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Predictors of major adverse cardiovascular events; results of population based MELEN study with prospective follow-up

S. ALBAYRAK, H. OZHAN, Y. ASLANTAS, I. EKINOZU, H. TIBILLI, O. KAYAPINAR; FOR THE MELEN STUDY INVESTIGATORS

Department of Cardiology, Düzce University, Faculty of Medicine, Duzce, Turkey

Abstract. – OBJECTIVE: In healthy persons, cardiovascular risk is the result of multiple interacting risk associates including demographic, clinical, genetic and environmental factors. Several non-invasive tools such as echocardiography, ultrasonography and electrocardiography as well as new biochemical markers were shown to be applicable to predict cardiovascular events. However, implementation of all of these tools has not been tested before. The aim of the study was to evaluate the independent predictors of major adverse cardiovascular events in a prospective population based study, with the use of bioempedance analysis, echocardiography, ultrasonography and ECG.

PATIENTS AND METHODS: The baseline measurements were conducted on 2230 participants (1427 women, 803 men with a mean age of 49±15). The follow-up was done 36 months after the baseline admission via telephone call. Major adverse event was defined as mortality or myocardial infarction or stroke.

RESULTS: Follow-up data was possible in 1495 participants (65%). During the follow-up of 36 months (4485 patient years), 42 major adverse events occurred (0.03%). Among them, 16 were death (1 stroke, 2 cancer, 13 cardiac related), 12 were stroke and 14 were myocardial infarction. Age, body mass index and atrial fibrillation were independent predictors of major adverse events; AF being the most powerful (Odds ratio 10.46; 95% confidence interval [1.73-63.14]; $p = 0.010$).

CONCLUSIONS: Age, lower body mass index and atrial fibrillation were independent predictors of major cardiovascular events in our cohort.

Key Words:
Cardiovascular event, Predictor, Atrial fibrillation.

Introduction

Cardiovascular events including myocardial infarction and stroke are the leading causes of death worldwide. In apparently healthy persons, cardiovascular risk is most frequently the result of multiple interacting risk factors[1]. Overall risk is affected by demographic, clinical, genetic and environmental factors. Evaluation of risk factors in different ethnic and social groups is essential to understand the variety of independent predictors of mortality and morbidity, as well as to optimally target preventive responses in that specific population. There are numerous multivariable risk prediction tools that synthesize vascular risk factor information to estimate absolute CVD risk in individual patients. Newer risk factors of atherosclerosis and various noninvasive tests of subclinical cardiovascular occlusive disease urge clinicians to improve and refine the risk assessment processes in specific ethnic populations.

Although major risk factors for developing cardiovascular disease were widely established there are various minor contributors. It is clear that, different combinations of risk factors may interact in complex ways that are difficult to model. Furthermore, new non-invasive tools such as echocardiography, ultrasonography and electrocardiography as well as new biochemical markers were shown to be applicable to predict cardiovascular events[2-7]. However, implementation of all of these tools has not been tested before, in a population based cohort.

The aim of the study was to evaluate the predictors of major adverse cardiovascular events in a prospective population based study, with the use of bioempedance analysis (visceral fat and muscle level measurement), echocardiography (left ventricular mass, ejection fraction and heart chamber dimension measurements, ultrasonography (carotid intima media thickness (CIMT) measurement) and electrocardiography (ECG; heart rate, rhythm, PR and QT wave measurements).

Corresponding Author: Hakan Ozhan, MD; e-mail: ozhanhakan@yahoo.com

Patients and Methods

Patients

The result of this report is part of the prospective MELEN study. Aim, patient selection, methods and definition of the MELEN study was described in detail[8]. Body weight categories were defined according to the World Health Organization body mass index (BMI) criteria as follows: BMI < 18.5 lean, 18.5-24.9 normal, 25-29.9 overweight, ≥ 30 obese and ≥ 40 morbidly obese. The aim of the Melen Study was to investigate the cardiovascular risk profile of Turkish adults by utilizing newest techniques. The baseline measurements were conducted on 2230 participants (1427 women, 803 men with a mean age of 49). The study protocol was approved by the Ethics Committee of Duzce University and every subject signed a consent form. The participants underwent a Doppler Ultrasound examination of carotid intima media thickness, echocardiographic examination, ECG recording, bioempedance meter analysis of body composition and several biochemical analysis.

