Incidence of and Risk Factors for Recurrent Cardiovascular Disease Events in Middle-Eastern Adults

Romona Devi Govender (✉ govenderr@uaeu.ac.ae)

UAEU <https://orcid.org/0000-0003-3393-9594>

Saif Al-Shamsi

UAEU

Elpidoforos S. Soteriades

United Arab Emirates University

Dybesb Regmi

United Arab Emirates University

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Abstract

Background Individuals with established cardiovascular disease (CVD) are at a much higher risk of either recurrent cardiovascular events or death. Previous research has shown that the incidence rate for recurrent CVD events varies across countries and populations. The association of traditional CVD risk factors, such as age, smoking, hypertension and diabetes mellitus increases the risk of recurrent CVD events or death particularly in individuals with a history of cardiovascular disease (CVD). The United Arab Emirates (UAE) has one of the highest age-standardized death rate for CVD worldwide. The aim of our study was to estimate the incidence rates and determine the predictors of recurrent CVD events among UAE nationals. **Methods** We investigated an outpatient-based cohort of patients with a history of prior CVD visiting Tawam Hospital between January 1, 2008 and December 31, 2008 and followed-up until the end of study period, July 31, 2018. Univariable and multivariable-adjusted Cox proportional hazard regression models were used to explore the association between different major CVD risk factors and the risk of recurrent CVD. **Results** A total of 216 patients (167 males, 49 females) with a history of CVD were included in our study. They were followed for a median of 8.1 years (interquartile range 5.5 to 9.3 years), with a total of 1184 patient-years of follow-up. The overall incidence rate of recurrent CVD events was 92.1 per 1000 patient-years. The 8-year cumulative incidence was 73.7%. Age, female sex, and diabetes mellitus were significant predictors of recurrent CVD events. Females had an 85% higher probability of recurrent CVD than males. **Conclusion** The overall incidence rate of recurrent CVD events in the UAE is 92.1 per 1000 patient-years and is one of the highest in Middle Eastern region. Primary and tertiary preventive measures are urgently needed in order to improve CVD morbidity and mortality and attempt to reverse the alarming rates of new and recurrent CVD events among UAE nationals. These interventions should comply with international guidelines for CVD management.

Introduction

Individuals with a history of cardiovascular disease (CVD) are at a much higher risk of recurrent CVD events or death [1]. Nonetheless, with the developments in early revascularization, antithrombotic medications, and other tertiary prevention measures including the control of traditional major CVD risk factors; CVD prognosis has improved [2]. The incidence rate of recurrent CVD events varies across countries and populations. The Second Manifestations of ARterial disease study conducted by the University Medical Centre Utrecht demonstrated a 53% reduction in the crude incidence rate of recurrent CVD events between 1996 and 2014 [3]. Studies from the United States and Western Australia have also documented decreasing trends in the incidence rates and mortality [4–6]. However, the increasing prevalence of traditional risk factors, such as obesity and diabetes mellitus [2], and novel ones including biochemical, cellular, and imaging parameters [7] challenge these trends.

Independent traditional predictors of recurrent CVD or death include age, smoking, hypertension (HTN), dyslipidemia, diabetes mellitus, chronic kidney disease, and the underutilization of medications based on current treatment guidelines [8, 9]. A previous study conducted in the UAE showed 35% with HTN, 34% having dyslipidemia, 14.4% had a history of coronary artery disease (CAD) and 29.5% with diabetes

mellitus had macrovascular complications [10]. The United Arab Emirates (UAE) has one of the highest age-standardized death rates from CVD worldwide, with 308.9 and 203.9 per 100,000 for males and females, respectively [11].

The UAE is in transition economically since the discovery of oil over 4–5 decades ago and following the economic trend is a change in the lifestyle among UAE populations propelling the negative effect on CVD risk and outcome. To the best of our knowledge, studies on the epidemiology of recurrent CVD in the UAE are few. Thus, this research is highly relevant and our results would be available for future studies in the region, to assess and compare trends in incidence, impact of interventions on outcomes as well as assist clinicians with evidence-based management guidelines. Thus, we aimed at assessing the incidence rate of recurrent CVD events in males and females and evaluated the influence of major traditional CVD risk factors on the recurrence rate of CVD events among UAE nationals.

