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Relation of Waist-Hip Ratio to Long-term Cardiovascular Events in Patients with Coronary Artery Disease

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Abstract

Aiming to assess the association between measures of obesity and outcomes in coronary artery disease (CAD) patients. We included consecutive patients referred to cardiac rehabilitation because of prior CAD events, who were classified using BMI groups and sex-specific tertiles of waist-to-hip ratio (WHR). Follow-up was ascertained using a population-based, record linkage system that consists of complete data on all residents. A major cardiovascular event (MACE) was defined as the composite outcome including acute coronary syndromes, coronary revascularization, ventricular arrhythmias, stroke or death from any cause. The association between obesity measures and MACE was assessed using cox proportional hazards models adjusted for potential confounders. The cohort included 1529 patients (74% men) mean age ± SD 63.1±12.5 years, 40% were obese by BMI. Eighty-eight percent of men and 57% of women were classified as having central obesity by WHR. Median follow-up was 5.7 years and 415 patients had a MACE event. After adjustment, a high WHR tertile was a significant predictor for MACE in women (HR=1.85 [95% Cl: 1.16, 2.94]; p=0.01), but not in men (HR=0.92 [95%CI: 0.69, 1.22]; p=0.54). This relationship in women persisted after further adjustment for BMI (HR=1.75 [95%CI: 1.07, 2.87]; p=0.03). Obesity by BMI was not associated with MACE in either men (HR=1.07 [95%CI: 0.76, 1.51]; p=0.69) or women (HR=0.98 [95%CI: 0.62, 1.56]; p=0.95). In conclusion WHR is associated with a higher risk of MACE among women with CAD but not in

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men. There was no obesity paradox when assessing obesity by BMI and MACE in CAD patients when including non-fatal events.

Keywords

Obesity; Coronary artery disease; cardiac rehabilitation

Introduction

Assessing obesity with the body mass index (BMI) has limitations, not only because BMI does not perfectly correlate with body adiposity but also because BMI does not measure fat distribution. BMI has been paradoxically linked to lower total and cardiovascular mortality in patients with coronary artery disease (CAD)[1] while measurements of central obesity such as waist circumference (WC) or waist-to-hip ratio (WHR) have shown conflictive results.[2,3] Most of the evidence testing the obesity paradox or linking central obesity and outcomes in CAD patients has used mortality as the outcome of interest, with scant research testing the association between measures of obesity and major adverse cardiovascular events (MACE) including non-fatal clinical outcomes. In the general population WC and WHR are indirect estimations of visceral adiposity which is linked to insulin resistance, dyslipidemia, and increased cardiovascular risk.[4] It is reasonable to believe that those mechanisms will continue to be relevant in the presence of CAD. In this study we test the hypotheses that in CAD patients, central obesity would be associated with increased MACE while obesity by BMI would either have none or paradoxical association with MACE.

Methods

We conducted a population-based, historical cohort study of all Olmsted County, Minnesota, residents over the age of 18 years that enrolled in phase II cardiac rehabilitation (CR) between the years 2002 and 2012 following a CAD event. Patients were identified using the resources of the Rochester Epidemiology Project (REP),[5] a federally funded record linkage system that indexes medical records, medications, procedures, and other health related information from the primary providers of medical care in Olmsted County; Olmsted Medical Center, the Mayo Clinic and few other individual private providers. All tertiary care, cardiovascular procedures and CR occurred at Mayo Clinic during the study period. This serves as an ideal community-based infrastructure to investigate disease-associated risk factors and outcomes.[5] The study protocol was reviewed and approved by the institutional review board of both the Mayo Clinic and Olmsted Medical Center. All included patients provided research authorization, as required by the state of Minnesota.

