

Risk Factors, Use of Preventive Drugs, and Cardiovascular Events in Diabetes Mellitus: The PURE Türkiye Cohort

ABSTRACT

Background: The risk of cardiovascular disease is correlated with the frequency and control of associated risk factors in diabetes mellitus and may vary according to country. We evaluated risk factors for cardiovascular disease, cardiovascular events, and the use of preventive medications in patients with diabetes mellitus using the Prospective Urban and Rural Epidemiological Türkiye cohort.

Methods: Patients with diabetes mellitus versus without diabetes mellitus were compared for risk factors, cardioprotective drugs (angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists, statins, and antiplatelets), and cardiovascular events. The primary outcome was major cardiovascular events (composite of cardiovascular death, myocardial infarction, stroke, or heart failure).

Results: Among 4041 participants, 549 (13.6%) had diabetes mellitus. The mean age (54.8 ± 8.4 vs. 49.3 ± 9.0 years, $P < .001$) and proportion of women (65.4% vs. 59.9%, $P = .014$) were higher in diabetics compared with non-diabetics. Hypertension, history of coronary heart disease, and use of statin, antiplatelets, and angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists were more common in diabetics; however, the use of these medications at baseline was lower than optimal even in patients with diabetes mellitus and concomitant coronary heart disease (statin 31.2%, antiplatelets 46.9%, and angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists 54.7%). During 11.5 years of follow-up, major cardiovascular events occurred in 288 (7.1%) patients, and the risk was higher in diabetics [hazard ratio (95% confidence interval) 1.71 (1.30-2.24); $P < .001$]. The increase in the risk of future events was comparable for those with diabetes mellitus alone without cardiovascular disease [hazard ratio 1.62 (1.20-2.20)] versus those with cardiovascular disease alone without diabetes mellitus [hazard ratio 1.31 (0.83-2.07)] and was additive in those with both conditions [hazard ratio 2.79 (1.65-4.69)]. The risk of major coronary events (myocardial infarction, angina, percutaneous, or surgical coronary intervention) was also higher in diabetes mellitus [hazard ratio 1.64 (1.26-2.15); $P < .001$].

Conclusion: Patients with diabetes mellitus have a higher risk of major cardiovascular events, and the risk is comparable to that observed in those with cardiovascular disease but no diabetes mellitus. The use of preventive medicines for cardiovascular diseases is disturbingly low in diabetics.

Keywords: Diabetes mellitus, cardiovascular events, medications

INTRODUCTION

Diabetes mellitus (DM) is a strong independent risk factor for atherosclerotic vascular disease, and a dramatic increase in its prevalence has been observed globally.¹⁻³ It is prevalent especially in low- and middle-income countries.⁴ Despite increased awareness and therapeutic interventions, a 5% increase in premature mortality among those with DM was observed between 2000 and 2016, and it is estimated that 1.5 million deaths were directly caused by diabetes in 2019.¹

The Prospective Urban and Rural Epidemiological (PURE) study demonstrated that the high prevalence of DM in lower-income countries could not be explained by conventional risk factors such as the family history of diabetes, body mass index, level of physical activity, and diet.⁴ Also, cardiovascular (CV) and all-cause mortality rates did not change after adjustments for these risk factors in those

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countries.⁵ This suggests that DM is a complex heterogeneous disease and that the CV risk attributed to diabetes may differ for each population.

In this study, we aimed to assess CV events, risk factors, and the use of preventive drugs in DM in Türkiye, which was considered an upper-middle-income country in the PURE study.

METHODS

The PURE study is a multinational study led by McMaster University Population Health Research Institute (PHRI), Hamilton, Canada. The details of the design of the study were published elsewhere.^{6,7} Briefly, the participants were recruited from 27 countries with 4 income levels—low-income, lower-middle income, upper-middle income, and high-income countries—and Türkiye was included among the upper-middle-income countries. The data have hierarchical multilevel properties that include individual, household, community, and country levels. Prospective Urban and Rural Epidemiological Türkiye was conducted by the Metabolic Syndrome Society and approved by the Marmara University Ethics Committee (approval number: MAR-SBY-2005-0183) and the Ministry of Health.

Data Collection and Participants

In 2008, 7 cities (Kocaeli, Aydın, Nevşehir, Antalya, Samsun, Malatya, and Gaziantep) were selected by randomization and by considering the social and financial structure of Türkiye, according to data obtained from the Turkish Statistical Institute. Also, Istanbul was included as the eighth

city. Participation from different geographical areas and income groups was targeted. For each city, information regarding the income and population of the towns and villages was obtained from local authorities, and a list was created. From this list, a town or village was chosen randomly, and selected households were contacted.

In a selected household, participants aged between 35 and 70 years and expected to continue residency there for at least the next 4 years were included in the study. Informed consent was obtained from all of the participants. Interviewers were trained in groups regarding how to obtain data correctly.

Recruitment occurred between 2008 and 2009, and 4056 participants from 2576 households were included in Türkiye. This study includes 4041 (99.6%) of those participants with complete data. Blood pressure was measured, physical measurements were made, an electrocardiogram (ECG) was taken, and 10 mL of a blood sample and a urine sample were obtained from each participant at baseline. Blood and urine samplings were centrifuged and stored at -80°C freezers. Participants were called via telephone each year and asked for a diagnosis of a new disease, health conditions, morbidity, and death in each household from the last visit or interview. Every third year, the follow-up was conducted by a face-to-face visit in the field to obtain the information listed in the questionnaires, physical measurements, ECG, and blood samples.