Follow-up

The follow-up was done 36 months after the baseline admission via telephone call. The participants were asked whether they had myocardial infarction or stroke during the follow-up period. Mortality data was gathered from first degree relatives. Questions related with in-hospital death with a *medical diagnosis*, sudden death possibly due to cardiovascular origin and other causes such as accidents. Major adverse event (MAE) was defined as mortality or myocardial infarction or stroke.

Statistical Analysis

Statistical Package for Social Sciences software (SPSS 12, Chicago, IL, USA) was used for analysis. Descriptive parameters were shown as mean ± standard deviation or in percentages. Two-sided *t*-tests and Pearson's chi-square tests were used to analyze the differences in means and proportions between groups. Kolmogorov-Smirnov test was applied to test for a normal distribution. Abnormally distributed variables were compared using Mann-Whitney U test. Logistic regression analysis was used to determine the independent predictors of MAE. A p value of < 0.05 was considered significant.

Results

Mean age at entry was 50 ± 15 years (mean ± SD). Follow-up data was possible in 1495 participants (65%). During the follow-up of 36 months (4485 patient years), 42 MAE occurred. Among them, 16 were death (1 stroke, 2 cancer, 13 cardiac related), 12 were stroke and 14 were myocardial infarction. Comparison of subjects with and without MAE was shown in Table I. The participants who had MAE were older, had significantly lower body mass index and the frequency of hypertension, coronary artery disease or chronic obstructive pulmonary disease was higher in these subjects. Comparison of variables measured with ECG, echocardiography, ultrasonography and bioempedance analysis showed that participants who had MAE had significantly higher PR and corrected QT wave durations, EF, left ventricular mass, left atrial diameter and cor-

Table I. Comparison of demographic and clinical characteristics of subjects with and without major adverse events.

	MAE (n = 42)	No MAE (n = 1453)	*p* value
Age, years	66 ± 15	48 ± 15	< 0.001
Sex, female (%)	22 (52%)	903 (62%)	0.199
Marital status, married (%)	35 (83%)	1251 (86%)	0.569
Smoker, (%)	3 (7%)	263 (18%)	0.068
Hypertension, (%)	27 (64%)	567 (39%)	0.001
DM, (%)	16 (38%)	511 (35%)	0.700
Coronary artery disease, (%)	11 (26%)	80 (6%)	< 0.001
COPD	8 (20%)	102 (8%)	0.005
BMI, kg/m^2	27 ± 4	29 ± 6	0.010
Waist circumference, cm	92 ± 11	94 ± 14	0.305
Systolic blood pressure, mmHg	137 ± 28	125 ± 24	< 0.001
Diastolic blood pressure, mmHg	81 ± 17	78 ± 13	< 0.001

MAE: major adverse events; COPD: Chronic obstructive pulmonary disease.

Table II. Comparison of variables measured with ECG, echocardiography, ultrasonography and bioempedance analysis among subjects with and without major adverse events (MAE).

	MAE (n = 42)	No MAE (n = 1453)	*p* value
Heart rate; bpm	76 ± 14	73 ± 12	0.056
PR wave duration; ms	162 ± 25	153 ± 26	0.045
Corrected QT wave duration; ms	410 ± 27	402 ± 25	0.030
Atrial fibrillation; (%)	7 (17%)	14 (1%)	< 0.001
Ejection fraction, %	59 ± 11	64 ± 6	< 0.001
Left ventricular mass; gr	265 ± 80	209 ± 62	< 0.001
LA diameter; mm	37 ± 6	33 ± 4	< 0.001
Diastolic dysfunction; (%)	25 (66%)	526 (37%)	< 0.001
CIMTc; mm	0.83 ± 0.45	0.59 ± 0.17	< 0.001
Total skeletal mass (%)	31 ± 5	29 ± 6	0.160
Total body fat (%)	29 ± 10	34 ± 1 1	0.008
Goiter	12 (29%)	415 (29%)	0.970

MAE: major adverse events.

rected carotid intima media thickness where as mean body fat was significantly lower (Table II). Atrial fibrillation and diastolic dysfunction were also more frequent in participants with MAE. Among biochemical variables only creatinine significantly differed (Table III). Logistic regression analyses disclosed that age, body mass index and atrial fibrillation were independent predictors of MAE; AF being the most powerful (Odds ratio 10.46; 95% confidence interval [1.73-63.14]; $p = 0.010$) (Table IV). Lower family income, waist circumference and waist to height ratio in these participants showed that low BMI might be associated with malnutrition in our cohort.