We identified patients referred for CR because of a myocardial infarction (MI) (ST or non-ST-segment elevation MI), stable or unstable angina and coronary revascularization by either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). We excluded patients on whom anthropometric measurements were not performed. Baseline information was collected electronically from the Rochester Epidemiology Project (REP) within 3 months of CR entry using the International Classification of Diseases-9th revision; this approach has been previously validated.[6] Demographic and clinical characteristics, laboratory values, blood pressure measurements and medications prescribed for the treatment of CAD were ascertained. For internal validation, a portion of this information was reviewed in duplicate by 2 investigators (J.M.I. and F.L.J.) who were masked to the baseline characteristics of patients.

Anthropometry at baseline was assessed during the CR entry evaluation according to the World Health Organization (WHO) Anthropometric Guidelines using structured protocols by trained nurses.[7] Height without shoes was recorded to the nearest centimeter and weight was recorded to the nearest 0.1 kilogram using a stadiometer, BMI was calculated dividing weight in kilograms by height in meters squared. Hip circumference (HC) was measured at the widest portion of the buttocks with the tape horizontal in cm. WC was obtained at the midpoint between the lower margin of the lowest palpable rib and the top of the iliac crest in the mid-axillary line at the end of expiration. Measurements were performed standing. WHR was calculated by dividing WC by HC.

MACE included any of the following events: 1) any diagnosis of a new acute coronary syndrome, including both ST and non-ST-segment elevation myocardial infarction and unstable angina that required hospitalization; 2) coronary revascularization, including PCI and CABG; 3) stroke, including any non-traumatic brain hemorrhage or infarction; 4) ventricular arrhythmias warranting in-hospital management, and 6) death from any cause. Mortality information was obtained from the REP, which records vital status from federal and Minnesota state death registries. Each subject in the study sample was followed up from the date of cardiac rehabilitation entry (index date) until the occurrence of a first MACE event or date of last followup until December 1th 2014. All outcomes were passively followed through a review of the electronic medical records in the records-linkage system in duplicate by 2 physician investigators (J.M.I. and F.L.J.) who were blinded to baseline characteristics including WHR and BMI to assess inter-observer agreement. Consensus resolved all disagreements. We summarized baseline patient characteristics with frequencies and percentages, means ± standard deviations (SD), or medians and interquartile range (IQR), as appropriate. Patient characteristics were compared between men and women using, chi-square tests, fisher's exact test or two-sample nonpaired t-tests, as appropriate. The Kappa (K) statistic was used to assess inter-observer agreement over comorbidities and also for each outcome composing MACE. BMI was analyzed both continuously and categorically using preestablished cutoffs.[7] WHR was analyzed both continuously and categorically, using WHO criteria defining central obesity as WHR≥0.90 for men and WHR≥ 0.85 for women, and also using sex-adjusted tertiles due to differences in body composition by sex reported the literature demonstrating sex-specific outcomes when considering central obesity.[8–10] The association between WHR and the time to first recorded MACE was assessed separately within men and women as a pre-specified analysis using Kaplan-Meier curves and Cox proportional hazards regression models. The models were adjusted for age, smoking, and history of heart failure, all known potential confounders in the association between obesity and Cardiovascular Disease (CVD) events. An additional model included BMI and an exploratory model adjusted for optimal medical therapy for CAD (defines as prescription of cardioprotective medication classes (statins, ACE inhibitors/angiotensin II receptor blockers, β-blockers, and antiplatelet agents. The multiplicative interaction between BMI and WHR was also assessed as a separate term in our overall model. We did not adjust for history of hypertension, diabetes or dyslipidemia because they are mechanistic factors linking obesity and CVD events, as generally accepted and recommended in obesity-related epidemiology. Findings were summarized using hazard ratios and 95% confidence intervals. The assumption of proportionality for the Cox proportional hazards models was assessed graphically and fulfilled. The functional form for WHR ratio (continuous) on the outcome was explored graphically with splines. Two-sided p-values less than 0.05 were considered statistically significant. All analyses were completed using JMP®, Version 12.1 and SAS® 9.4 (SAS Institute Inc., Cary, NC).

