

Sex and Age Difference in Risk Factor Distribution, Trend, and Long-Term Outcome of Patients Undergoing Isolated Coronary Artery Bypass Graft Surgery

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Research Article

Keywords: Coronary artery bypass graft surgery, cardiovascular risk factor

Posted Date: July 1st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-618741/v1>

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Abstract

Background

Preoperative coronary artery disease risk factors (CADRFs) distribution and pattern may also have an important role in determining major adverse cardiovascular (MACEs). In this study, we aimed to evaluate the CADRFs distribution and trend over 10 years and also the long-term outcome of CABG in different age-sex categories.

Method:

In this registry-based serial cross-sectional study, we enrolled 24328 patients who underwent isolated CABG and evaluated the prevalence of CADRFs according to sex and age. We also used the Kaplan-Meyer method for long-term outcomes in different age-sex categories' survival plots.

Results

In general, DLP (56.00%), HTN (53.10%), DM (38.40%), and positive family history (38.30%) were the most frequent risk factors in all patients. Prevalence of HTN, DLP, DM, Obesity and positive family history were all higher in women, all statistically significant. The median follow-up duration was 78.1 months (76.31 to 79.87 months). Men under 50 had the best survival (93.6%) and least incident of MACE (20.8%). Worst survival observed in female patients older than 55 (83.4%) who also had the highest incident of MACE (30.6%)

Conclusion

Although DLP is still the most frequent CADRF among the CABG population, the level of LDL and TG is decreasing. Female patients have more risk factors and worse long-term outcomes (in terms of mortality and MACE incidence) Therefore, health care providers and legislators must pay greater attention to female population CADRFs and ways to prevent them at different levels.

Introduction

Coronary artery disease (CAD) is a chronic, progressive, multifactorial disease that is the leading cause of morbidity and mortality worldwide, especially in developing countries (1, 2). Coronary artery bypass grafting (CABG) has been an exquisite treatment for complex CAD since the 1960s (3). Despite the increasing rate of percutaneous coronary intervention (PCI), CABG is still the most prevalent cardiac surgery (4).

CAD's risk factors such as hypertension (HTN), diabetes mellitus (DM), dyslipidemia (DLP), cigarette smoking, and family history of CAD were introduced by the Framingham study (5). Sex and Age are among the most important non-modifiable risk factors, for example, CAD develops in women later in life comparing to men for an unknown reason (6). Late-onset of CAD in women results in underestimation of cardiovascular risk by healthcare providers and patients (7) and leads to a higher burden of CAD in women, especially at a young age.

Although surgical techniques in CABG improved in recent years, there is still a chance for adverse outcomes, in which pre-operative modifiable and non-modifiable risk factors play an important role. Preoperative coronary artery disease risk factors (CADRFs) distribution and pattern may have an essential role in determining major adverse

cardiovascular events (MACEs) and survival after surgery. The impact of CADRFs such as age (premature vs. older age) and sex in CAD is not distinguished (7–9).

Hence, in this article, we aimed to evaluate the following subjects: A. CADRFs distribution and trend over 10 years among isolated CABG patients; B. Sex difference in CADRFs distribution and C. Post-CABG survival and MACE in the whole population and also in premature population.

Methods

Tehran Heart Center

Tehran heart center (THC) is a major tertiary referral center in Tehran, Iran, dedicated to the treatment of heart diseases. From 2001 to the end of 2017, approximately 1,300,000 patients were referred to the outpatient clinics, more than 800,000 patients visited the emergency rooms, over 280,000 patients were hospitalized, and more than 55,000 patients underwent open-heart surgeries THC. Additionally, more than 150,000 coronary angiographies and over 35,000 angioplasties were done in this center.

Data regarding risk factors were collected in THC clinics, including the risk factors clinic, open heart surgery clinic, and angioplasty clinic. The risk factors clinic was established in 2005 to control the CAD risk factors for all patients. Patients who undergo either coronary artery angioplasty or open-heart surgery receive additional follow-up in the angioplasty follow-up clinic for 3–5 years or the open-heart surgery clinic for up to 10 years (10).

Coronary angiography data bank

The coronary angiography data bank, established in January 2005, registers collected data from all patients who undergo angiography at THC. As part of the THC protocol, demographic, clinical, and laboratory data are collected during the admission to the catheterization laboratory and are recorded in an electronic registry. Informed consent is required by patients for inclusion in the data bank.

