International Journal of Cardiology 155 (2012) 144–148

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Gender difference in cardiovascular risk factors in the elderly with cardiovascular disease in the last stage of lifespan: The PROTEGER study ☆

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ARTICLE INFO

Article history:
Received 13 July 2011
Received in revised form 3 September 2011
Accepted 17 September 2011
Available online 15 October 2011

Keywords:
Gender
Mortality
Cardiovascular disease
Systolic dysfunction
Arrhythmia

ABSTRACT

Background: It is known that the prognostic value of cardiovascular risk factors differed between men and women, but data in the elderly are very limited.
Methods: We assessed cardiovascular structural and functional measurements (intima-media thickness, pulse pressure, pulse wave velocity, left atrial dimension (LAD), arrhythmia, deceleration time of transmitral early diastolic flow and left ventricular ejection fraction (LVEF)), by ultrasonography, blood pressure monitor, electrocardiography and applanation tonometry, as well as conventional cardiovascular risk factors (age, body mass index, smoke, total to high density lipoprotein (HDL) cholesterol ratio, and plasma glucose), and investigated their associations with all-cause mortality in men and women, separately, in 331 consecutive patients (87 ± 7 years, 74.0% female) with a history of cardiovascular disease from the geriatric departments. After a mean follow-up of 378 days, 110 deaths were recorded.
Results: In the full adjusted models, we found that increased LAD (hazard ratio [HR] = 2.24 per 1-standard deviation [SD]; 95% confidential interval [CI]: 1.23–4.09), reduced LVEF (HR = 0.60 per 1-SD; 95% CI: 0.38–0.96), and increased total-to-HDL cholesterol ratio (HR = 1.99 per 1-SD; 95% CI: 1.05–3.78) were significant predictors of all-cause mortality in men, whereas the presence of arrhythmia (HR = 2.47; 95% CI: 1.28–4.78), increased plasma glucose (HR = 1.32 per 1-SD; 95% CI: 1.06–1.64) and decreased body mass index (HR = 0.60 per 1-SD; 95% CI: 0.44–0.83) could significantly predict all-cause mortality in women.
Conclusions: Even in the last stage of lifespan, risk factors for all-cause death still differ significantly in men and women with cardiovascular disease.

1. Introduction

Many studies have indicated that, although men and women share the similar cardiovascular (CV) risk factors, but the two genders differ in the outcome of cardiovascular diseases (CVD), such as coronary heart disease [1,2], heart failure [3–5], stroke [6], and even congenital heart disease [7]. For instance, it has been frequently reported that, men suffer more from coronary heart disease and heart failure [1–5], whereas women are more vulnerable to hypertension and diabetes [8,9]. These findings indicated that CV risk factors would probably have a different impact on CV events and mortality in men and women.

Furthermore, CVD in women evolves about 10 years later than men, but after menopause, the prevalence and mortality of CVD in women increased progressively with age [10], which was probably attributable to the loss of protective effect of ovarian hormones in women's postmenopause [11–13]. It, however, remains unclear whether this menopause-associated modification in women, perhaps lasting for many years, would eventually result in an equivalent prognosis of those CV risk factors in men and women in their last stage of lifespan.

In addition to conventional CV risk factors, certain clinical measurements of CV structure and function are recognized CV risk factors, and can be presently evaluated reliably and conveniently in routine clinical practice. The objective of the present study was to investigate the prognostic value of the newer measurements of CV structure and function in comparison with conventional CV risk factors in high-risk men and women, separately, in the oldest-of-old population of the PROTEGER study.

2. Materials and methods

2.1. Study cohort

From May 2000 to November 2001, 331 consecutive patients hospitalized in the Geriatric Departments of Charles Foix and Emile Roux Hospitals (Ile de France), for

☆ Role of the funding source: This work was supported by the Société Française d'Hypertension Artérielle and the Fondation de France, France.

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doi:10.1016/j.ijcard.2011.09.073

either CV cause or non-CV cause, were included in the PRonostic cardiovasculaire et Optimisation Therapeutique En GERiatrie (PROTEGER) Study, if they met all the following inclusion criteria: 1) age>70 years old; 2) a history of CV disease involving either coronary heart disease, cerebrovascular disease, hypertension or any other CV events of the upper or lower limbs, thoracic or abdominal aorta, or renal arteries; 3) Mini Mental Status Examination>15/30; 4) absence of fatal disease with life expectancy<1 month; and 5) willingness to give a written informed consent to participate in this study. Patients with cachexia (BMI<17 kg/m2) and/or evolutive cancer and/or chronic renal disease were excluded from the study.

