.001	40(21.4)	12(12.6)	28(30.4)	0.003
Obstructive (≥50%) CAD	96(33)	18(18.9)	78(39.8)	<0.001	52(27.4)	18(18.9)	34(35.8)	0.009
MACE, n(%)	39(13.4)	11(11.6)	28(14.3)	0.53	22(11.6)	11(11.6)	11(11.6)	1.0
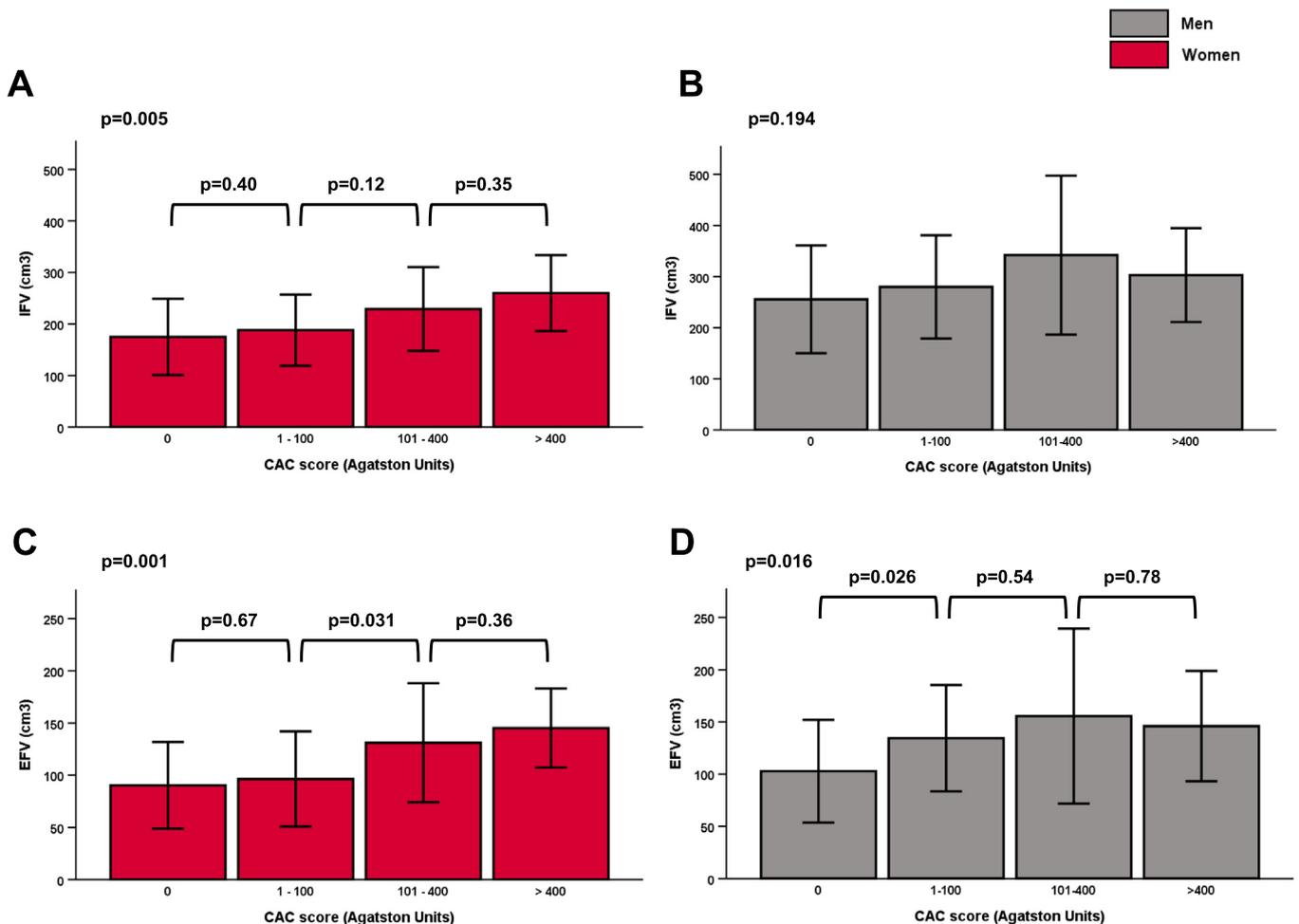
Fig. 1. Association between intrathoracic (IFV) and epicardial fat volume (EFV) and coronary artery calcium score (CACS) in women (**A and C**) and men (**B and D**).

have the largest relative merit of cardiac fat quantification as an adjunct to MPI-SPECT and CACS [15,16]. We now extend these findings by demonstrating that IFV improve risk models in a female, intermediate-risk population beyond the information provided by clinical risk factors and imaging findings. As only weak correlations were observed between fat volumes and abnormal MPI-SPECT in women in our study, our data suggest that IFV measurement may provide additive value to MPI by referring to different and complementary aspects of the disease. Notably, in contrast to many previous reports, our population is representative of a real world setting where MPI-SPECT is used in daily clinical routine to evaluate suspected or known chronic stable CAD.