Design and participants

In this single-center registry-based serial cross-sectional study, all patients in the coronary angiography data bank of the THC from 2007 through 2017 were reviewed. Patients with obstructive CAD (defined by an angiography report of more than 50% stenosis in at least one vessel) were eligible. We excluded patients with implausible data which is defined as following, age younger than 20 or older than 100, fasting blood sugar less than 50 or higher than 600, LDL cholesterol of less than 20 or higher than 500, HDL cholesterol of less than 5 or greater than 100, total cholesterol of less than 50 or greater than 700, triglyceride level of less than 20 or greater than 1200, and creatinine level of less than 0.2 or greater than 10. The prevalence of conventional CAD risk factors including hypertension (HTN), dyslipidemia (DLP), diabetes mellitus (DM), obesity, cigarette smoking, and family history of CAD were analyzed according to sex and age, and the 10-year trends were demonstrated.

Definitions and protocols

HTN was defined by at least two office blood pressure (BP) measurements exceeding 140 over 90 mmHg. Blood pressure was measured using a manual mercury sphygmomanometer in all cases. Trained nurses measured blood pressure in both hands in a sitting position after resting for 5 minutes. The higher BP was registered in a pre-specified datasheet. This protocol was repeated after 3 minutes. In case of difference (more than 10 mmHg in

systolic blood pressure of 5 mmHg in diastolic blood pressure), the measurement was repeated for the third time and the two measurements closer together were used. The mean systolic and diastolic blood pressure of the two measurements was calculated. Participants with high blood pressure were defined as follows: mean systolic blood pressure \geq 140 mmHg or mean diastolic blood pressure of \geq 90 mmHg or who were taking blood pressure medications. DM was defined by measurements of fasting plasma glucose \geq 126 mg/dL or glycated hemoglobin A1C (HbA1C) \geq 6.5% in the presence of confirmatory testing. Patients on antidiabetic medications were also included as diabetic in the study. Determination of DLP was according to either total serum cholesterol \geq 200 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL in men and < 50 mg/dL in women, or triglycerides \geq 250 mg/dL, measured after at least ten hours of fasting. Patients with a previous diagnosis of DLP who were on lipid-lowering agents were also included. Obesity was considered in patients who had a body mass index (BMI) \geq of 30 kg/m². The definition of smoking was having ever smoked more than 100 cigarettes. Family history was considered in the presence of atherosclerotic cardiovascular disease (ASCVD) in first-degree male relatives aged < 55 years or in females aged < 65 years. Premature CAD was defined as the occurrence of CAD in men under 50 and women under 55. We defined MACE as cardiovascular death, myocardial infarction, or ischemic stroke.

Statistical analysis

Categorical variables are presented as numbers (percentage) and compared using the Chi-square test. Numerical variables demonstrated as mean \pm standard deviation and compared using T-test. Survival analysis was performed using *Kaplan–Meier method*. All statistical analyses were performed using IBM SPSS® version 26.

Result

1- Population

During this study, we evaluated 24328 patients who underwent CABG in THC from 2007 to 2017. The mean age was 60.8 ± 9.52 , 6428 (26.4 %) were women and 17900 (73.6%) were men. The mean age of patients increased from 60.7 ± 9.46 to 61.7 ± 9.5 and the male to female ratio remained nearly constant at approximately 2.8 (Table 1). The median follow-up duration was 78.1 months (76.31 to 79.87 months).

Table 1
Patients' demographic characteristics in each 3 years

Year	Age	Sex	Coronary artery disease risk factors						
			HTN	DLP	DM	Cigarette smoking	Obesity	Opium addiction	Family History
2007–2010	60.7 ± 9.46	Male 73.2%	5210 (51.90%)	6201 (61.70%)	3491 (34.70%)	1645 (16.40%)	2361 (23.6%)	1122 (11.40%)	4278 (42.60%)
		Female 26.8%							
2011–2013	60.81 ± 9.53	Male 73.3%	2945 (48.30%)	3003 (49.20%)	2483 (40.70%)	961 (15.80%)	1366 (22.4%)	629 (10.80%)	2594 (42.50%)
		Female 26.7%							
2014–2017	61.7 ± 9.5	Male 74.3%	4760 (58.40%)	4387 (53.90%)	3363 (41.20%)	1656 (20.40%)	2017 (24.9%)	1509 (18.60%)	2449 (30.00%)
		Female 25.7%							
Total	60.8 ± 9.52	Male 73.6%	12915 (53.10%)	13591 (56.00%)	9337 (38.40%)	4262 (17.60%)	5744 (23.7%)	3260 (13.70%)	9321 (38.30%)
		Female 26.4%							