The study cohort was composed of 331 subjects (86 men and 245 women) with mean age ± standard deviation (SD) of 86.8 ± 6.9 years, ranged from 72 to 104 years. The PROTEGER study was approved by the Committee for the Protection of Human Subjects in Biomedical Research of Saint Germain Hospital. Written informed consent was obtained from all participants after relevant information was provided to themselves and to their relatives. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [14].

2.2. Social, clinical and biological parameters

Information obtained from the questionnaire filled out at inclusion contained gender, age, body weight, body height, the presence of hypertension, coronary heart disease, heat failure, diabetes mellitus and dyslipidemia, smoking habits and previous CV medication. In all cases, such information was in line with that given by relatives and/or recorded from the most recent previous hospitalization.

Venous blood sample was obtained in subjects after an overnight fast. Total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured by standard methods, and low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. Fasting plasma glucose was assayed by the glucose-oxidase method.

2.3. Measurement of blood pressure and pulse wave velocity

Blood pressure was measured in the morning with each patient in the supine position. Brachial blood pressure was measured after rest using the semi-automatic oscillometric device Dinamap (Kontron, Paris, France). Five measurements with 2 min apart were averaged.

Aortic pulse wave velocity (PWV) was measured using Complior system (Colson, France) with the foot-to-foot method as previously described [15]. The superficial distance covered by the pulse wave was measured directly from the carotid to the femoral artery.

2.4. Electrocardiography

A 12-lead resting electrocardiogram was recorded in the supine position in accordance with classical recommendations [16], and arrhythmia was defined by an experienced cardiologist, as non-sinus cardiac rhythm, including atrial fibrillation (85.0%; 57/67), atrial flutter (4.5%; 3/67) and other supra-ventricular arrhythmia (10.5%; 7/67).

2.5. Ultrasonography

The common carotid intima-media thickness (IMT) was measured by an ultrasound system Sigma 440 (Kontron, Paris, France) with a 7.5-MHz transducer. Measurements were taken on the left common carotid artery, within 2 cm from the bifurcation, and always performed on plaque-free arterial segments. IMT was automatically determined from changes of density on the section perpendicular to the vessel wall using specific software [17,18]. Data on reproducibility have been previously published [18].

M-mode and 2-dimensional echocardiography were performed with the same device as the IMT measurement, using a 2.5-MHz transducer, according to the guideline of the American Society of Echocardiography (ASE) [19]. Left atrial dimension (LAD) was measured by M-mode echocardiography from the parasternal view, according to ASE recommendation [19]. Left ventricular end-diastolic diameter, interventricular septal and posterior wall thickness were measured by M-mode or 2-dimensional echocardiography from the parasternal view as recommended by ASE [19], and they were used to calculate left ventricular mass (LVM) with Devereux formula [20]. Left ventricular ejection fraction (LVEF) was evaluated by M-mode echocardiography using the Teicholz formula [21]. The deceleration time of the transmitral early diastolic flow (DTE) was detected by 2-dimensional Doppler echocardiography according to ASE recommendation [22]. All the ultrasonographic measurements were performed by a single experienced sonographer, who was blinded to all clinical details.

2.6. Follow-up procedures

Follow-up started from the baseline examination of each individual to April 2004. Of all 331 participants in the present study, 3 (1%) were lost to follow-up. Information was obtained from the patient himself, from relatives, or from general practitioners. Interim telephone and clinic contacts were used to assess all of the hospitalizations, outpatient CV diagnosis, and overall mortality. Fatal and nonfatal CV events and CV and all-cause and CV mortality were reported. Follow-up time was defined by the time from the baseline visit until the first event date (for those who had an event) or was censored at the last contact date (for those who did not have any event). Since some patients had multiple CV and non-CV complications, at the end of the study, it was extremely difficult to distinguish the CV from non-CV deaths in most cases. Thus, only all-cause mortality was taken into account in the multivariate Cox regression analyses. After a mean follow-up of 378 days, 110 deaths occurred.