Definitions of Variables and Outcomes

A diagnosis of DM was made if there was a fasting plasma glucose level of ≥ 7.0 mmol/L (126 mg/dL), or a history of diabetes or use of antidiabetic medications is present.

Two sitting blood pressures were measured in the right arm after at least 5 minutes of rest using Omron digital blood pressure device (Omron HEM-711, Omron Corp, Tokyo, Japan), and the mean of the measurements was used for the analyses. Hypertension was defined if the blood pressure was $\geq 140/90$ mm Hg or the use of antihypertensive medication was present.

Standardized case report forms were used to record the data on major CV events and mortality during follow-up.⁸ These data were adjudicated by trained physicians (A.O. and M.V.K.) using standard definitions, then were electronically transferred to the PHRI, Canada, where further quality controls have been made.

The main outcomes were major CV events, which were the composite of CV death, fatal or non-fatal myocardial infarction (MI), stroke, or heart failure. Other composite outcomes were major events and coronary events. Major events were defined as the composite of all-cause mortality, MI, stroke, and heart failure, and coronary events were defined as the composite of new MI, new angina, percutaneous coronary intervention (PCI), and coronary artery bypass surgery (CABG).

Components of the major CV events and major events were assessed as an exploratory analysis.

HIGHLIGHTS

- As of the inception of the study (2008-2009), the Turkish cohort of the Prospective Urban and Rural Epidemiological study demonstrated that the prevalence of diabetes mellitus is 13.6% in participants aged between 35 and 70, and the use of preventive medications at baseline was lower than optimal even in patients with diabetes mellitus and concomitant coronary heart disease (statin 31.2%, antiplatelets 46.9%, and angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonists 54.7%).
- Diabetes mellitus increases the risk of major cardiovascular outcomes (cardiovascular death, myocardial infarction, stroke, or heart failure) by 1.71 times and coronary events (new myocardial infarction, new angina, percutaneous coronary intervention, and coronary artery bypass surgery) by 1.64 times.
- The increased risk for major cardiovascular outcomes seems to be comparable for patients with diabetes mellitus alone without cardiovascular disease and for those with cardiovascular disease alone without diabetes mellitus at baseline and was additive in those with both conditions.
- It seems that patients with diabetes mellitus present with more myocardial infarction than angina.

Statistical Analysis

Continuous variables were given as mean and standard deviation (SD) or median and interquartile range (IQR) and compared using *t*-test or Mann–Whitney *U* test. Categorical variables were expressed as frequency and percentages and compared using the chi-squared test.

For each outcome, the crude incidence rate was expressed as incidence per 1000 person-years. Kaplan–Meier and Cox proportional hazard regression was applied for the time-to-event data. To account for hierarchical data, a shared frailty model for Cox regression analysis, taking the community level (level 2) as a clustering variable, was used. The exception was the outcome of heart failure, where conventional Cox regression analysis was preferred because the shared frailty model did not converge.

Hazard ratio (HR) and 95% CI were calculated using age- and sex-adjusted models and a fully adjusted model, in which the risks were adjusted for age, sex, low-density lipoprotein (LDL) cholesterol, smoking, hypertension, prior history of coronary heart disease (CHD), statin use, and antiplatelet use. The individual components of the major CV events and major events were adjusted only for age and sex due to a relatively low number of events. For the same reason, unadjusted HRs were also given for heart failure. The proportional hazard assumption was assessed by plotting Schoenfeld residuals. Log-linearity was assessed by plotting Martingale residuals against each covariate.

Analyses were performed using Stata v.17 (StataCorp, Tex, USA), and *P*-value of <.05 was considered significant.

RESULTS

A diagnosis of DM was documented in 549 (13.6%) participants aged between 35 and 70 years at baseline. The mean age (54.8 ± 8.4 vs. 49.3 ± 9.0 years, $P < .001$) and the proportion of women (65.4% vs. 59.9%, $P = .014$) were higher in patients with DM than in non-DM.

Cardiovascular Risk Factors

Most of the CV risk factors were more common in patients with DM at baseline. Specifically, HT (63.8% vs. 35.4%) and history of CHD (11.7% vs. 4.6%) were significantly higher in participants with DM (Table 1). The mean body mass index was 30.4 ± 5.8 kg/m², and the values were higher in participants with DM (32.5 ± 5.7 vs. 30.1 ± 5.7 kg/m², $P < .001$). As expected, waist circumference (98.7 ± 11.3 vs. 92.1 ± 11.9 cm), systolic and diastolic blood pressure (136.9 ± 23.7 vs. 128.1 ± 21.5 , and 82.0 ± 12.1 vs. 79.9 ± 11.8 mm Hg), total cholesterol (5.49 ± 1.17 vs. 5.28 ± 1.12 mmol/L), and triglyceride levels [1.80 (IQR: 1.44; 2.49) vs. 1.52 (1.23; 1.96) mmol/L] were significantly higher, but high-density lipoprotein (HDL) cholesterol (1.11 ± 0.32 vs. 1.18 ± 0.36 mmol/L) was significantly lower in participants with DM (all *P*-values were <.001). On the other hand, there was no significant difference in LDL cholesterol levels between the 2 groups (3.38 ± 1.01 vs. 3.32 ± 0.95 mmol/L in DM vs. non-DM, $P = .199$).