Data are presented as mean ± standard deviation and number (%)

HTN: hypertension, DLP: dyslipidemia, and DM: diabetes mellitus

2- Risk factor distribution

2 – 1. Total Population

We compared risk factors distribution in 3 time periods, 2007–2010, 2011–2013, and 2014–2017. In all of these periods, HTN and DLP were the most prevalent risk factors, present in more than half of the patients. Although not at a steady pace, HTN, DM, cigarette smoking, opium addiction tended to increase over the years. On the other hand, positive family history decreased significantly in the last period. As for DLP, despite a significant decrease in 2011–2013, it showed a slight increase in 2014–2017. Obesity remains nearly constant through the years being present in nearly a quarter of patients. In general, DLP (56.00%), HTN (53.10%), DM (38.40%), and positive family history (38.30%) were the most frequent risk factors in all patients (Table 1, Fig. 1).

2–2. Premature Population, Men vs. women

Based on the age of premature CAD in men and women, risk factors distribution was categorized into 4 groups, men ≤ 50 (2883; 11.9%), men > 50 (15018; 61.7%), women ≤ 55 (1448; 6.0%) and women > 55 (4979; 20.4%).

In premature CAD in men, DLP and positive family history were the most frequent risk factors, with DM and opium addiction being the least frequent ones. In men older than 50, DLP then HTN had the highest, and opium addiction and cigarette smoking had the lowest prevalence. Positive family history showed the biggest difference between the men of two age groups (52.6% in men ≤ 50 vs 33.2% in men > 50). In men of all ages, DLP (51.3%) and HTN (46.5%)

were the most frequent risk factors. In women ≤ 55 , DLP, HTN, DM, and positive family history were all present in more than 50% of patients being the most prevalent risk factors respectively. HTN, DLP, and DM had the highest prevalence in women > 55 . Similar to men, positive family history prevalence had the highest difference between women of the age groups. HTN (72.3%), DLP (69.7%), and DM (55.4%) were the most prevalent risk factors in all women. In all age-sex groups, DLP was the most frequent risk factor except for women > 55 whose HTN was slightly higher than DLP. Both TG and LDL had a nearly declining trend in 2007–2016, with women ≤ 55 having the highest levels and men over 50 having the lowest levels. In comparison between men and women, HTN, DLP, DM, Obesity, and positive family history were all higher in women, all statistically significant. Cigarette smoking and opium addiction were significantly lower in the female group, present in less than 5% of the patients despite increasing prevalence over the years. (Table 2, Fig. 1).

Table 2
Risk factors distribution in each age-sex group

Age-sex category	Coronary artery disease risk factors						
	Hypertension	Dyslipidemia	Diabetes mellitus	Cigarette smoking	Obesity	Opium addiction	Family History
Men ≤ 50	1023 (35.50%)	1620 (56.30%)	708 (24.60%)	998 (34.60%)	775 (27.0%)	734 (25.90%)	1517 (52.60%)
Men > 50	7269 (48.50%)	7513 (50.10%)	5081 (33.90%)	3080 (20.60%)	2562 (17.1%)	2394 (16.40%)	4986 (33.20%)
Women ≤ 55	930 (64.30%)	1008 (69.70%)	844 (58.30%)	56 (3.90%)	646 (44.7%)	44 (3.00%)	803 (55.50%)
Women > 55	3693 (74.30%)	3450 (69.50%)	2704 (54.40%)	128 (2.60%)	1761 (35.6%)	88 (1.80%)	2015 (40.50%)
Men	8292 (46.4%)	9133 (51.1%)	5789 (32.3%)	4078 (22.8%)	3337 (18.7%)	3128 (17.8%)	6503 (36.3%)
Women	4623 (72.0%)	4458 (69.5%)	3548 (55.2%)	184 (2.8%)	2407 (37.6%)	132 (2.0%)	2818 (43.8%)
P-value [¶]	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Data are presented as mean \pm standard deviation and number (%)							
[¶] Men vs women risk factor distribution difference, statistically significant values are bolded							