Methods

Study setting

This retrospective cohort study was conducted in Tawam hospital, Al Ain City, which is the fourth largest city in the UAE, with a population of 650,000 of which approximately 30% are UAE nationals. Tawam hospital, is one of the largest tertiary care hospitals in Al Ain, providing health care services to UAE nationals and the expatriate community.

The United Arab Emirates University and Tawam Hospital Review Boards (CRD 239/13) granted ethical approval for this study. The Cerner® electronic medical record (EMR) management system was utilized to obtain patient data retrospectively. Patient information was anonymized to protect patient identity. Informed consent was waived, as identifying data was not collected from the EMR.

Study population

The original study population enrolled all patients who visited the outpatient clinics of Tawam Hospital between April 1, 2008 and December 31, 2008 and were followed-up until the end of the study period, July 31, 2018. All patients who were ≥ 18 years old and had an established diagnosis of CAD, cerebrovascular disease, or peripheral vascular disease (PVD) were included in this study. Established CAD was defined as a documented history of stable angina, unstable angina, percutaneous coronary intervention, coronary artery bypass graft surgery, or myocardial infarction. Cerebrovascular disease was defined as a documented diagnosis of transient ischemic attack (TIA) or stroke; PVD, as a documented diagnosis of peripheral artery disease. Patients were followed from the time of the first diagnosis of CVD until a recurrent CVD event, death, or the end of the study period on July 31, 2018.

The study's sample size was calculated using a formula for a study designed to estimate incidence in a population [Rosner B. Fundamentals of biostatistics. 7th ed. Boston: Cengage Learning, Inc; 2010.]. A

sample size of 194 was determined based on an anticipated 60% incidence of recurrent CVD [3] and utilizing 80% power at a 2-sided level of significance of 0.05.

Baseline characteristics

Data retrieved from the EMR included sociodemographic parameters, such as age, sex, body mass index (BMI); traditional CVD risk factors, included smoking, history of HTN, blood pressure (BP), history of diabetes mellitus, total cholesterol, and low-density lipoprotein (LDL); other parameters, such as anti-hypertensive medications, lipid-lowering medications, and antiplatelet therapy. Smokers were defined as current smokers or having a history of smoking. BMI was calculated as weight in kilograms divided by the square of the height in meters. Commonly accepted BMI ranges are those recommended by the World Health Organization as follows: overweight (BMI 25–29.99 kg/m²), obese class I (BMI 30–34.99 kg/m²), obese class II (BMI 36–40 kg/m²), and obese class III (≥ 41 kg/m²) [12]. Diabetes was defined as receiving oral hypoglycemic medications; HTN, as receiving anti-hypertensive medications or having a SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg, blood pressure was categorized as follows: normal (SBP < 140 or DBP < 90); grade 1 HTN (SBP 140–159 or DBP 90–99); grade 2 (SBP 160–179 or DBP 100–109); and grade 3 (SBP ≥ 180 or DBP ≥ 110) [13]. Based on Adult Treatment Panel III guidelines, LDL level ≥ 2.6 mmol/L (≥ 100 mg/dL) is suboptimal, and total cholesterol > 5.17 mmol/L (> 200 mg/dL) is suboptimal [14].

Recurrent CVD events

The outcome of our study included recurrent CVD events and/or death. Recurrent CVD events included stable angina, unstable angina, percutaneous coronary intervention, myocardial infarction, TIA, and cerebral infarction confirmed by computed tomography scan, magnetic resonance imaging, or ankle-brachial index < 0.9 . Death was defined as death due to myocardial infarction, stroke, and/or sudden death. The data for comorbidities and CVD events were collected using the definitions in the documented history in the EMR. Those with missing data were excluded.

The overall incidence rate of recurrent CVD events, the incidence rates in males and females, and the incidence rates according to different age categories were calculated by dividing the number of study participants with recurrent CVD event by the total patient-years of follow-up for the study population and for each subgroup accordingly.