Current or former smoking history was significantly less common in patients with DM compared with non-DM (38.8%

vs. 45.3%, $P = .004$); however, after adjusting for sex and age, the association between DM and smoking status became non-significant ($P = .576$). Although low education level (none or primary school) was slightly higher in patients with DM (80.5% vs. 76.8%), the association between education and DM was not significant ($P = .090$).

Medications at Baseline

Use of statins (15.5% vs. 3.3%), antiplatelets (acetylsalicylic acid or clopidogrel use 14.4% vs. 4.8%), and angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers (ACEI/ARB) (36.8% vs. 10.4%) was significantly higher in participants with DM (all $P < .001$; Table 1). However, the use of these cardioprotective medications, particularly the use of statins and antiplatelets, was lower than acceptable levels. Moreover, in patients with concomitant DM and CHD, the use of cardioprotective medications was far below what would be expected based on the recommendations for widespread use in several guidelines (statin use 31.2%, antiplatelet use 46.9%, and ACEI/ARB use 54.7%) (Table 1).

Among patients with DM, 49.9% were using only oral hypoglycemic medications, 3.3% were using only injectable hypoglycemic medications, and 4.6% were using both oral and injectable hypoglycemic medications. None of the participants with DM were on glucagon-like peptide-1 (GLP-1) receptor agonists or sodium-glucose co-transporter-2 (SGLT-2) inhibitors, as these medications were not available in Türkiye when this study was initiated in 2008.

Cardiovascular Events

During a median follow-up of 11.5 years, major CV events occurred in 288 (71%) patients. The crude incidence rate of major CV events (CV death, fatal or non-fatal MI, stroke, or heart failure) was nearly 3 times higher in participants with DM than in those without DM (Table 2). The risk of major CV events was 2 times and 71% higher in patients with DM in the age- and sex-adjusted and the fully adjusted models, respectively [HR and 95% CI were 2.01 (1.54-2.62), $P < .001$; and 1.71 (1.30-2.24); $P < .001$; Table 2]. As a sensitivity analysis, excluding patients with a prior history of CV disease from the analysis did not change the main findings (Supplementary Table 1). While the CV risk was higher in males than in females [HR 2.06 (1.53-2.76) in the fully-adjusted model, $P < .001$] DM and sex interaction were not significant (P -interaction = .996), suggesting that the risk of major CV events for DM was not modified by sex.

The risk of major CV events for patients with DM or CV disease at baseline is given in Figure 1. The increase in the risk of major CV events was similar in those with DM alone without CVD [HR 1.62 (1.20-2.20)] compared to those with CVD alone without DM [HR 1.31 (0.83-2.07)], *P*-value for the comparison of the 2 groups 0.698 and 0.389 for age and sex-adjusted and fully adjusted models, respectively.

The risk of major events that include the composite of total mortality, MI, stroke, and heart failure was 75% and 57% higher in patients with DM in the age- and sex-adjusted model and in the fully-adjusted model, respectively (Table 2).

Table 1. Baseline Characteristics

	DM (-), n = 3492 (86.4%)	DM (+), n = 549 (13.6%)	Total, n = 4041	P
Sex, n (%)				
Female	2091 (59.9)	359 (65.4)	2450 (60.6)	.014
Male	1401 (40.1)	190 (34.6)	1591 (39.4)	
Age, mean (SD)	49.3 (9.0)	54.8 (8.4)	50.0 (9.1)	<.001
Smoking (current or former), n (%)	1583 (45.3)	213 (38.8)	1796 (44.4)	.004
Hypertension, n (%)	1237 (35.4)	350 (63.8)	1587 (39.3)	<.001
Prior coronary heart disease, n (%)	161 (4.6)	64 (11.7)	225 (5.6)	<.001
Body mass index (kg/m ²), mean (SD)	30.1 (5.7)	32.5 (5.7)	30.4 (5.8)	<.001
Waist circumference (cm), mean (SD)	92.1 (11.9)	98.7 (11.3)	93.0 (12.1)	<.001
Female	90.2 (12.0)	97.9 (11.2)	91.3 (12.2)	<.001
Male	95.1 (11.3)	100 (11.4)	95.7 (11.4)	<.001
Systolic blood pressure (mm Hg), mean (SD)	128.1 (21.5)	136.9 (23.7)	129.3 (22.1)	<.001
Diastolic blood pressure (mm Hg), mean (SD)	79.9 (11.8)	82.0 (12.1)	80.2 (11.8)	<.001
Total cholesterol (mmol/L), mean (SD)	5.28 (1.12)	5.49 (1.17)	5.31 (1.13)	<.001
LDL cholesterol (mmol/L), mean (SD)	3.32 (0.95)	3.38 (1.01)	3.33 (0.96)	.178
HDL cholesterol (mmol/L), mean (SD)	1.18 (0.36)	1.11 (0.32)	1.17 (0.36)	<.001
Triglycerides (mmol/L), median (IQR)	1.52 (1.23; 1.96)	1.80 (1.44; 2.49)	1.56 (1.25; 2.04)	<.001
Education, n (%)				
None, primary	2683 (76.8)	442 (80.5)	3125 (77.3)	.090
Secondary/higher	515 (14.7)	62 (11.3)	577 (14.3)	
University	294 (8.4)	45 (8.2)	339 (8.4)	
Statin use, n (%)	115 (3.3)	85 (15.5)	200 (4.9)	<.001
Statin use in patients with CHD, n (%)	29 (18.0)	20 (31.2)	49 (21.8)	.030
Statin use in patients without CHD, n (%)	86 (2.6)	65 (13.4)	151 (4.0)	<.001
Acetylsalicylic acid use, n (%)	160 (4.6)	76 (13.8)	236 (5.8)	<.001
Acetylsalicylic acid use in patients with CHD, n (%) (n for denominator = 225)	53 (32.9)	28 (43.8)	81 (36.0)	.127
Acetylsalicylic acid use in patients without CHD, n (%) (n for denominator = 3816)	107 (3.2)	48 (9.9)	155 (4.1)	<.001
ASA or clopidogrel, n (%)	167 (4.8)	79 (14.4)	246 (6.1)	<.001
ASA or clopidogrel in patients with CHD, n (%)	58 (36.0)	30 (46.9)	88 (39.1)	.132
ASA or clopidogrel in patients without CHD, n (%)	109 (3.3)	49 (10.1)	158 (4.1)	<.001
ARB or ACE, n (%)	363 (10.4)	202 (36.8)	565 (14.0)	<.001
ARB or ACE in patients with CHD, n (%)	42 (26.1)	35 (54.7)	77 (34.2)	<.001
ARB or ACE in patients without CHD, n (%)	321 (9.6)	167 (34.4)	488 (12.8)	<.001
Only oral hypoglycemic medications, n (%)	—	274 (49.9)		
Only injectable hypoglycemics, n (%)	—	18 (3.3)		
Oral and injectable hypoglycemics, n (%)	—	25 (4.6)		