3- Long term outcome, Men vs. Women

We evaluated patients' post-CABG prognosis based on our follow-up data and compared the results in different age-sex groups. Men under 50 had the best survival (93.6%) and least incident of MACE (20.8%). Worst survival observed in female patients older than 55 (83.4%) who also had the highest incident of MACE (30.6%). In comparison, men had better survival than women (86.2% vs. 84.9%) with fewer MACE incidents (24.6% vs 29.7%) which both were statistically significant. In general, patients had 85.9% overall survival and 74.1% of them survived without any MACE (Table 3). We used the Kaplan-Meyer method to draw age-sex group survival plots. As for overall survival men ≤ 50 , women ≤ 55 , men > 50 , and women > 55 had the best to worst survival respectively. Men > 50 and women > 55

survival declined greater than those with premature CAD after CABG. In terms of MACE incident men, ≤ 50 had the best and women > 55 had the worst MACE-free survival and men > 50 and female ≤ 55 had near-identical plot after surgery (Fig. 2)

Table 3
Overall survival and survival without major adverse cardiovascular events after CABG

Age-sex category	Overall survival	MACE-free survival
Men ≤ 50	93.6%	79.2%
Men > 50	84.80%	74.70%
Women ≤ 55	90.5%	73.6%
Women > 55	83.4%	69.4%
Men	86.2%	75.4%
Women	84.9%	70.3%
P-value [¶]	0.013	< 0.001
Total	85.9%	74.1%
MACE: major adverse cardiovascular event		
[¶] Men vs women risk factor distribution difference, statistically significant values are bolded		

Finally, we compared men and women in the number of CADRFs. Near half of the patients had 3 or more risk factors and on average female patients had slightly more risk factors. (Fig. 3)

Discussion

Based on the results of this registry-based study, patients undergoing CABG are becoming older (13-15). HTN, DM, obesity, and cigarette smoking increased in nearly all age-sex groups but positive family history and dyslipidemia tend to decrease over the years. LDL level is decreasing which is mainly due to higher statin use in the general population based on previous practice guidelines. CADRFs except smoking and opium addiction was significantly higher in female patients but probably the most important clinically relevant finding was higher mortality and MACE incident in women of both age groups in line with previous studies which raise the necessity for better surveillance of CADRFs in female patients.

Hypertension

In our data registry, hypertensive patients in all 4 subgroups had been decreased until 2012; but started to rise again. An increasing number of hypertensive patients among CABG candidates is in contrast to reports by Esteghamati et al in 2017 and Azizi et al in 2019 regarding the prevalence of HTN among the general population of Iran (16, 17). In our study, HTN was the most frequent risk factor among females older than 55 and is less frequent among males younger than 50 in comparison to other subgroups. Although it is decreasing in the general population, HTN is still a major risk factor for severe CAD. This is an alarming sign for the Iranian population. Preventive and diagnostic

measures in the general population as the primary prevention and also precise therapeutic measures for secondary prevention should be taken in hypertensive patients (18).

Dyslipidemia

DLP as a well-known CADRFs decreased in our patients who underwent CABG. According to trends of cardiovascular risk factors (based on STEPS reports) in the diabetic and non-diabetic general population in Iran, between 2007-2017, level of Triglyceride(TG), Low-Density Lipoprotein(LDL) are also decreasing (19). Increased Statins prescription and general awareness of healthier diets and national primary prevention programs lead to lower lipid profile in both patients and the general population (20).

Diabetes mellitus

The number of diabetic patients increased from 2007-2017 in all subgroups. It was one of the most prevalent risk factors especially in female patients in both age groups which were present in nearly two-thirds of them. A similar uptrend is also observed in other studies (21-23). As for the general Iranian population, DM had an increasing trend with a higher prevalence among women similar to our study (24).

Family history

As expected based on the results of our study positive family history was more prevalent among the premature group (Almost half of young men and women had a positive family history of CAD) We also observed that positive family history was higher in women \leq 55.

Obesity

Obesity (as defined by BMI $>$ 30 kg/m²) was most prevalent in women \leq 55 and higher in female patients in general. In our study, the trend of obesity was not increased in contrast to other studies (27, 28). Although obesity is higher among women, an increasing trend is visible among the young male population which is an alarming sign and primary prevention measures should seriously focus on this age group.