2.7. Statistical analysis

Quantitative and qualitative variables were presented as mean ± standard deviation (SD) and numbers with percentage in parenthesis, respectively. Social, clinical and biological parameters, as well as CV and all-cause mortality, were compared between men and women, by student's t test for quantitative variables and by chi-squared test for qualitative variables. The similar comparisons of CV structural and functional measurements were conducted between the survivors and non-survivors in men and women, separately. We also performed the multivariable Cox regression to investigate the association of CV structure and function with all-cause mortality in men and women, separately. Statistical analysis was performed using SAS software, version 9.1 (SAS institute, Cary, USA). $p<0.05$ was considered statistically significant.

3. Results

3.1. Participants

Comparisons of characteristics between men and women were showed in Table 1, including conventional CV risk factors, CV and metabolic disorders, CV agents, and CV and all-cause mortality. Men, compared to women, had significantly higher prevalence of atrial fibrillation (25.6% vs 15.4%, $p=0.04$), and more frequently reported smoking (75.3% vs 9.4%, $p<0.001$) and antidiabetic treatment (20.9% vs 11.8%, $p=0.04$). Women, in contrast, were significantly older

Table 1
Characteristics of patients by gender.

	Overall (n=331)	Men (n=86)	Women (n=245)	p
Conventional cardiovascular risk factors				
Age, years	86.8 ± 6.9	83.4 ± 6.9	88.0 ± 6.5	<0.001
Body mass index, kg/m^2	27.2 ± 5.7	26.3 ± 4.2	27.6 ± 6.1	0.03
Smoking, n (%)	87 (26.4)	64 (75.3)	23 (9.4)	<0.001
Systolic BP, mm Hg	131.7 ± 20.8	129.4 ± 20.2	132.5 ± 20.9	0.25
Diastolic BP, mm Hg	65.3 ± 11.6	67.3 ± 13.3	64.6 ± 10.9	0.10
Glucose, mmol/L	5.94 ± 2.31	6.31 ± 3.05	5.81 ± 1.99	0.17
Total cholesterol, mmol/L	5.27 ± 1.20	4.80 ± 1.18	5.44 ± 1.16	<0.001
HDL, mmol/L	1.11 ± 0.31	1.02 ± 0.30	1.15 ± 0.31	0.002
LDL, mmol/L	3.42 ± 1.00	3.14 ± 1.02	3.53 ± 0.97	0.002
Triglyceride, mmol/L	1.57 ± 0.89	1.37 ± 0.62	1.64 ± 0.95	0.004
Cardiovascular and metabolic disorders				
Hypertension, n (%)	249 (75.2)	54 (62.8)	195 (79.6)	0.002
CHD, n (%)	109 (33.0)	32 (37.2)	77 (31.6)	0.34
Heart failure, n (%)	73 (22.2)	18 (21.2)	55 (22.5)	0.79
Atrial fibrillation, n (%)	57 (17.2)	21 (25.6)	36 (15.4)	0.04
Diabetes, n (%)	69 (20.9)	24 (27.9)	45 (18.4)	0.06
Dyslipidemia, n (%)	57 (17.3)	19 (22.4)	38 (15.6)	0.16
Cardiovascular agents				
ACEI/ARB, n (%)	98 (29.6)	23 (26.7)	75 (30.6)	0.50
β-Blocker, n (%)	41 (12.4)	14 (16.3)	27 (11.0)	0.20
CCB, n (%)	90 (27.2)	22 (25.6)	68 (27.8)	0.70
Diuretics, n (%)	126 (38.0)	28 (32.6)	98 (40.0)	0.22
Antidiabetics, n (%)	47 (14.2)	18 (20.9)	29 (11.8)	0.04
Hypolipidemics, n (%)	10 (3.0)	4 (4.7)	6 (2.5)	0.30
Outcomes				
CV mortality, n (%)	35 (10.6)	10 (11.6)	25 (10.2)	0.71
All-cause mortality, n (%)	110 (33.2)	31 (36.1)	79 (32.2)	0.52

Data are mean ± standard deviation or numbers with percentages in parenthesis. BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; CHD = coronary heart disease; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CV = cardiovascular. Cardiovascular disorders and therapies were defined by reviewing patients' medical documents.

Table 2
Comparisons of cardiovascular structural and functional measurements between the survivors and non-survivors in men and women.