Results

Baseline patient characteristics are shown in Table 1. During a median follow-up of 5.7 years (IQR: 3.5–8.8), 415 patients (73% men) had at least 1 MACE,representing 9,586 person years, incidence of MACE was no different between sexes (p=0.10), as seen in Table 2. Central obesity measured using WHR tertiles was associated with an increased risk of MACE in women whose 3 year event-free-survival rates were 90.0, 84.5, 77.4% (log rank p=0.01); but not in men, in whom event-free survival rates were 84.8, 82.0, and 85.0% (log rank p=0.10), as observed in Figure 1-A/B.

As seen in Table 3, multivariate modeling demonstrated that WHR tertile remained a significant predictor for MACE for women; The risk of MACE for women in the highest WHR tertile was almost two-fold higher when compared to those in the lowest tertile. This relationship did not change after further adjusting for BMI (HR=1.75 [95%CI: 1.07, 2.87]; p=0.03). For men, the adjusted risk of MACE for those in the highest WHR tertile was no different when compared to the lowest tertile, after adjusting for BMI (Adjusted HR=1.09, [95%CI: 0.79, 1.50] p=0.58). When assessing WHR as a continuous variable, a 0.10 increase in WHR was associated with a 32% increase in risk of MACE among women,but not among men, as seen in Table 3.This relationship remained constant after further adjusting for optimal medical therapy for CAD (Data not shown). Obesity by BMI was not a significant predictor for MACE in either the whole cohort (HR 0.99, [95%CI: 0.76, 1.31] p=0.99) or in either men (HR=1.07 [95%CI: 0.76, 1.51]; p=0.69) or women (HR=0.98 [95%CI: 0.62, 1.56]; p=0.95) when analyzed separately. This association remained constant when only considering waist circumference, as seen in Appendix 1.

Discussion

In this historical cohort study of patients with known CAD attending CR, we found that there is no obesity paradox when assessing the association between BMI and MACE, as seen for mortality.[1] However, while WHR is not related to MACE in men, we observed that in women, a higher WHR was related to a higher risk of MACE, independent of BMI. Few studies have tested the association between obesity and MACE in CAD patients, while this is the first study to assess the risk of MACE when compared by WHR in patients with CAD.

Several studies have suggested that measures of central obesity, particularly WHR, provide incremental information beyond BMI, particularly in women.[5,11–14] Cerhan et al.[13] and Lassalle C et al.[14] have shown the value of WC over BMI in prediction of total mortality even with BMI units or categories, while Li et al.[10] and Sahakyan et al.[8] found that WHR relates to increased cardiovascular and mortality risk in women in all BMI categories. This was only seen in men with normal body weight.[12] We found no significant association between central obesity and MACE in men; a finding that may be related to the high prevalence of central obesity in men, with only 12% with a normal WHR, so the statistical and discriminatory power to detect associations was limited (Unadjusted C-statistic, for Men=0.50 and for Women=0.60). These results are consistent with other cohorts where this relationship has also been considered modest.[11,15] In the case of CAD patients undergoing cardiac rehabilitation, sex differences also appear to contribute additionally to the effect of obesity on clinical outcomes[8,10,16]. This relationship was demonstrated in a meta-analysis by Coutinho et al.[9] that concluded that in patients with CAD with either normal or high BMI, measures of central obesity were directly associated with an increased mortality rates and that this association was significantly greater in women.

Our sex-specific differences in the relationship between WHR and MACE provide some insight into the effects that predict long-term outcomes, and expands on what we and other authors have found before.[10,11,15,17,18] First, women are at higher risk in other populations, including post-myocardial infarction in-hospital mortality,[19] incident CVD,[10] total mortality in elderly patients,[15,16] and CAD patients.[9] These sex differences could be due to several physiologic, metabolic and hormonal differences between sexes. Second, fat and muscle distribution differs by sex. Men store more visceral fat[20] while women with greater fat in pelvis and gluteo-femoral muscle [17,21] The distribution in women changes on the post-menopausal state due to changes in steroid hormones, specifically estrogen.[22,23] maintaining after this stage their pre-menopausal BMI concomitant with an increase in WC and decrease in HC leading to an increase in WHR.[22] Third, those with enlarged abdominal adiposity may have an increased amount of androgen production and thus higher risk of CVD.[23] Further studies are needed to confirm these hypotheses.