To date, only few studies have addressed sex-specific aspects of visceral fat quantification and its role in the pathophysiology of CAD. Consistent with our data, de Vos and colleagues observed that epicardial adipose tissue was strongly related to vascular risk factors and coronary calcification in a population of 573 healthy postmenopausal women and Bettencourt et al. reported a significant interaction between epicardial adipose tissue volume and sex in patients without known CAD [17,18]. Further, increased epicardial fat thickness, as assessed by echocardiography, has recently been suggested as an independent predictor of pre-eclampsia in pregnant women [19]. However, Miao et al. observed a positive correlation between epicardial fat and atherosclerotic plaque eccentricity that was significant only in men, while Bos et al. found that EFV as well as coronary and carotid artery calcification volumes were associated in men, but not in women, after adjustment for cardiovascular risk factors [20,21]. Notably, none of these studies assessed the value of fat volume quantification in women with regard

to clinical endpoints, and no data exist on IFV and its relation with CAD in a female cohort. Nevertheless, it is remarkable that a positive association between epicardial fat and plaque eccentricity lost significance in women in a previous study, when models were adjusted for cardiovascular risk factors and C-reactive protein (CRP) levels [20]. The latter has been suggested to carry important prognostic information in women as women with CAD tend to have higher CRP levels than men, and only in women, but not in men, inflammatory markers were related to BMI, blood pressure levels and CACS [22–25]. As it is well documented that visceral fat is a source of pro-inflammatory and pro-atherogenic markers, thereby explaining its association with CAD and metabolic syndrome, our data support the notion that the link between inflammatory pathways, visceral fat and atherosclerotic disease might be of particular importance in females [26–28]. Indeed, the increasing obesity epidemic, the higher prevalence of metabolic syndrome amongst women, and the stronger association of these risk factors with cardiovascular disease progression in women further emphasize the need to improve strategies for effective cardiovascular risk assessment in this demographic group [29].

Irrespective of the potential causal mechanistic pathways that underlie the above mentioned associations which require further investigation, our findings also indicate that IFV might provide similar or even better risk stratification as compared to EFV. Indeed, IFV outperformed EFV in risk prediction models for MACE in women, although similar associations between both parameters and coronary calcium/plaque burden were observed. Consistent with our results, Forouzandeh et al. observed a significant association between
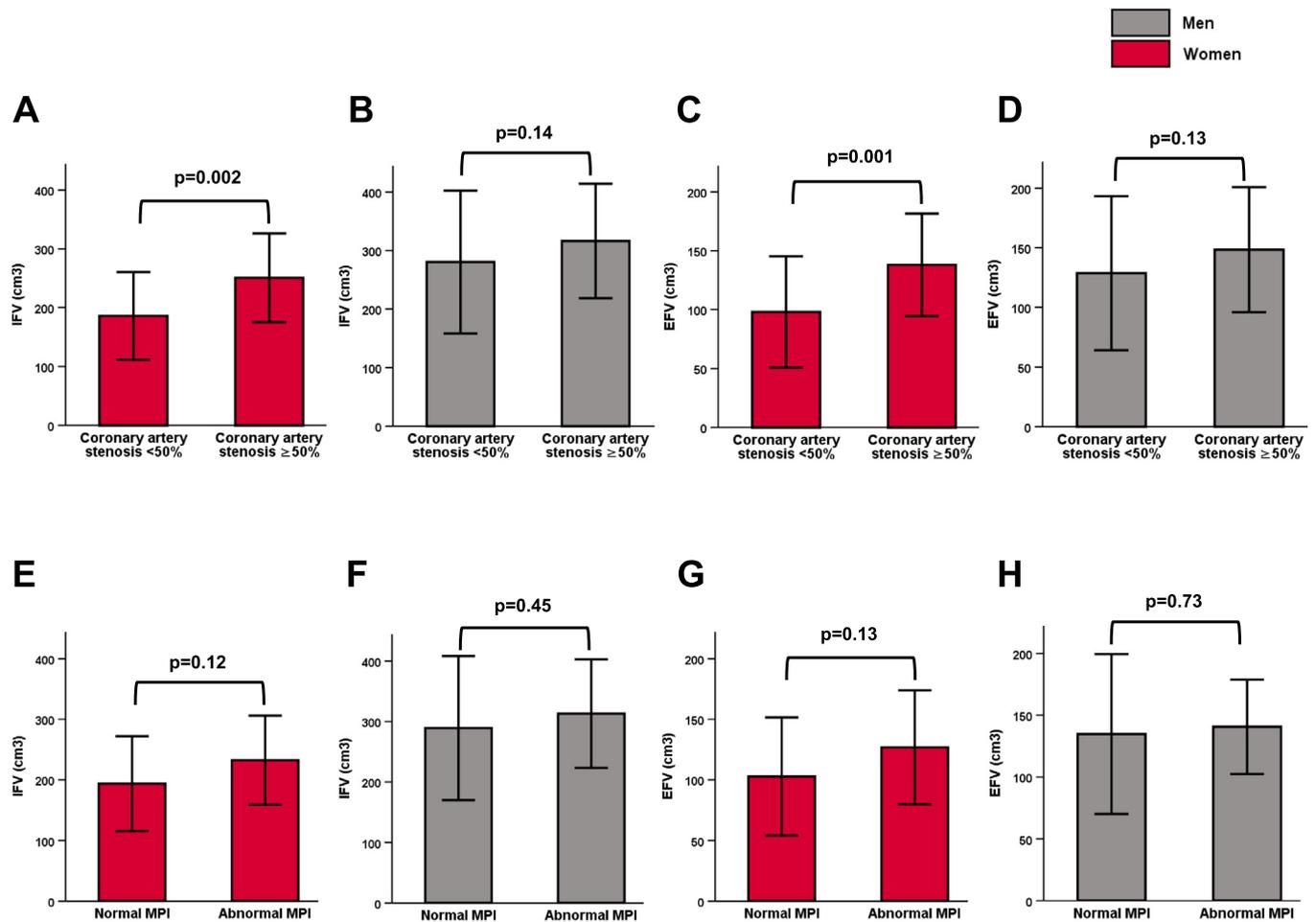
Fig. 2. Association between intrathoracic (IFV) and epicardial fat volume (EFV) and coronary computed tomography angiography (CCTA) myocardial perfusion imaging by single-photon emission computed tomography (MPI-SPECT) findings in women (**A**, **C**, **E**, **G**) and men (**B**, **D**, **F**, **H**).