ACE, angiotensin-converting enzyme; CHD, coronary heart disease; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

Most of the individual components of the composite outcomes were around 2 times higher in patients with DM compared to non-DM (Table 2). Although it was not found to be statistically significant, the risk of non-CV mortality was clinically relevant and 27% higher in patients with DM [HR and 95% CI 1.27 (0.89-1.83); $P = .191$]. Total mortality was found to be 56% higher in these patients (HR and 95% CI, 1.56 and 1.17-2.06; $P = .002$).

The risk of major coronary events (composite of new MI, new angina, PCI, or CABG) was 2 times higher in the age- and

sex-adjusted model (HR and 95% CI 2.01 (1.55-2.60); $P < .001$) and 64% higher in the fully adjusted model in patients with DM compared with non-DM (Table 2). The risk of major coronary events for patients with DM or CV disease at baseline is presented in Figure 2 and in Supplementary Table 2. The risk of major coronary events was nominally higher in patients with CV disease alone without DM compared with patients with DM alone without CV disease at baseline, and the risk was even higher in those with concomitant DM and CV (Figure 2 and Supplementary Table 2).

Table 2. Risk of Cardiovascular Events in Diabetes Mellitus

Events*	DM (-), n = 3492 Event, n (%)	DM (+), n = 549 Event, n (%)	Incidence Rate in Non-Diabetics Per 1000 Person-Years	Incidence Rate in Diabetics Per 1000 Person-Years	Age- and Sex- Adjusted Model, HR (95% CI)	Fully Adjusted Model, HR (95% CI)
Major CV events	203 (5.8)	85 (15.5)	5.42 (4.72-6.22)	14.79 (11.90-18.39)	2.01 (1.54-2.62); <i>P</i> < .001	1.71 (1.30-2.24); <i>P</i> < .001
Major events	323 (9.2)	118 (21.5)	8.62 (7.73-9.61)	20.82 (17.33-25.01)	1.75 (1.41-2.18); <i>P</i> < .001	1.57 (1.25-1.97); <i>P</i> < .001
Coronary events	238 (6.8)	82 (14.9)	6.40 (5.64-7.27)	15.14 (12.19-18.79)	2.01 (1.55-2.60); <i>P</i> < .001	1.64 (1.26-2.15); <i>P</i> < .001
Individual components						
Total mortality	198 (5.7)	68 (12.4)	5.18 (4.50-5.95)	11.64 (9.18-14.76)	1.56 (1.17-2.06); <i>P</i> = .002	1.51 (1.13-2.02); <i>P</i> = .005
CV mortality	60 (1.7)	29 (5.3)	1.57 (1.22-2.02)	4.96 (3.45-7.14)	2.22 (1.41-3.50); <i>P</i> = .001	
Non-CV mortality	138 (4.0)	39 (7.1)	3.61 (3.05-4.26)	6.68 (4.89-9.14)	1.27 (0.89-1.83); <i>P</i> = .191	
Stroke	54 (1.5)	29 (5.3)	1.42 (1.09-1.85)	4.90 (3.39-7.10)	2.16 (1.35-3.45); <i>P</i> = .001	
Heart failure	34 (1.0)	18 (3.3)	0.89 (0.64-1.25)	2.77 (1.70-4.52)	2.08 (1.13-3.83); <i>P</i> = .018	‡3.08 (1.70-5.58); <i>P</i> < .001
New angina	109 (3.1)	25 (4.6)	2.88 (2.39-3.48)	4.37 (2.95-6.46)	1.34 (0.86-2.09); <i>P</i> = .200	
MI	120 (3.4)	51 (9.3)	3.18 (2.66-3.80)	8.87 (6.72-11.71)	2.23 (1.59-3.12); <i>P</i> < .001	

*Composite events are as follows:

Major cardiovascular events: cardiovascular death, myocardial infarction, stroke, or heart failure.

Major events: total mortality, myocardial infarction, stroke, or heart failure.

Coronary events: new MI, new angina, percutaneous coronary intervention, or coronary artery bypass surgery.