Importantly, we did not observe the “obesity paradox”, where individuals classified as overweight or obese by BMI have better survival than those with normal weight. Results that may be justified because of the inability of BMI to discriminate between fat mass and lean mass and so it leads to misclassification regarding CVD risk.[11] Studies showing the obesity paradox have only included mortality as outcome.

This study has several strengths. The infrastructure of the REP provides excellent generalization to the US caucasian population in a community-based setting. Complete ascertainment of outcomes leads to minimization of loss to follow-up since they are applied to a relatively stable population,[5] thereby reducing referral bias and increasing the generalizability of the results. Our blinded investigators independently verified comorbidities and outcomes improving the validity of our data. Our sex-stratified analysis evaluated the association of WHR and the composite endpoint of MACE, an important and widely used measure since it has a significant impact on medical decision making for cardiovascular patient care and treatment. MACE offers more information when it is included as an outcome, because it provides a better idea of safety, effectiveness of treatments, disability and reduction of quality of life, along with costs through the evaluation of non-fatal events, which has not been extensively studied. Lastly, our study had a considerably longer follow-up compared to previous studies about prognosis of patients with CAD.[9]

This study is susceptible to a number of sources of bias. First, by limiting our sample exclusively to patients with CAD and measures of central obesity, we might introduce selection bias and limit the generalizability of our results . Second, our sample included mostly non-Hispanic white men, given the target population and the well-known lack of CR participation among women.[24] Third, we could not account for additional confounders (genetic susceptibility, nutritional quality, physical activity, daily environment, sedentary behaviors, cardiorespiratory fitness, sleep disorders, duration of obesity, socio-economic status along with others).Fourth, because our estimates are based on a single measure of WHR as the exposure variable, assuming that it will not change through follow-up, misclassification bias could potentially affect our sample. Finally, subjects without central obesity who develop CAD do so as a result of other risk factors and therefore their risk for recurrent events would theoretically depend on the persistance of those non-obesity related factors. Although such sources of bias can limit causal inferences, the results of our study are still informative.

These results expand upon studies that have found a relationship between WHR and cardiovascular risk factors,[25] metabolic syndrome,[26] total and cardiovascular mortality,[8,27] and other CVD outcomes.[18,27,28] Our study has potential implications for clinical care of individuals with CAD referred for CR. An early assessment of central adiposity in addition to BMI and application of lifestyle changes focused on caloric balance, healthy nutrition and tailored exercise prescription may have a positive impact on these patients as MACE events.

In conclusion, WHR was associated with a higher risk of MACE among women with CAD undergoing CR. Measuring WHR could be used as an additional measure to BMI for assessment of cardiovascular event risk in CAD patients with a higher impact among women.

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Appendix 1.: Adjusted Cox proportional hazard models testing the association between waist circumference tertiles and major adverse cardiovascular events among Men and Women.