MACE and both EFV and IFV [8]. In contrast, several studies have attributed EFV a more prominent role in the pathogenesis of atherosclerosis as compared to IFV due its close anatomical proximity to the epicardial coronary arteries and its common embryological origin with abdominal visceral fat [7,30,31]. Paracrine production of cytokines, leucocyte infiltration, and adiponectin secretion by epicardial adipose tissue have all been suggested to account for the stronger association observed between EFV and CAD in some studies [27,32–34]. However, as IFV comprises both, EFV and thoracic fat, the strong predictive power of IFV observed in our study indicates that quantification of IFV alone may be a sufficient marker for cardiovascular risk assessment with the advantage that acquisition of the latter is less time-consuming and more reproducible than EFV analysis [12]. Finally, as women are more prone than men to develop a restrictive myocardial phenotype, a potential 'mechanical compressor' effect of IFV might account, at least in part, for the stronger prognostic value of IFV over EFV seen in women [35,36].

There are limitations to this study that should be pointed out. First, fat volumes vary widely across different patient populations and ethnicities [15]. Thus, given that our study is a single-center retrospective analysis in mainly Caucasian patients, its generalizability is limited. Second, our study is observational and does not provide information on the underling mechanism. Third, although a comprehensive group of adjustment variables was employed, unmeasured variables not incorporated into regression models may have affected the results. Also, unmeasured variables not incorporated into the propensity-matched

models may have affected the results. Fourth, the binary cut-off values for IFV and EFV in our study were chosen based on receiver operation curve (ROC) analysis and calculation of Youden's index as currently no standardized quantitative categories for IFV and EFV are available. Future studies will have to establish optimal fat volume thresholds in women and men to provide consistency amongst studies.