	Men (n = 86)			Women (n = 245)		
	Survivors (n = 55)	Non-survivors (n = 31)	*p*	Survivors (n = 166)	Non-survivors(n = 79)	*p*
Arterial measurements:						
Intima-media thickness, μm	843.4 ± 117.2	843.4 ± 131.7	0.99	834.2 ± 114.0	799.8 ± 104.2	0.04
Pulse pressure, mm Hg	61.4 ± 17.0	63.5 ± 16.4	0.59	67.9 ± 15.7	67.8 ± 15.8	0.94
Pulse wave velocity, m/s	15.0 ± 3.7	15.2 ± 4.0	0.78	13.9 ± 3.5	14.8 ± 3.7	0.11
Cardiac measurements:						
Left atrial dimension, mm	40.6 ± 8.1	45.1 ± 5.9	0.01	40.4 ± 8.3	43.6 ± 7.7	0.004
Left ventricular mass, g	217.0 ± 69.5	222.9 ± 72.3	0.73	173.2 ± 64.2	176.6 ± 63.3	0.70
Arrhythmia, n (%)	14 (26.9)	12 (40.0)	0.22	17 (10.8)	24 (31.4)	<0.001
Deceleration time of the E wave, ms	198.0 ± 69.6	217.7 ± 75.0	0.22	209.1 ± 64.5	205.1 ± 75.5	0.67
Left ventricular ejection fraction, %	57.1 ± 11.7	49.8 ± 15.4	0.03	64.1 ± 10.5	60.2 ± 12.1	0.02

Data are mean ± standard deviation or numbers with percentages in parenthesis. Arrhythmia was defined as non-sinus rhythm, including atrial fibrillation, atrial flutter and other supra-ventricular arrhythmia. Deceleration time of E wave indicates deceleration time of transmitral early diastolic flow.

(88.0 ± 6.5 years vs 83.4 ± 6.9 years, $p<0.001$), had higher prevalence of hypertension (79.6% vs 62.8%, $p=0.002$), and higher levels of all forms of plasma cholesterol than men ($p\leq0.004$). Of note, neither CV nor all-cause mortality was significantly different between men and women ($p=0.71$ and $p=0.52$, respectively).

3.2. Comparisons of CV structure and function between the survivors and non-survivors

In Table 2, in both men and women, non-survivors consistently had greater LAD (45.1 ± 5.9 mm vs 40.6 ± 8.4 mm, $p=0.01$ in men; 43.6 ± 7.7 mm vs 40.4 ± 8.3 mm, $p=0.004$ in women) and lower LVEF (49.8 ± 15.4% vs 57.1 ± 11.7%, $p=0.03$ in men; 60.2 ± 12.1% vs 64.1 ± 10.5%, $p=0.02$ in women), as compared to the survivors. Besides, in women, non-survivors had significantly higher prevalence of arrhythmia (31.4% vs 10.8%, $P<0.001$) and slightly but significantly lower IMT (799.8 ± 104.2 μm vs 834.2 ± 114.0 μm, $p=0.04$) than the survivors.

3.3. Prognostic significance of conventional CV risk factors and CV structural and functional measurements

As shown in Fig. 1, all CV structural and functional measurements, including carotid IMT, pulse pressure, aortic PWV, LAD, the presence of arrhythmia, LVM, DTE and LVEF, were put in the multivariate Cox regression model to predict all-cause mortality, in men and women, separately. In men, significant predictors of overall mortality were increased LAD (hazard ratio [HR] = 2.24 per 1-SD; 95% confidential interval [CI]: 1.23–4.09) and reduced LVEF (HR = 0.60 per 1-SD; 95% CI: 0.38–0.96). In women, the only significant predictor was the presence of arrhythmia (HR = 2.47 presence vs absence; 95% CI: 1.28–4.78). Reduced LVEF could also predict women's all-cause mortality, but with a marginal p value ($p=0.052$).