Measure	Men (N=807) Model 1 Hazard Ratio (95%CI)	Men Model 1 P Value	Men Model 1 C-Statistic	Men Model 2 Hazard Ratio (95%CI)	Men Model 2 P Value	Men Model 2 C-Statistic	Women (N=309) Model 1 Hazard Ratio (95%CI)	Women Model 1 P Value	Women Model 1 C-Statistic	Women Model 2 Hazard Ratio (95%CI)	Women Model 2 P Value	Women Model 2 C-Statistic
Waist circumference sex-adjusted tertiles*												
Low	Referent			Referent			Referent			Referent		
Middle	1.27 (0.89,1.83)		0.50	1.24 (0.86,1.78)		0.61	1.57 (0.79, 3.15)		0.61	1.57 (0.78,3.17)		0.63
High	1.30 (0.91, 1.85)	0.25		1.21 (0.84, 1.73)	0.40		3.28 (1.75,6.36)	0.0008		3.42 (1.80, 6.74)	0.0006	
			0.50			0.61			0.61			0.62
Waist circumference continuous for 1 cm increase	1.00 (0.99,1.01)	0.16		1.00 (0.99, 1.01)	0.26		1.02 (1.01,1.04)	0.0003		1.02 (1.01, 1.03)	0.0006	

Cl= confidence interval

Model 1: Adjusted for age, Model 2: Adjusted for Age, smoking and history of heart failure. (The variable Waist circumference was available in less subjects than those included in table 3)

Interaction between Body mass index and waist circumference (in a model with Body mass index and waist circumference), was not statistically significant (p=>0.05).

* Waist circumference sex-adjusted tertiles [Men Low: <98 cms (N=291 ,MACE=64), Middle: 98 cms to <108.56 cms (N=247, MACE=58), High: ≥108.56 cms (N=269, MACE=60); Women Low: 87 cms (N=106,MACE=19), Middle: 87 cms to <101 cms (N=100,MACE=18), High: ≥101 cms (N=103,MACE=29)j

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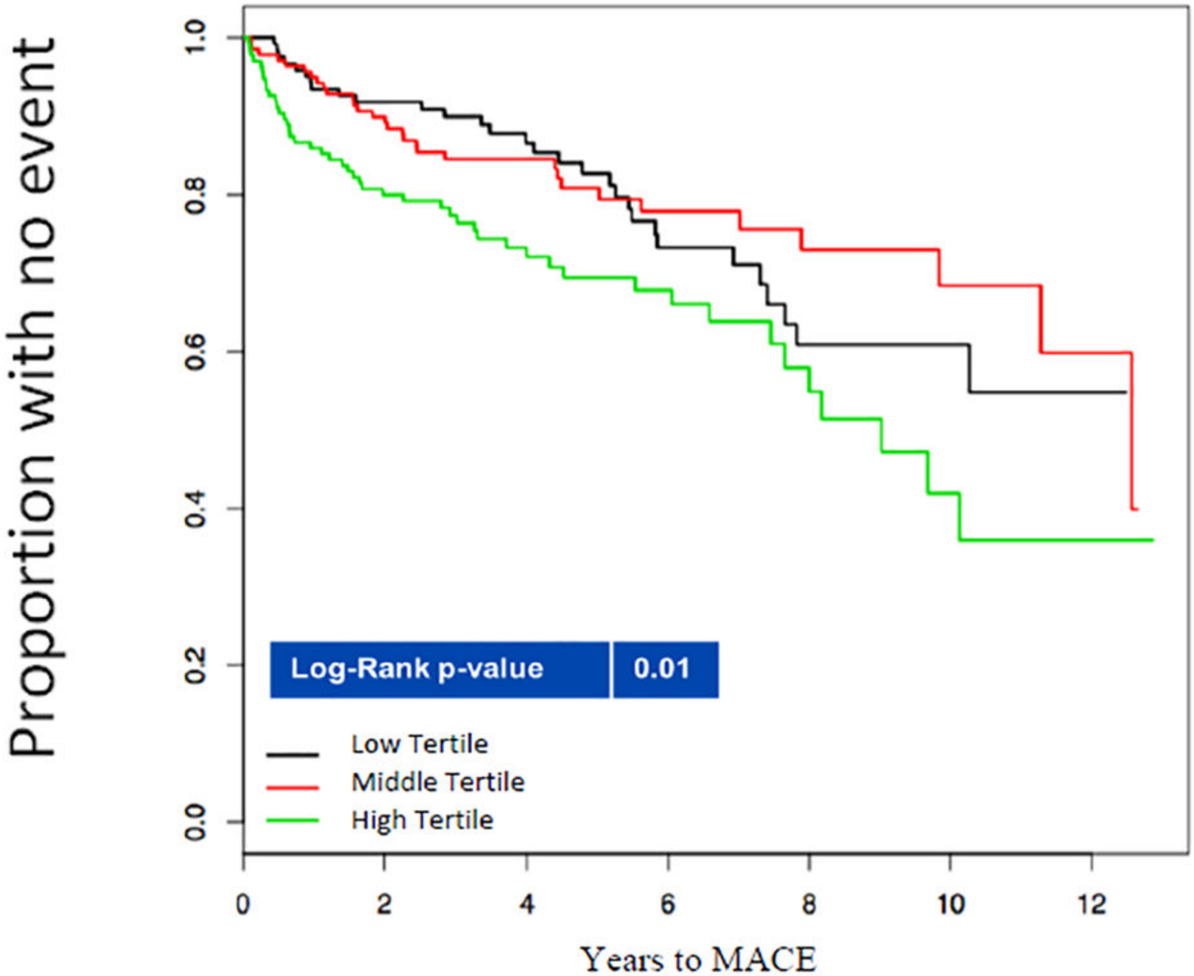
Highlights