Statistical analysis

Baseline variables were tested for association between males and females using independent-samples t-test for continuous variables and Fisher's exact test (two-tailed) for categorical variables. Continuous variables are presented as means ($\pm$ standard deviation (SD)), while categorical variables are presented as

proportions. The patient-years at risk for recurrent CVD events were calculated for each subject from the baseline visit until the occurrence of a recurrent CVD, death, or the last outpatient clinic visit, whichever occurred first. Univariable and multivariable-adjusted Cox proportional hazard regression models were used to evaluate the risk factors for recurrent CVD events. The independent predictors included in the multivariable-adjusted Cox regression model were age (continuous), sex, smoking, HTN, diabetes mellitus, LDL (continuous), and BMI (continuous). Proportional hazards assumption was assessed by log-log plots, while multi-collinearity was evaluated by examining the tolerance value. The results are expressed as hazard ratios and 95% confidence intervals (CIs). A p value <0.05 (two-sided) was considered statistically significant for all tests. All statistical analyses were performed using IBM SPSS software, version 25 (IBM Corporation, Armonk, NY, USA).

Results

A total of 216 patients (167 males, 49 females) with a history of CVD at baseline were included in our study. They were followed for a median of 8.1 years (interquartile range 5.5 to 9.3 years), with a total of 1184 patient-years of follow-up. Mean age ($\pm$ SD) was 65.7 $\pm$ 11.2 (range 28–96) years. A total of 109 patients developed a recurrent CVD event (79 males, 30 females).

The overall incidence rate of recurrent CVD events was 92.1 per 1000 patient-years of follow-up (95% CI 76.0–110.6). Assuming a constant incidence rate over time, the 8-year cumulative incidence of recurrent CVD event was 73.7%. The incidence rate of recurrent CVD event among females and males was 119.8 (95% CI 82.3–168.9) and 84.6 (95% CI 67.4–104.9) per 1000 patient-years of follow-up, respectively. The incidence rates for different age categories were as follows: 51.1, 35.5, 68.4, 70.8, and 115.2 for patients aged $\leq$ 34, 35–44, 45–54, 55–64, and $\geq$ 65 years per 1000 years of follow-up, respectively.

Table 1 shows the sociodemographic and risk factor characteristics of our study population. The prevalence of CVD at baseline was 3.7% for patients aged 35 to 44 years, and increased to 7.4% in patients aged 45–54 years. A sizeable portion of the population was smoking (27%) despite having a history of CVD. Although the vast majority of patients were receiving anti-hypertensive medications, uncontrolled HTN stages 1, 2, and 3 were observed in 31.8%, 9.0%, and 3.5% of the patients, respectively. An extremely high percentage of patients with diabetes mellitus (62.5%) was noted in our cohort. In addition, while 85% of the patients were on lipid-lowering medications, half of them failed to achieve the recommended LDL levels for patients with a history of CVD. Furthermore, two-thirds of the study population was either overweight (38.4%) or obese (27.3%). Notably, obesity among female patients with CVD was up to 40%.

Table 2 shows univariable and multivariable-adjusted Cox proportional hazard regression models for the association between different major CVD risk factors and the risk of recurrent CVD. The proportional hazards assumption was not significant, and the tolerance ranged from 0.83 to 0.97, which indicated an absence of multicollinearity. Age, sex, and diabetes mellitus were significant predictors of recurrent CVD

events or death in both the univariable and multivariable-adjusted models. Females had an 85% higher probability of experiencing a recurrent CVD compared to males.

A multivariable-adjusted survival curve comparing males to females for recurrent CVD events is shown in Fig. 1. We found that for every 1-year increase in age, patients had a 4% higher probability of developing a recurrent CVD event. Furthermore, a history of diabetes mellitus and prior CVD doubled the risk of recurrent CVD events.

Discussion

To our knowledge, this is the first study to examine the incidence rates of and explore the associated risk factors for recurrent CVD events among UAE nationals. The overall incidence rate of recurrent CVD events in this study (92.1 per 1000 patient-years) appears to be one of the highest reported rates in literature [15–18] and in the Middle Eastern region [19]. Furthermore, prior research findings confirmed our results on the association of traditional CVD risk factors, such as age and diabetes mellitus, with the risk of recurrent CVD. One of the intriguing findings in our study was the significantly higher risk of recurrent CVD events among females than among males. In addition, we found that the patients with a history of CVD had uncontrolled HTN and failed to achieve the recommended LDL levels despite receiving anti-hypertensive and lipid-lowering medications.