Discussion

The present study showed that higher age, lower body mass index and atrial fibrillation were independent predictors of major cardiovascular events in our cohort. Frequency of hypertension, chronic obstructive pulmonary disease, coronary artery disease, carotid intima media thickness, left ventricular mass, corrected QT wave duration, creatinine, body fat and ejection fraction differed significantly among subjects with MAE; however, lost independence in multivariate logistic regression.

The dynamics of cardiovascular events and mortality vary greatly in pattern, magnitude and

Table III. Comparison of biochemical variables of subjects with and without major adverse events (MAE).

	MAE (n = 42)	No MAE (n = 1453)	*p* value
Hemoglobin, g/dl	12.8 ± 1.5	13.1 ± 1.6	0.153
Neutrophyl/ Lymphocyte ratio	1.8 ± 0.8	1.8 ± 1.5	0.856
Mean platelet volume	8.8 ± 1.0	8.8 ± 1.4	0.857
Total cholesterol, mg/dl	171 ± 40	180 ± 39	0.155
HDL cholesterol, mg/dl	44 ± 12	44 ± 11	0.755
Triglycerides, mg/dl	144 ± 76	175 ± 115	0.095
LDL-C, mg/dl	99 ± 30	103 ± 33	0.508
Creatinine, mg/dl	0.88 ± 0.17	0.80 ± 0.21	0.029
ALT, mg/dl	13 ± 5	17 ± 5	0.616
AST, mg/dl	22 ± 9	21 ± 8	0.505
High sensitive CRP, mg/dl	2.1 ± 1.9	2.0 ± 2.1	0.819
Glucose, mg/dl	112 ± 26	115 ± 48	0.702
HOMA	3.5 ± 2.9	2.9 ± 2.3	0.572
Metabolic syndrome, (%)	9 (21%)	405 (29%)	0.293

MAE: major adverse events.

Table IV. Logistic regression for prediction of major adverse events (MAE).

	OR	95% CI	*p* value
Age	1.05	1.01-1.09	0.009
Hypertension	1.23	0.48-3.16	0.673
Coronary artery disease	3.06	0.98-9.56	0.054
COPD	1.68	0.56-5.05	0.352
Body mass index	0.89	0.82-0.97	0.007
Corrected CIMT	4.28	0.86-21.38	0.076
Ejection fraction	1.01	0.95-1.07	0.805
Diastolic dysfunction	1.89	0.76-4.72	0.172
Corrected QT wave duration	1.01	0.98-1.02	0.919
Atrial fibrillation	10.46	1.73-63.14	0.010
Creatinine	0.79	0.14-4.31	0.790

timing in different parts of the world. Although different non-invasive tools were introduced for better prediction of hard end-points, their applicability in a simultaneous multi-scan fashion is still unknown. Therefore, the aim of the current study should be interpreted as an important goal in cardiovascular disease epidemics.

The most important finding of the current study is the determination of AF as the most powerful predictor of MAE. Atrial fibrillation increases the risk of embolic stroke, cardiovascular mortality and the occurrence increases with age, hypertension, heart failure, coronary artery disease, obesity and chronic obstructive pulmonary disease[9,10]. In other words, AF stays in the intersection of risks and end-points related with cardiovascular events. Therefore, it is not surprising to detect it as the most important predictor of MAE, taking into account that it is poorly maintained and proper anticoagulation is defective in our country[11]. Age, on the other hand is the most important well known risk factor of MAE in both genders[12].