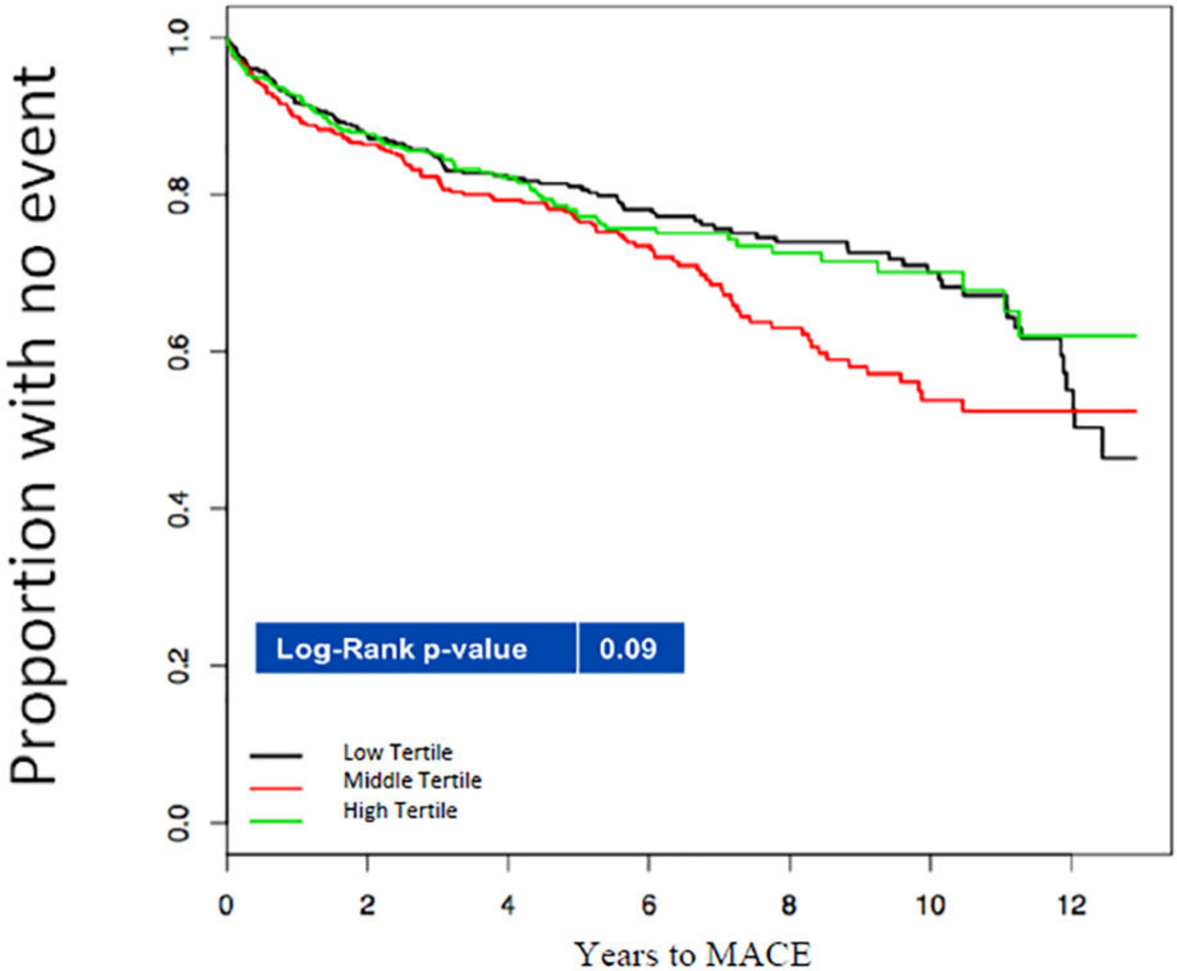
- Women with CAD attending cardiac rehabilitation with higher WHR had a greater long-term risk of major adverse cardiovascular events when compared to those with a lower WHR.
- A higher WHR was not associated with major adverse cardiovascular events in men.
- BMI was not associated with major cardiovascular events.