Fully adjusted model: adjusted for age, sex, smoking, hypertension, LDL cholesterol, history of coronary heart disease, statin, acetylsalicylic acid.

‡Unadjusted risk due to a low number of events.

CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; MI, myocardial infarction; HR, hazard ratio.

The relative risk of new angina in patients with DM was not significant; however, the risk of new MI increased significantly in these patients (age and sex-adjusted HR and 95% CI for new MI 2.23 (1.59-3.12); *P* < .001). Of note, in non-DM participants, the proportion of new angina and new MI was similar (3.1% vs. 3.4%, respectively); however, in patients with DM, presentation with MI was 2 times higher than the presentation with new angina (4.6% vs. 9.3%).

DISCUSSION

Diabetes mellitus is a heterogeneous disease, and the risk of CV events varies according to several factors, including the income levels of countries. This Turkish cohort of the PURE study demonstrated that major CV outcomes, major events (which includes total mortality in addition to the major CV outcomes), and major coronary events increased by 71%, 57%, and 64%, respectively, in patients with DM compared with those without DM. Except for the non-CV mortality and new angina, all individual outcomes are significantly higher in DM. Also, DM and CV disease at baseline lead to a comparable increase in the risk of major CV outcomes.

Diabetes mellitus is associated with many CV risk factors. In the present study, in line with other studies, hypertension and

previous history of CV events were more common in patients with DM. Also, blood pressure, body mass index, waist circumference, total cholesterol, and triglyceride levels were higher, but HDL cholesterol was lower in these patients. On the other hand, LDL cholesterol levels were similar between the 2 groups. These findings demonstrate that patients with DM have a similar metabolic profile that is observed in patients with metabolic syndrome. Although the increased risk of CV events attributed to DM is independent of these factors, individual CV risk increases exponentially as the number of risk factors increases.⁹ Preventive measures for these risk factors will be an important cost-effective step in reducing future risk of CV events.

In 1998, Haffner et al¹⁰ demonstrated that the risk of death from CHD is equivalent for patients with diabetes and those with prior MI in the Finnish population. The same group replicated their findings in another publication with a longer period of follow-up.¹¹ However, the results of various studies contradicted these findings.¹²⁻¹⁴ In our exploratory analyses, the risk of primary outcomes of major CV events was similar in those with DM alone without CVD compared to those with CVD alone without DM and was additive in those with both conditions (Figure 1). The controversial findings regarding