Cigarette Smoking

Cigarette smoking increased in men in both groups. Women had a relatively low prevalence of smoking (under 5%). Our findings are similar to the general Iranian population and probably cultural differences between the two sexes are the main reason for fewer women smokers (31). The smoking uptrend in the general population and our study may suggest the difficulty of controlling cigarette smoking as one of the major modifiable CADRFs and the necessity of better primary prevention (32).

Opium addiction

The trend of opium addiction was very similar to cigarette smoking. In contrast to cigarette smoking, there is controversy regarding opium addiction as a CADRF and people usually don't see it as a serious risk factor for heart problems (33). Some recent studies revealed a connection between opium addiction and adverse outcomes in post-CABG patients (34, 35). In our study, the prevalence of opium addiction is higher in premature CAD patients in both sexes. Hence it is important to increase public knowledge about this modifiable risk factor of CAD in, especially young age group.

Despite the strengths of our study, including large sample size and detailed follow-ups years after CABG surgery, we need to mention our limitations. First, due to its observational nature, there are possible inherent biases. Second, this is a single-center study on the Iranian population. Another limitation was that some of the data like cigarette and opium addiction were based on patients' statements which can lead to reporting bias. Also, we did not separate patients with acute coronary syndrome from chronic coronary syndrome which might affect our post-CABG survival results.

Conclusion

The burden of CAD among all age-sex groups is considerable and most of its major risk factors are increasing in the general population. On the other hand, according to our study, the survival of female patients is significantly lower and they have a higher chance of MACE incidents after CABG surgery. These observations combined with underestimation of CAD in women especially in younger patients can lead to high mortality and morbidity among women with cardiovascular problems. As reported by the American heart association 2019 national women's survey, a decrease in awareness of CAD is a leading cause of mortality among all age and ethnic groups of women (36). Therefore, health care providers and legislators must pay greater attention to the female population' CADRFs and ways to prevent them at different levels.

Declarations

Ethics approval and consent to participate

The protocol of this study is in line with the 2013 Helsinki declaration and was approved by the Ethics Committee of Tehran University of Medical Sciences. All participants or their legal guardians gave written informed consent before inclusion in the study.

Consent for publication

Not applicable.

Availability of data and materials

The data of this study is registered in a database and is available upon request.

Competing interests

The authors have no conflicts of interest to declare.

Funding

All funding support was provided by the Tehran Heart Center research division.

Authors' contributions

A.A. and B.S. wrote original manuscript and prepared the figures. M.P. prepared and analyzed the data. A.J., S.S., H.M., S.M., J.B. and A.K. reviewed and edited the manuscript and K.H. provided the concept and designed the study.

Acknowledgments:

We acknowledge all healthcare workers involved in the diagnosis and treatment of patients in Tehran Heart Center.