Another important finding of the current study is the independent contribution of body mass index to MAE. In a large prospective study, body weight and mortality were directly related, although the relation lost significance after accounting for confounding by cigarette smoking and bias resulting from illness-related weight loss[13]. Association between mortality and body mass index is U-shaped making malnutrition and obesity important mortality contributors. Adjustment for smoking and the exclusion of subjects with preexisting and subclinical disease did not alter the association in properly designed prospective studies[14]. Low body weight is also a well known risk factor of mortality in patients with heart failure[15]. In our cohort, subjects who had MAE had 2 points lower body mass index than their healthy counterparts. Logistic regression analysis also revealed an inverse relation with BMI and MAE, every point increase in BMI involving 11% risk reductions. This is contradictory with what reported in the general literature unless we do not consider malnutrition as a cause of lower BMI. Therefore, we further analyzed association of family income with BMI. The participants who had MAE during follow-up had significantly lower income (606 ± 303 vs 833 ± 658 lira per month; $p = 0.03$). Furthermore, waist circumference and waist to height ratio were lower in these subjects but did not reach significance (91 ± 11 vs 94 ± 14 cm; $p = 0.845$ and 0.58 ± 0.08 vs 0.59 ± 0.9; $p = 0.305$; respectively). Therefore, low BMI might be associated with malnutrition in our cohort, which is a well known risk of mortality. On the other hand, lower body weight might promote chronic diseases and become an independent predictor of MAE.

In our study, carotid intima media thickness, chronic obstructive pulmonary disease, established coronary artery disease, hypertension, ejection fraction, diastolic dysfunction and creatinine level lost their significance in the logistic regression analysis. Of these, carotid intima media thickness had the greatest Odds ratio (4.28; 95% confidence interval 0.86-21.38; $p = 0.0763$). A meta-analysis showed that carotid intima media thickness is a strong predictor of future vascular events; with the relative risk per 0.1 mm carotid intima media thickness difference is 18% higher for stroke and 15% higher for myocardial infarction[16]. Carotid intima media thickness is associated with vascular risk factors and it is particularly useful as an end point in young populations[16]. The results of MESA Study (Multi-Eth-

nic Study of Atherosclerosis) showed that at 7.8-year mean follow-up carotid intima media thickness significantly predicted adverse cardiovascular events when added to Framingham risk score[17]. It is likely that our follow-up time is not sufficient enough to see the absolute effect of carotid thickening on adverse events.

Resting heart rate was shown to be a predictor of adverse events. A recent study conducted on 5,713 men without known or suspected cardiovascular disease who had been followed up for a mean of 23 years, showed that all-cause mortality, sudden cardiovascular death and myocardial infarction increased progressively with resting heart rate[18]. Moderate (QTc, 420-440 msec) and extensive (QTc, more than 440 msec) QTc prolongations were also shown to be predictive for all-cause mortality during follow-up[19]. However, we could not confirm an independent association with electrocardiographic variables and cardiovascular risk in our cohort. After adjustment for other potential confounding variables, QTc lost its significance as an independent risk predictor.

The loss of independent collaboration of established diseases such as hypertension, chronic obstructive pulmonary disease and coronary artery disease may be related with their better treatment and follow-up compared to the apparently healthy counterparts.

There are several unexpected findings of the current study. One of them is the loss of significance of echocardiographic variables (ejection fraction and diastolic dysfunction) on MAE. Copenhagen City Heart Study reported that combined diastolic and systolic performance index measured with tissue Doppler was an independent predictor of death[20]. Furthermore, left ventricular systolic dysfunction and left ventricular diastolic dysfunction were independent predictors of a first cardiovascular event in Olmsted County study[21]. We think that body mass index is a more powerful risk contributor in our subjects with heart failure, eliminating contribution of ejection fraction and diastolic filling parameters. Another finding of our study was the ineffectiveness of HsCRP as a risk factor for MAE. Several studies have consistently shown Hs-CRP as a powerful predictor of MAE in apparently healthy men and women[22,23]. Unfortunately, we could not establish such a correlation in our study cohort. Single measurement of Hs CRP at baseline and relatively short follow-up duration may be a possible explanation for this result.

Conclusions

Age, lower body mass index and atrial fibrillation had the most important impact on major cardiovascular events in our cohort. Electrocardiographic and anthropometric measurements were the most important tools of risk assessment. Taking into account that classic risk factors explain only a fraction of the causes of cardiovascular diseases, evaluation of all major prognostic determinants are mandatory in order to implement efficient programs for the prevention and control of cardiovascular events. Patients with atrial fibrillation should also be subjects of careful follow-up and core of nationwide preventive acts.

Declaration of Funding Interests

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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