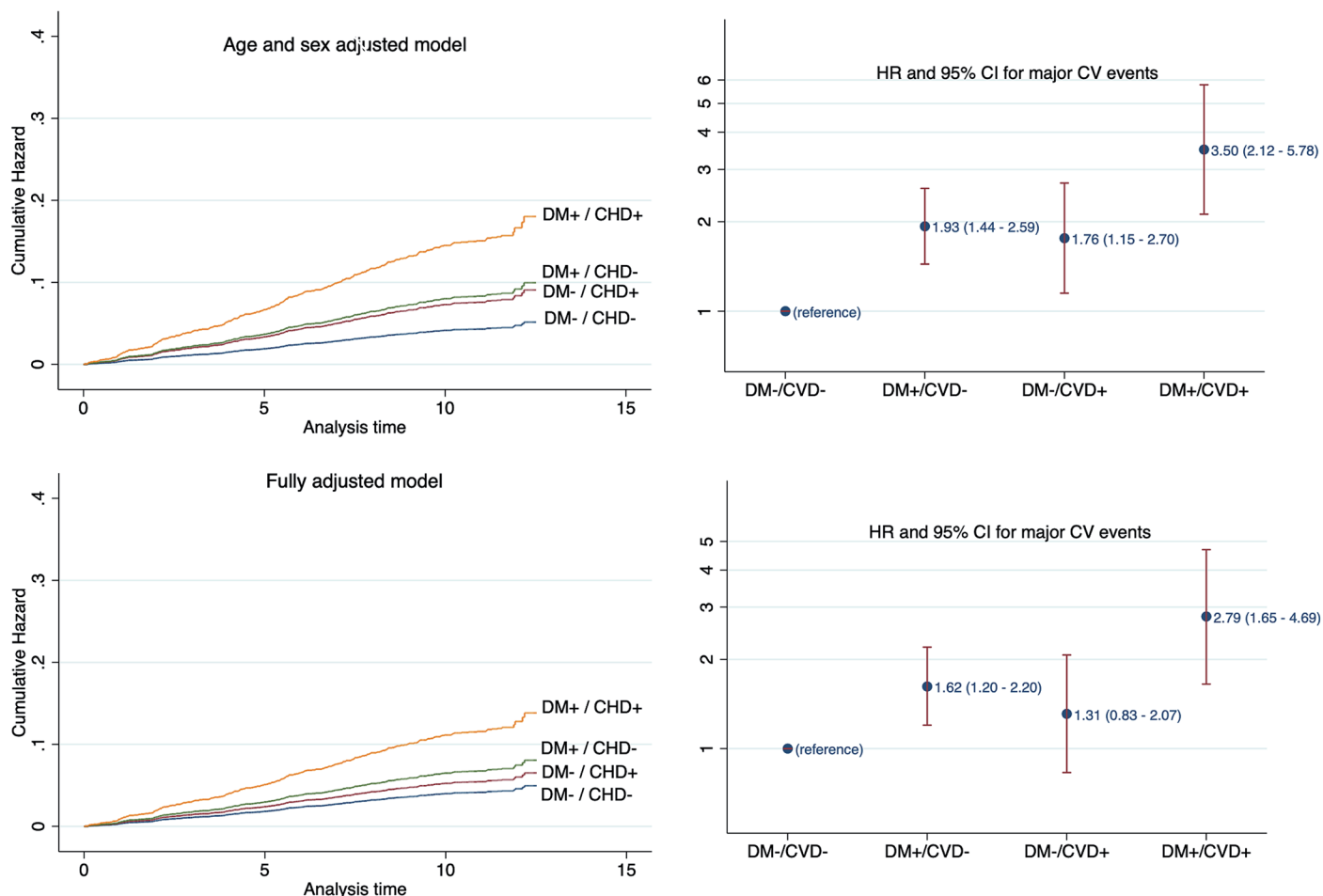


Figure 1. Cumulative hazards and hazard ratio (95% CI) for major cardiovascular outcomes in the age and sex-adjusted model (upper panel) and in the fully adjusted model (lower panel). On the right panel, the y-axes are given in logarithmic scale.

whether DM is equivalent to the presence of CHD in terms of the future CV risk seem to be caused by different definitions of CV outcomes and previous history of CV disease, and different adjustments, particularly the duration of DM and population characteristics such as populations' income level. Data suggest that patients with DM may have different risk profiles; therefore, the recent guidelines propose a treatment approach based on the individual risk, including the duration of DM, rather than a simplified approach using the term "equivalency."¹⁵⁻¹⁷

The absolute risk of CV events is usually higher in men compared with women.¹⁸ However, several studies show that the "relative" risk of major CV events in DM is higher in women than in men.^{9,19,20} This has been explained by the abolishment of sex-related protection.²¹ On the other hand, other studies show that the relative risk is higher in men.^{14,22} In the present study, while men had a higher risk of CV events than women, the CV risk of DM was not modified by sex. Although there is no plausible explanation for these differences between the studies, it might be due to several factors specific to the population or differences in the duration of DM, or definitions of the outcomes. For example, in our study, the percentage of smokers (active or

former) was profoundly higher in men than in women (77% vs. 24%, $P < .001$). A similar figure was observed in the epidemiological studies conducted in Türkiye.²³ Although we adjusted for the smoking status for the risk of major CV events, the cumulative effect of smoking cannot be ruled out. Therefore, smoking and other unmeasured confounding factors may be responsible for the differences between the studies.

Diabetes mellitus is an independent risk factor for CAD. The present study showed that the risk of composite major coronary events (new MI, new angina, PCI, or CABG) was 2 times higher in patients with DM in the age and sex-adjusted model. This figure was similar to the data obtained in the Emerging Risk Factors Collaboration's meta-analysis which includes 698 782 people from 102 prospective studies.¹⁹ Although new angina is a frequent way of presentation, the increase in the risk of new angina did not reach the statistical significance. Of note, while the frequency of new angina and MI is very similar in non-DM patients (3.1% vs. 3.4%, respectively), the frequency of MI is twice of new angina in patients with DM (9.3% vs. 4.6%). These suggest that these patients present more often with MI than with new angina. However, as this is an epidemiologic study, we did not systematically search for