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Figures

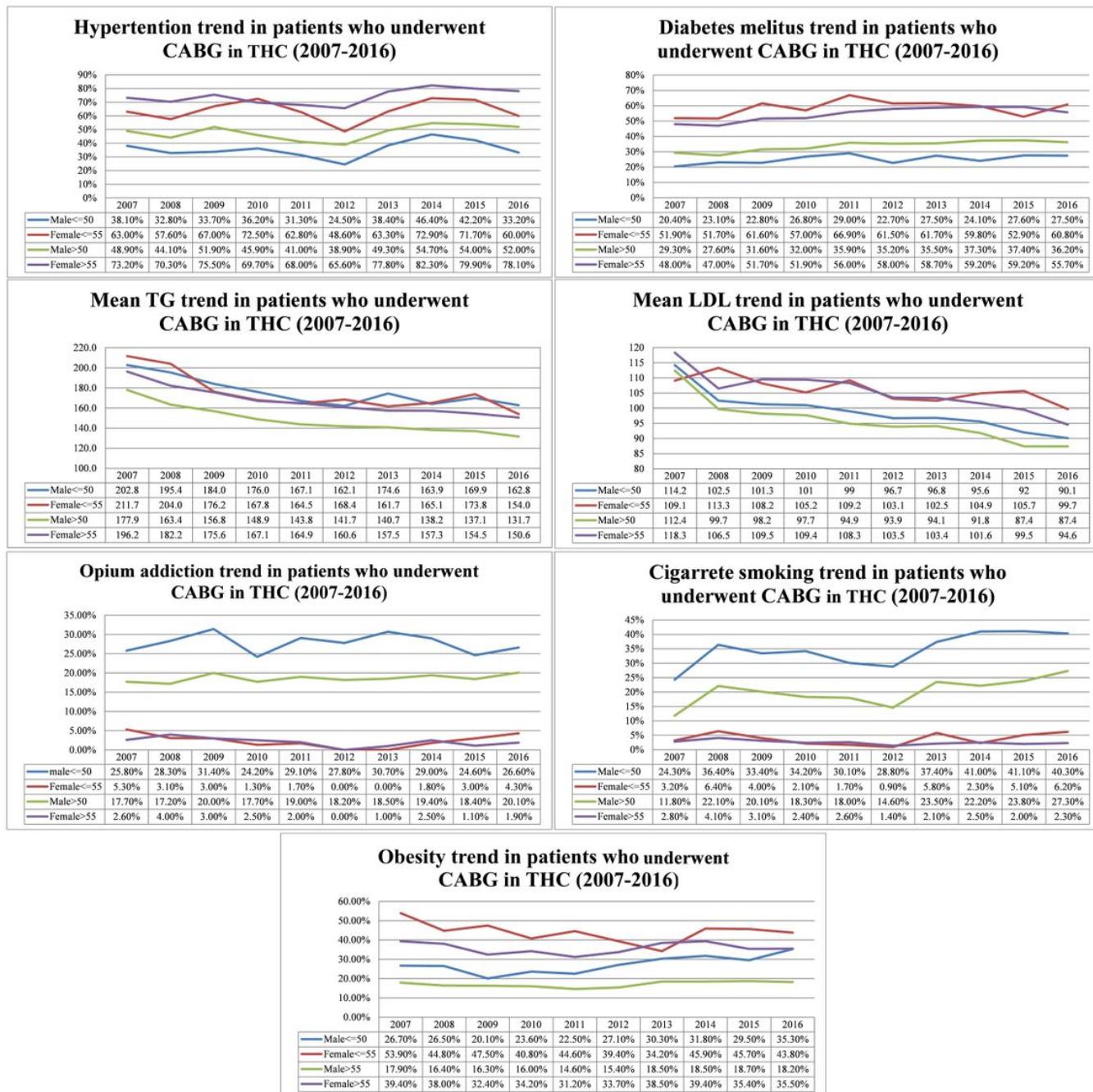


Figure 1

Trends of coronary artery disease risk factors after coronary artery bypass grafting among different age-sex groups between 2007-2016