WHR adjusted Tertile	Low	Middle	High
Events	30	31	47
Censored patients	92	108	88

Figure 1A.

Kaplan-Meier curves indicating the relationship between waist to hip ratio tertiles and major adverse cardiovascular events among Women.



WHR adjusted Tertile	Low	Middle	High
Events	101	115	301
Censored patients	271	253	91

Figure 1B.

Kaplan-Meier curves indicating the relationship between waist to hip ratio tertiles and major adverse cardiovascular events among men.

Table 1.

Baseline patient characteristics

Variable	All (n= 1529)	Men (N=1133)	Women (N=396)
Age (years)	63.20 ±12.5	62.10 ±11.87	66.24 ± 13.58 §
Non-Hispanic white	1472(96.3%)	1090(96.2%)	382(96.5%)
Black or African American	24(1.6%)	16(1.4%)	8(2.0%)
Asian	29(1.9%)	23(2.0%)	7(1.8%)
American Indian or Alaska Native	3(0.2%)	3(0.3%)	0
Native Hawaiian/Pacific Islander	1(0.1%)	1(0.1%)	0
Heart failure	274 (17.9%)	180 (15.9%)	94 (23.7%) §
Ever smokers	901 (58.9%)	716 (63.2%)	185 (46.7%) §
Diabetes mellitus	683 (44.7%)	509 (44.9%)	174 (43.9%)
Hypercholesterolemia	1419 (92.8%)	1059 (93.5%)	360 (90.9%)
Hypertension	894 (58.5%)	636 (56.1%)	258 (65.2%) §
Beta blockers use	1107 (72.4%)	816 (72.0%)	291 (73.5%)
Angiotensin converting enzyme inhibitor use	642 (42.0%)	472 (41.7%)	170 (42.9%)
Calcium channel blockers	166 (10.9%)	110 (9.7%)	56 (14.1%) §
Diuretics	447 (29.2%)	295 (26.0%)	152 (38.4%) §
Waist to hip ratio	0.95 (0.1)	0.98 (0.1)	0.86 (0.1)§
Waist to hip ratio sex-adjusted tertile[1]			
Low		0.91 (0.05)	0.79 (0.05)
Middle		0.98 (0.03)	0.86 (0.04)
High		1.04 (0.06)	0.94 (0.07)
Central obesity	1229 (80.4%)	1003 (88.5%)	226 (57.1%) §
Body mass index (Kg/m^2)	29.7 ±5.7	29.9 ±5.5	28.9 ±6.2

Values are mean ± standard deviation SD or n (%), unless otherwise indicated.