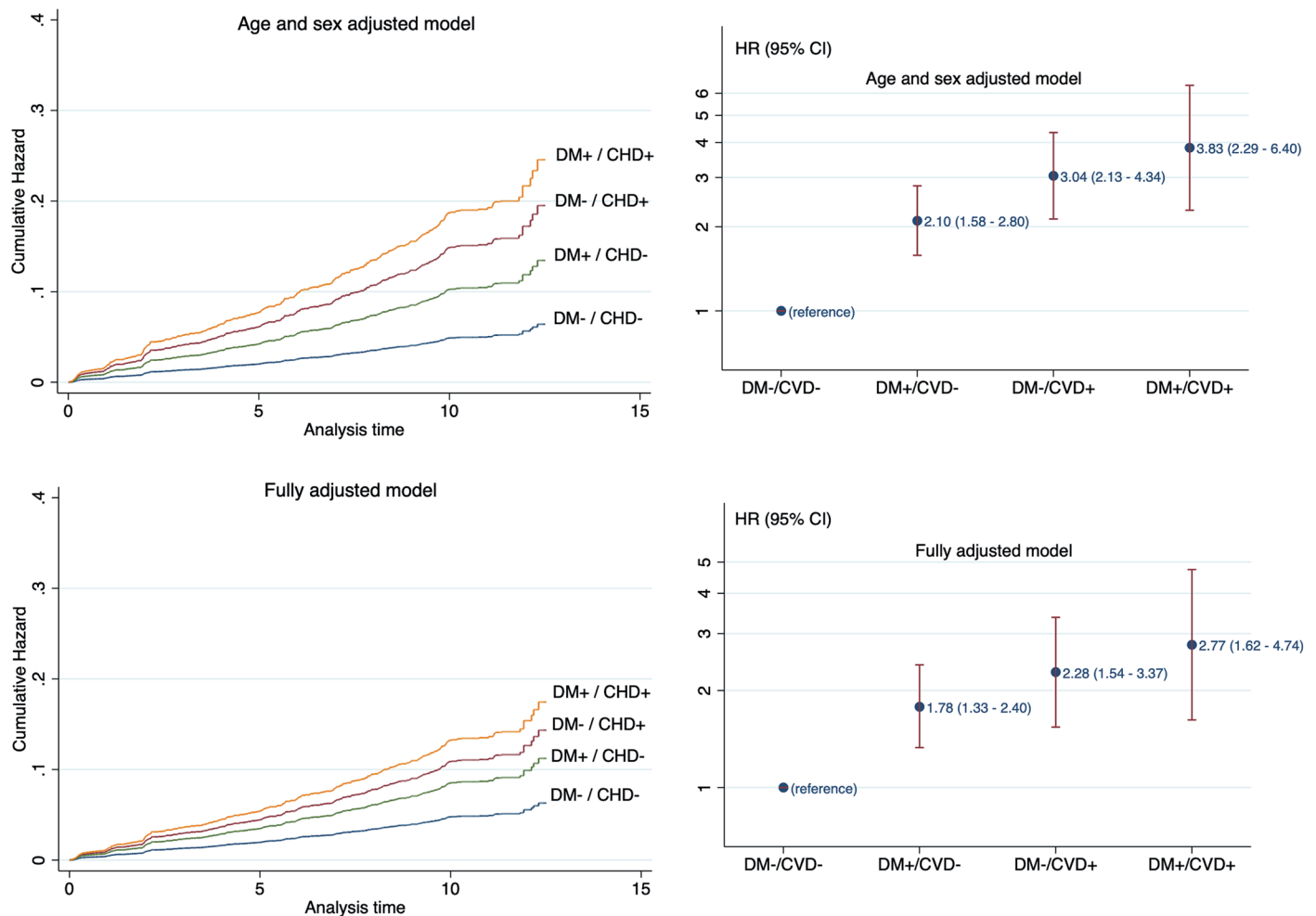


Figure 2. Cumulative hazards and hazard ratio (95% CI) for major coronary events in the age- and sex-adjusted model (upper panel) and in the fully adjusted model (lower panel). On the right panel, the y-axes are given in logarithmic scale.

the presence of silent ischemia. Whatever the mode of presentation, the impact on public health is substantial as the prevalence of DM is expected to increase.^{1-3,24}

As of 2021, 537 million adults have DM worldwide, and the number is expected to reach 643 million by 2030 and 783 million by 2045.²⁴ In the present study, the prevalence of DM was found to be 13.6% as of the time of the recruitment period of this study (2008-2009). The Turkish Diabetes Epidemiology (TURDEP) study demonstrated that the crude prevalence of diabetes was 7.2% in Türkiye in 1998.²⁵ The TURDEP-II study was conducted in the same centers 12 years later (in 2010), and the age-standardized prevalence was found 13.7%.² There are several differences between the TURDEP and the PURE studies. While TURDEP-II recruited participants aged ≥ 20 years old, the PURE study enrolled participants aged between 35 and 70 years. Also, we did not assess the hemoglobin-A1c (HbA1c) and glucose tolerance test as diagnostic criteria at baseline. Similar to the values obtained from the present study and the TURDEP-II study, a recent meta-analysis of epidemiological studies with a low risk of bias calculated the prevalence of DM in Türkiye as 13.5%.³ The high prevalence of DM is an important public health problem in

Türkiye. Considering the high CV risk of diabetes and the low use of CV-protective drugs, it is obvious that the high prevalence of diabetes exposes the Turkish population to a serious risk of CV events.

With regard to the individual components of the outcomes, except for the risk of non-CV mortality and new angina, all other outcomes were significantly higher in diabetics. Notably, the risk of heart failure was prominent but with wide confidence intervals due to the low number of events. Consistent with our finding, a 1.9 million people cohort study showed that heart failure is one of the most common CV manifestations of DM.²⁶ The increased risk might be caused by the constellation of several risk factors, increased risk of micro- and macrovascular disease, or diabetic cardiomyopathy.

We observed that the use of antiplatelets, statin, and ACEI/ARB at baseline was very low especially for patients with DM and concomitant CHD despite these medications being reimbursed by the government in Türkiye. The global PURE study demonstrated that the use of secondary prevention drugs for CV disease is low worldwide, and it is associated with the income level of the country.²⁷ This is, along with the

high percentage of smoking in our population, one of the responsible factors for the increased number of CV events requiring strict measures.

This study has several limitations. First, HbA1c was not included in the diagnosis of DM. However, the effect size of diabetes for major CV disease is consistent with those obtained in other studies^{26,28} and is so high that is unlikely to observe a major change in the main conclusion in case the HbA1c value had been included in the diagnostic criteria. Second, the duration of DM was not taken into consideration. Nevertheless, the median follow-up is nearly 12 years, which is long enough even for participants who are newly diagnosed with DM at baseline.

On the other hand, the present study has some strengths. First, the study population was selected considering the population density and the income level of people in each city using the national database. Second, the study has very few missing values at baseline, and follow-up data were obtained from 88% of participants during the 12-year follow-up. Third, the follow-up duration is long enough to obtain reliable information for the occurrence of CV disease.

CONCLUSION

This Turkish cohort of the PURE study demonstrated that the prevalence of DM is 13.6% in participants aged between 35 and 70; the risk of major CV outcomes is increased by 1.71 times, and coronary events by 1.64 times in patients with DM compared with non-DM. The increased risk for major CV outcomes seems to be comparable for patients with DM alone without CV disease and for those with CV disease alone without DM at baseline. The increase in non-CV mortality and new angina were non-significant. All other individual components of the outcomes were increased significantly in DM. Also, our analysis shows that patients with diabetes present with more MI than angina. The use of antiplatelet medications and statins is not at an acceptable level, particularly for those with DM and concomitant CHD. These findings underline that strict measures against the risk factors should be taken and that a nationwide intervention is required urgently to improve the undertreatment of patients with diabetes, especially those with CHD.