In Table 3, the final multivariate Cox regression models were applied to predict all-cause mortality in men and women, separately, taking both the above-mentioned CV structural and functional measurements and conventional CV risk factors (age, body mass index, smoke, total-to-HDL cholesterol ratio, and plasma glucose) into account. In men, increased LAD and reduced LVEF remained as significant predictors in the model, with HR = 2.30 (95% CI: 1.15–4.60) and HR = 0.58 (95% CI: 0.36–0.94), respectively. The third independent predictor in men was increased total-to-HDL cholesterol ratio (HR = 1.99 per 1-SD; 95% CI: 1.05–3.78). In women, the presence of arrhythmias was retained in the all-cause death prediction model, with HR = 3.05 (95% CI: 1.57–5.95). In addition, decreased BMI (HR = 0.60 per 1-SD; 95% CI: 0.44–0.83) and increased plasma glucose (HR = 1.32 per 1-SD;

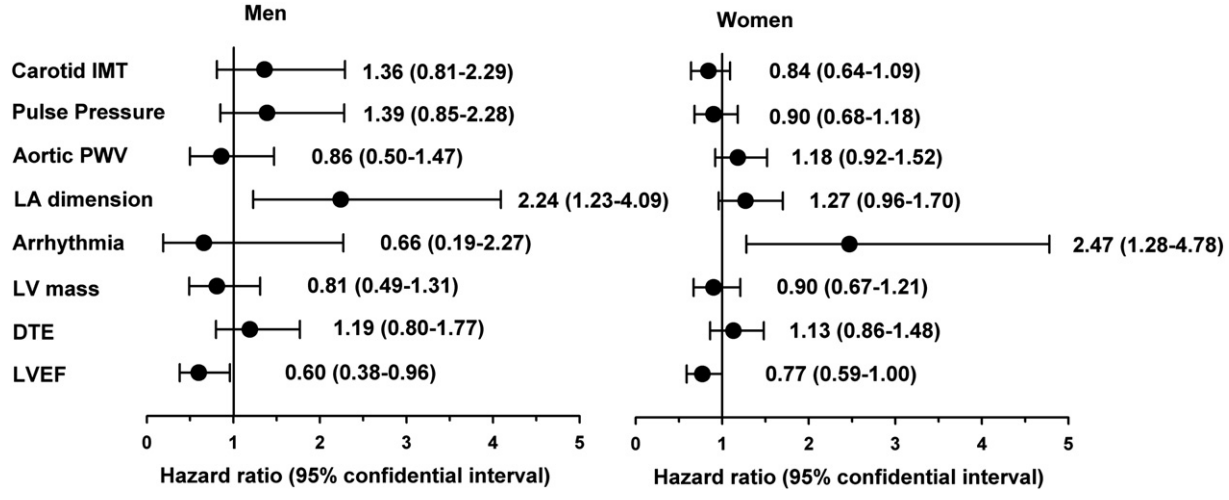

Fig. 1. Association of all-cause mortality with cardiovascular structural and functional measurements by Cox regression models in men and women. The multivariate Cox regressions are conducted in men (left) and women (right), separately, with all the cardiovascular structural and functional measurements considered in each model. Hazard ratio and 95% confidential interval are present on the right side of each plot. Hazard ratio is calculated per SD unit in quantitative variables and the presence against absence in qualitative variables. Arrhythmia is defined as non-sinus rhythm, including atrial fibrillation, atrial flutter and other supra-ventricular arrhythmia. IMT = intima-media thickness; PWV = pulse wave velocity; LA = left atrial; LV = left ventricular; DTE = deceleration time of transmitral early diastolic flow; LVEF = left ventricular ejection fraction.

Table 3
Associations of all-cause mortality with CV structural and functional measurements and conventional CV risk factors in men and women.

	HR	95% CI	*p*
Men (n = 86)			
Left atrial diameter, mm	2.30	1.15–4.60	0.02
Left ventricular ejection fraction,%	0.58	0.36–0.94	0.03
Total/HDL cholesterol	1.99	1.05–3.78	0.04
Women (n = 245)			
Arrhythmia, (1 = presence, 0 = absence)	3.05	1.57–5.95	0.001
Body mass index, g/m^2	0.60	0.44–0.83	0.002
Plasma glucose, mmol/L	1.32	1.06–1.64	0.01

The multivariate Cox regression models were conducted in men and women, separately, with full adjustment for CV structural and functional measurements (intima-media thickness, pulse pressure, pulse wave velocity, left atrial dimension, the presence of arrhythmia, deceleration time of E wave, and left ventricular ejection fraction) and CV risk factors (age, body mass index, smoke, total to HDL cholesterol ratio, and plasma glucose). HR is calculated per SD in quantitative variables and the presence against absence in qualitative variables. Arrhythmia was defined as non-sinus rhythm, including atrial fibrillation, atrial flutter and other supra-ventricular arrhythmia. CV = cardiovascular; HR = hazard ratio; CI = confidential interval; HDL = high-density lipoprotein.