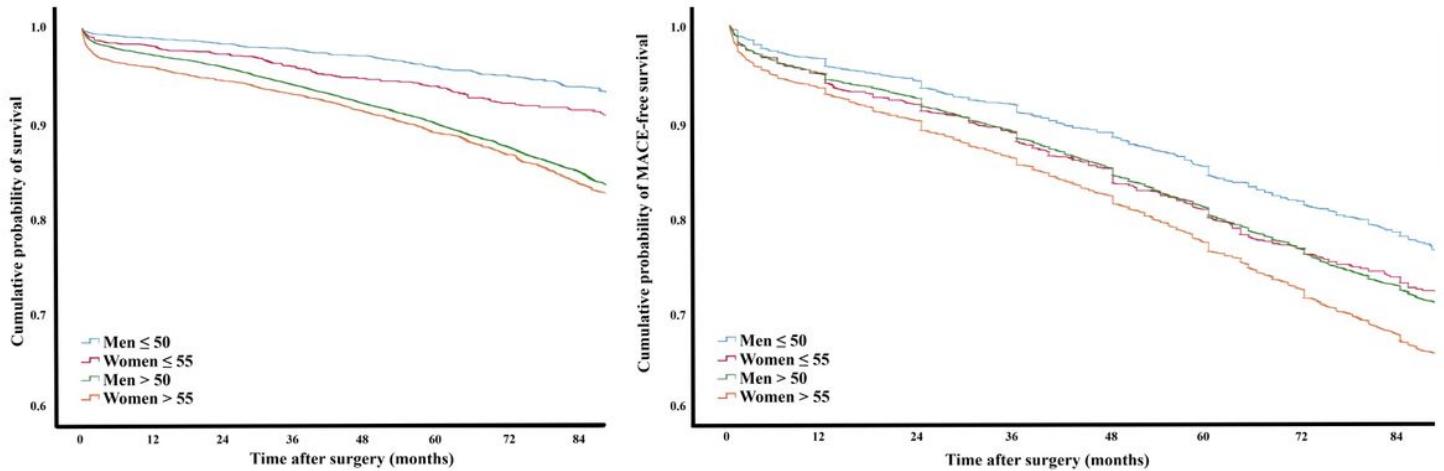


Figure 2

Overall survival and survival without major adverse cardiovascular events after coronary artery bypass grafting

Coronary artery disease risk factors

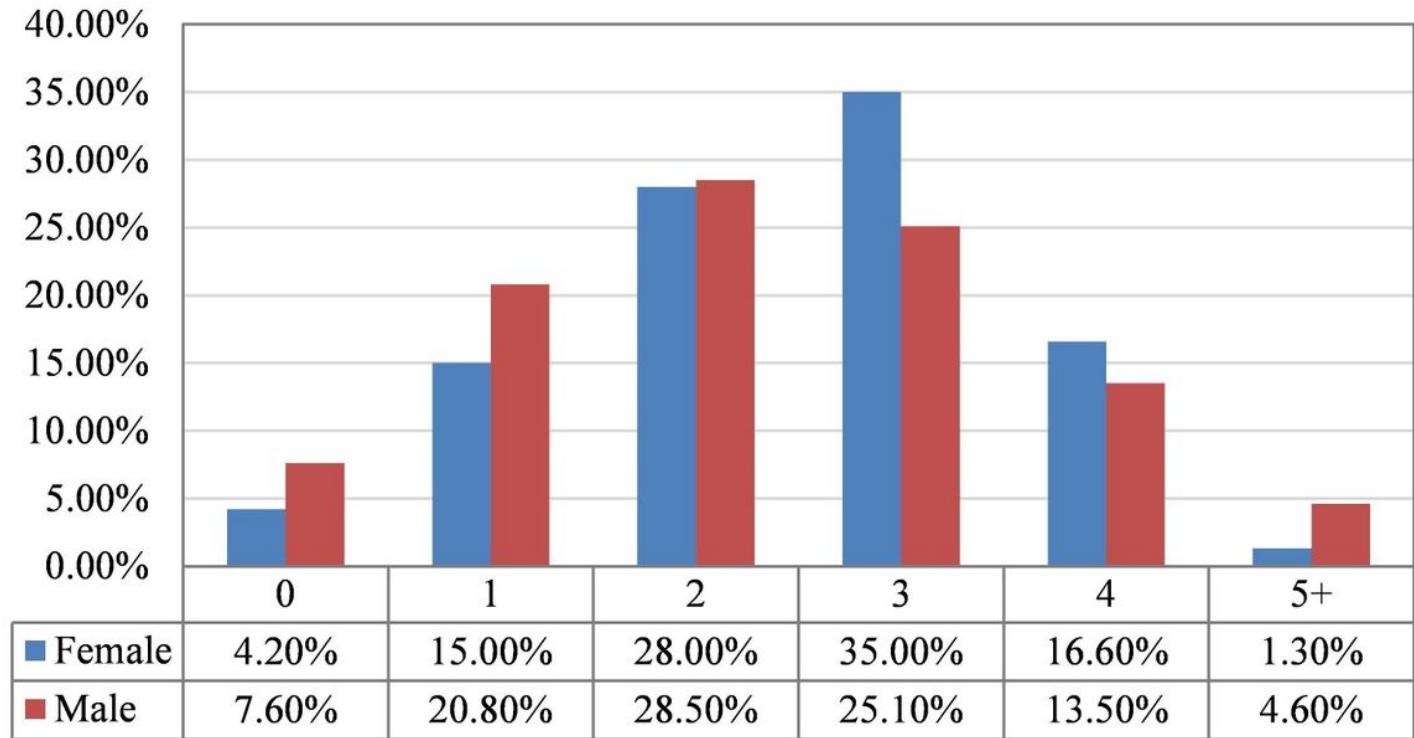


Figure 3

Total risk factor counts between two sexes