Ethics Committee Approval: This study was approved in 2005 by the Marmara University Ethics Committee (approval number: MAR-SBY-2005-0183) and the Ministry of Health.

Informed Consent: Informed consent was obtained from all of the participants.

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M.V.K., S.R., S.Y.; Analysis and/or interpretation – A.O., M.K., S.G., Y.A., K.K., A.T., B.Ç.T., O.T.C., M.V.K., S.R., S.Y.; Literature search – A.O., M.K., S.G., Y.A., K.K., A.T., B.Ç.T., O.T.C., M.V.K., S.R., S.Y.; Writing – A.O., M.K., S.G., Y.A., K.K., A.T., B.Ç.T., O.T.C., M.V.K., S.R., S.Y.; Critical review – A.O., M.K., S.G., Y.A., K.K., A.T., B.Ç.T., O.T.C., M.V.K., S.R., S.Y.

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Supplementary Table 1. Cardiovascular risk of DM in participants without coronary heart disease at baseline

Events*	DM (–) n=3331 (87.3%) Event n (%)	DM (+) n=485 (12.7%) Event n (%)	Incidence Rate in non-diabetics per 1000 person- years	Incidence Rate in diabetics per 1000 person- years	Age and sex adjusted HR (95% CI)	Fully adjusted model** HR (95% CI)
Major CV events	178 (5.3)	65 (13.4)	4.97 (4.29-5.75)	12.75 (9.96-16.32)	1.90 (1.41-2.55); <i>P</i> < .001	1.65 (1.22-2.24); <i>P</i> = .001
Major events	286 (8.6)	94 (19.4)	7.98 (7.11-8.96)	18.62 (15.18-22.85)	1.72 (1.35-2.18); <i>P</i> < .001	1.56 (1.22-2.00); <i>P</i> < .001
Coronary events	199 (6.0)	65 (13.4)	5.58 (4.86-6.42)	13.31 (10.44-16.98)	2.07 (1.55-2.76); <i>P</i> < .001	1.83 (1.36-2.46); <i>P</i> < .001
Individual components						
Total mortality	178 (5.3)	58 (12.0)	4.87 (4.21-5.65)	11.19 (8.65-14.47)	1.63 (1.20-2.21); <i>P</i> = .002	1.60 (1.17-2.18); <i>P</i> = .003
CV mortality	55 (1.7)	25 (5.2)	1.51 (1.16-1.96)	4.82 (3.26-7.14)	2.26 (1.39-3.67); <i>P</i> = .001	
Non-CV mortality	123 (3.7)	33 (6.8)	3.37 (2.82-4.02)	6.37 (4.53-8.96)	1.35 (0.91-2.00); <i>P</i> = .134	
MI	99 (3.0)	42 (8.7)	2.74 (2.25-3.34)	8.34 (6.17-11.29)	2.50 (1.73-3.62); <i>P</i> < .001	
New angina	92 (2.8)	19 (3.9)	2.88 (2.39-3.48)	4.37 (2.95-6.47)	1.34 (0.81-2.23); <i>P</i> = .254	
Stroke	49 (1.5)	20 (4.1)	1.35 (1.02-1.78)	3.73 (2.38-5.84)	1.72 (1.00-2.95); <i>P</i> = .051	
Heart failure	31 (0.9)	11 (2.3)	0.85 (0.60-1.21)	1.94 (1.04-3.60)	Unadjusted: 2.25 (1.10-4.60); <i>P</i> = .016	

*Composite events are:

Major cardiovascular events: cardiovascular death, myocardial infarction, stroke, or heart failure

Major events: Total mortality, myocardial infarction, stroke, or heart failure

Coronary events: New MI, new angina, percutaneous coronary intervention, or coronary artery bypass surgery

**Fully adjusted model: adjusted for sex, age, hypertension, smoking, LDL-cholesterol, statin use, and aspirin use

CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; HR, hazard ratio; MI, myocardial infarction

Supplementary Table 2. Comparison of DM and history of coronary heart disease for the future risk of major coronary events (New MI, new angina, percutaneous coronary intervention, or coronary artery bypass surgery)

Major Coronary events		DM (–) n = 3492 (86.4%) Event n (%)	DM (+) n = 549 (13.6%) Event n (%)	Age and sex-adjusted model	Fully adjusted model
		No event	Events (+)		
Coronary Events (n and row percentages)*	DM-/CHD-	3132 (94.03)	199 (5.97)	Ref.	Ref.
	DM-/CHD+	122 (75.78)	39 (24.22)	3.04 (2.13-4.34); <i>P</i> < .001	2.28 (1.54-3.37); <i>P</i> < .001
	DM+/CHD-	420 (86.60)	65 (13.40)	2.10 (1.58-2.80); <i>P</i> < .001	1.78 (1.33-2.40); <i>P</i> < .001
	DM+/CHD+	47 (73.44)	17 (26.56)	3.83 (2.29-6.40); <i>P</i> < .001	2.77 (1.62-4.74); <i>P</i> < .001

Major Coronary events: New MI, new angina, percutaneous coronary intervention, or coronary artery bypass surgery

*Fully adjusted model: adjusted for sex, age, hypertension, smoking, LDL-cholesterol, statin use and aspirin use

DM, diabetes mellitus; Ref, reference.