§Denotes statistical significance <0.05, compares males vs females.

** Median and (Interquartile range)

[1]Waist to hip ratio sex-adjusted tertiles (male Low Tertile: <0.94, Middle Tertile: 0.94 to <1.01, High Tertile: ≥1.01; women Low Tertile : <0.83, Middle Tertile: 0.83 to <0.89, High Tertile: ≥0.89).

Table 2.

Major adverse Cardiovascular Events by Gender

	Overall N=1529	Men N=1133	Women N=396
# Major Adverse Cardiovascular Events per Total person years	584/9586	430/7333	154/2253
Major adverse cardiovascular events	415 (27.1%)	307 (27.1%)	108 (27.3%)
Total years of follow up (median)	5.7 (3.58.4)	5.9 (3.8–9.2)	4.9 (3.2–7.7)
Percutaneous Coronary Intervention	133 (32.0%)	101 (32.9%)	32 (29.6%)
Death	107 (25.8%)	77 (25.0%)	30 (27.8%)
Myocardial Infarction	58 (14.0%)	39 (12.7%)	19 (17.6%)
Stroke	42(10.0%)	27 (8.8%)	15 (14.0%)
Coronary Artery Bypass Graft	34 (8.3%)	33(10.8%)	1 (0.9%)
Angina	33 (8.1%)	24 (7.8%)	9 (8.3%)
Ventricular Arrhythmia	8 (1.8%)	6 (2.0%)	2 (1.8%)

Values presented are frequencies and percentages.

Outcomes ascertained electronically: Myocardial infarction ICD-9,410. X; Unstable Angina ICD-9,411.X; Percutaneous Coronary Intervention CPT/ ICD-9, 92980– 92982/V45.82; Coronary Artery Bypass Graft CPT/ ICD-9 337700–337735/V45.81; Ventricular arrhythmias ICD-9,427.X; Stroke ICD-9, 433.X

Table 3.

Adjusted Cox proportional hazard models testing the association between Waist to Hip Ratio tertiles and major adverse cardiovascular events among Men and Women.

	Men						Women					
	Model 1			Model 2			Model 1			Model 2		
Measure	**Hazard Ratio (95%CI)**	**P Value**	**C-Statistic**	**Hazard Ratio (95%CI)**	**P Value**	**C-Statistic**	**Hazard Ratio (95%CI)**	**P Value**	**C-Statistic**	**Hazard Ratio (95%CI)**	**P Value**	**C-Statistic**
Waist to hip ratio sex-adjusted tertiles *												
Low	Referent			Referent			Referent			Referent		
Middle	1.27		0.54	1.21		0.58	0.94		0.58	0.99		0.62
	(0.97,1.66)			(0.92,1.58)			(0.57, 1.56)			(0.60,1.64)		
High	0.97 (0.73, 1.29)	0.11		0.92	0.12		1.77	0.008		1.85	0.007	
				(0.69,1.22)			(1.12–2.82)			(1.16, 2.94)		
Waist to hip ratio continuous, for 0.10 increase	1.00 (0.88,1.15)	0.96	0.54	0.98 (0.85, 1.13)	0.81	0.58	1.30 (1.07,1.58)	0.008	0.58	1.32 (1.08, 1.61)	0.007	0.61

Cl= confidence interval

Model 1: Adjusted for age, Model 2: Adjusted for Age, smoking and history of heart failure.

Interaction between Body mass index and Waist to hip ratio (in a model with Body mass index and waist hip ratio), was not statistically significant (p=>0.05).

* Waist to hip ratio sex-adjusted tertiles (male Low Tertiles: <0.94, Middle Tertile: 0.94 to <1.01, High Tertile: ≥1.01; women Low Tertile : <0.83, Middle Tertile: 0.83 to <0.89, High Tertile: ≥0.89)