95% CI: 1.06–1.64) could also significantly predict all-cause mortality in women.

4. Discussion

The present study contains two major findings: 1) gender difference still existed in the very elderly in terms of prognostic value of CV structural and functional parameters. Specifically, left ventricular systolic dysfunction and left atrial enlargement could significantly predict all-cause mortality in men, while the presence of arrhythmia was the most pronounced predictor in women; and 2) besides CV structural and functional parameters, dyslipoproteinemia was a significant and independent predictor of all-cause death in men but not in women. In contrast, in women, hyperglycemia and malnutrition appeared to be significant predictors for all-cause death, in the last stage of lifespan.

4.1. Gender difference in prognosis of CV risk factors

In literature, many studies were aimed to investigate the gender difference in prognosis of CV risk factors in the middle-age population, and most of their findings are in line with what we found in the very elderly, which indicates the differences between genders, to some extent, remained unaltered till the last stage of lifespan. For CV structure and function, it was frequently reported that, as compared to women, men were more vulnerable to coronary heart disease and heart failure with systolic dysfunction [3–5]. From a pathophysiological point of view, left atrial volume can be influenced by either pressure overload or volume overload, so the observed significant predictive value of left atrial enlargement in men can therefore be attributable to their more pronounced systolic dysfunction. On the other hand, it was reported that, women with atrial fibrillation had a poorer prognosis than men, because of the higher thromboembolic events [23]. For biochemical measurements, some investigators indicated that diabetes mellitus was more harmful in women than in men [8,24], and others documented that, although dyslipoproteinemia could predict fatal CV events in both men and women, its prognostic significance in women was largely attenuated with age [25]. It is interesting that, physical exercise, but not BMI, was frequently reported as a strong predictor of CV events and mortality in the middle-age women [26, 27], whereas we observed that the decreased BMI was an independent and significant predictor of all-cause mortality in the very elderly women. The discrepancy in findings just highlighted the importance of nutritional condition in women's prognosis in the last stage of lifespan.

4.2. Explanation of gender difference in prognosis of CV risk factors

Gender difference in prognosis of CV risk factors was considered to be attributable mostly to the hormone effect, more specifically, to the direct and indirect protective effect of estrogen on the CV physiology [11–13]. Nevertheless, we found in the present study that gender difference remains stable in the very elderly. Of note, only very limited modification in prognosis of CV risk factors was achieved in women about 20–30 years after the initiation of their estrogen withdraw. Furthermore, some clinical trials, specifically conducted in the post-menopause women, like HERS [28,29] and WHI studies [30], also failed to provide any favorable effect of estrogen replacement therapy in terms of CVD prevention. All these findings indicated that, hormone discrepancy between genders, or effect of estrogen in women, was only one potential explanation of gender difference in prognosis of CV risk factors. Other mechanism still existed to account for the observed gender difference, and further studies were apparently warranted.

4.3. Considerations on this population

The population of the present study had many particularities. First, this population was extremely old, with 80 subjects under 80 years and 131 subjects over 90 years. Second, all these participants, enrolled from two geriatric departments, had a high prevalence of CV disease (coronary, cerebral and peripheral vascular disease). Third, a very high one-year mortality rate (33%) was observed in the present study. To sum up, those characteristics indicated that this population was mainly composed of "survivors" from "physiological" CV aging. Although this is a very elderly population with a high CV risk, given ever-growing elderly population and increasing burden of CV diseases, our study is of importance in regard of the general elderly population.

4.4. Limitations

Findings of the present study need to be carefully interpreted within the context of its limitation. In addition to the limited generality mentioned above, we also noted that, the sample size of men in this population is relatively small (n = 86). However, it is common to have more women in such a geriatric population because of the longer life expectancy in women. Moreover, with a high mortality in men (death = 31, mortality = 36.0%), we had sufficient statistic power.

4.5. Conclusion

In conclusion, gender difference in prognostic significance of CV structural and functional parameters and conventional CV frisk factors still exists in the last stage of lifespan. Specifically, men, compared with women, suffer more from left ventricular systolic dysfunction and dyslipoproteinemia, whereas women are more vulnerable to arrhythmia, hyperglycemia and malnutrition.

Acknowledgment

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [31].

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