In summary, the present study demonstrates that quantification of IFV derived from non-contrast-enhanced CT scans provides incremental prognostic value beyond traditional risk factors and imaging findings in women. Non-contrast cardiac CT for attenuation correction is commonly performed in combination with MPI-SPECT. In women, attenuation correction has been shown to improve the diagnostic accuracy of MPI-SPECT as breast attenuation artifacts are a major cause of false-positive results in this population. Our study demonstrates that quantification of IFV derived from non-contrast CT provides incremental prognostic value in women, but not in men, and emphasizes the value of examining and reporting IFV in female patients undergoing attenuation-correction for MPI-SPECT. Importantly, a recent report has demonstrated that women with larger sized and more numerous calcium lesions as detected by non-contrast CT had a 2.2-fold higher cardiovascular mortality risk as compared to men [14]. Taken together with these previous data, our study emphasizes the prognostic importance of variables derived from non-contrast CT as the latter may further refine risk detection in women and promote preventive strategies of cardiovascular care.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.092.
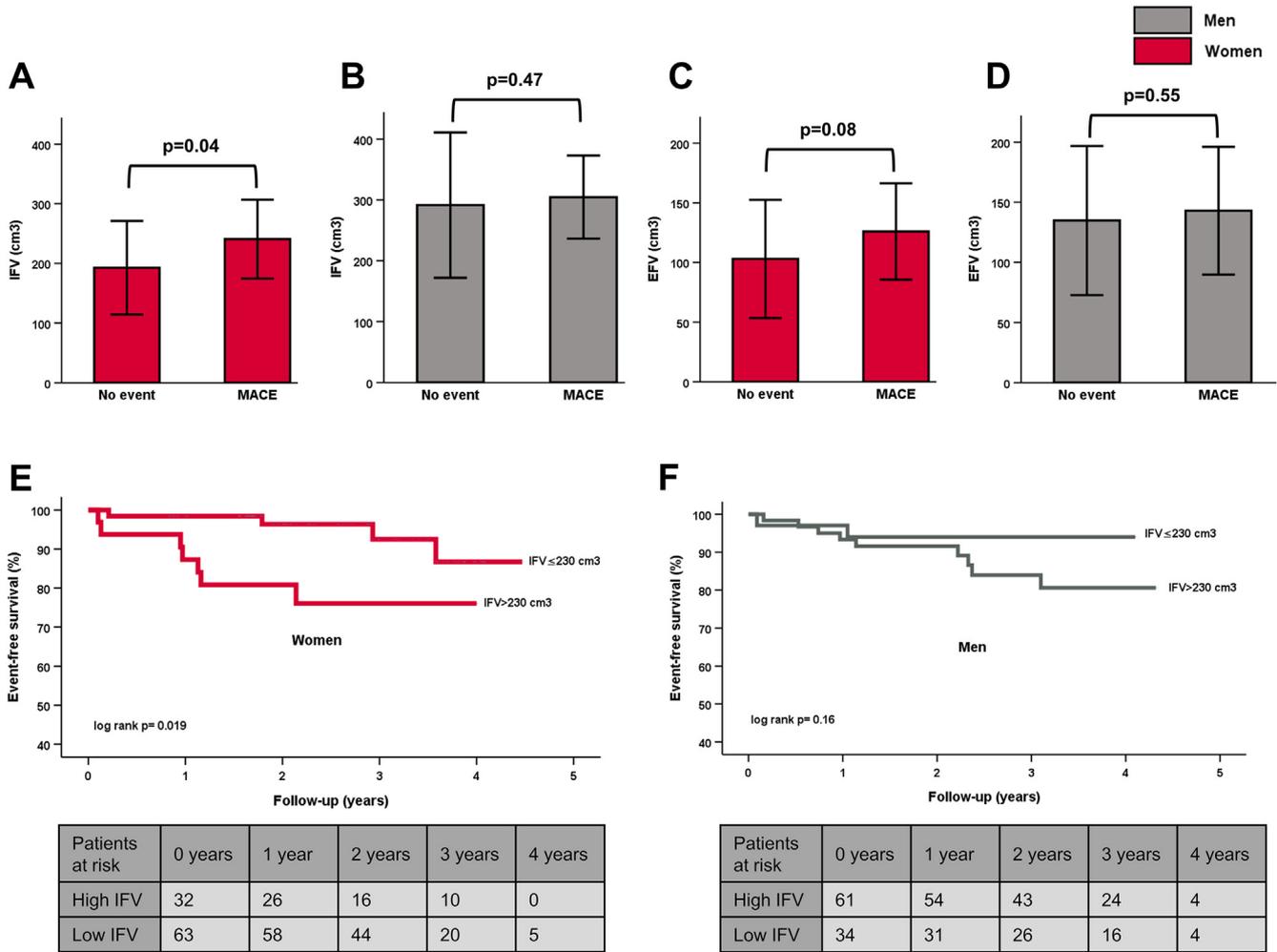
Fig. 3. Event-free survival according to epicardial and intrathoracic fat volume. **A.** Intrathoracic (IFV) and epicardial fat volume (EFV) in women (**A** and **C**) and men (**B and D**) who experienced a major adverse cardiovascular events (MACE) during follow-up. Kaplan-Meier Survival Curves (Unadjusted) for the occurrence of MACE in women (**E**) and men (**F**) with low (≤230 cm^3) versus high (>230 cm^3) IFV. Log rank p-values are indicated.

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