In this study, recurrent CVD increased exponentially with advancing age, which was supported by the findings of previous studies [5, 16, 19–20]. For every 1-year increase in age, we found a 4% higher probability for recurrent CVD in the UAE, whereas in a neighboring country, the probability was at 2% [19]. Moreover, our finding that diabetes mellitus is a traditional independent risk factor for recurrent CVD event is consistent with that of Giorda et al [20]. In a study conducted in Al Ain and published in 2007, 29.5% of patients with diabetes mellitus had established CVD [10], and alarmingly, although not surprising, our results showed a two-fold increase (62.5%) since then. The probability of CVD recurrence in our study increased by 98% among patients with diabetes mellitus, while in other studies, the probability ranged between 65%¹⁵ and 75% [21]. For sex-based differences, particularly related to prognosis and mortality, previous studies showed that females have more favorable results than males [22–24]. In our study, females are at an 85% higher risk for recurrent CVD, although the differences between the sexes for those with diabetes mellitus and poorly controlled lipid levels are marginal, it was not the same for smoking.

Although smoking, HTN, and abnormal LDL levels are major modifiable CVD risk factors for recurrent CVD, no statistically significant associations between these risk factors and recurrent CVD events were found. This may be attributed to the limited sample and multiple adjustments. For poorly controlled HTN, Abdulle [et.al.](#) reported that 76% of the cohort in Al Ain had undertreated HTN [25]. Underutilization of lipid-lowering medications despite having a history of CVD seems to be a common finding, which is consistent with the result in our study [26–29]. Among the patients who were prescribed lipid-lowering medications (85%), only about half of them had LDL cholesterol levels within the internationally recommended range.

Whether this is an issue of poor adherence to treatment or inadequate treatment regimens remains to be further investigated.

Strengths and Limitations

Our study is the first to report the incidence rates and risk factors associated with CVD recurrence in UAE over a median follow-up period of 8 years and 109 documented CVD events supporting the relative robustness of our results despite this being a single-center study. This relatively long duration assessing recurrent CVD, where available data is sparse, in our opinion, filled a gap in the literature such as our study for this region.

This study has some limitations. We analyzed the composite causes of CVD and thus were not able to separate them into different subcategories of CVD. Moreover, prediction models to evaluate the effect of some medical comorbidities such as heart failure, atrial fibrillation and chronic kidney disease, medications and preventive treatment strategies which may influence CVD outcomes and prognosis were not included in the analysis. Thus, future studies should consider such parameters.

Conclusions

Our study found excessively high incidence rates of recurrent CVD events among patients with a history of CVD attending the outpatient clinics in a tertiary hospital in Al Ain. We also found an alarming prevalence of smoking, uncontrolled HTN, diabetes mellitus, obesity, and abnormal lipid levels in these patients with CVD. Furthermore, age, female sex, and diabetes mellitus were strong independent predictors of recurrent CVD events. Therefore, primary and tertiary preventive measures, complying with international guidelines for CVD management should target the general population and in particular patients with a history of CVD in order to improve CVD morbidity and mortality among UAE nationals.

Abbreviations

BMI: Body mass index; BP: blood pressure; CVD: cardiovascular disease; CAD: coronary artery disease; CI: confidence intervals; DBP: diastolic blood pressure; HTN: hypertension; LDL-C: Low-density lipoprotein-cholesterol; PVD: peripheral vascular disease; SBP: systolic blood pressure; TIA: transient ischemic attack; SD: standard deviation; UAE: United Arab Emirates

Declarations

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Contributors

The study was conceived by RDG, who also designed the study in collaboration with SS, DR and ESS. SS conducted all statistical analyses. RDG wrote the first draft of the manuscript, while all authors interpreted the data, contributed to the writing of the subsequent versions of the manuscript and approved the final version.

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Availability of data and materials

The dataset supporting the conclusions of this article is included within the article and its additional file.

Ethics approval and consent to participate

The study protocol was approved by Tawam Hospital and the United Arab Emirates University research and ethics board (CRD 239/13). The requirement for informed consent was waived because patient records and information were anonymized and de-identified prior to analysis.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹ Department of Family Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al Ain, United Arab Emirates. ² Department of Internal Medicine, College of Medicine and Health Sciences, United Arab Emirates University, ³ United Arab Emirates University, College of Medicine and Health Sciences, Institute of Public Health, Al Ain, United Arab Emirates, ⁴ Harvard University T. H.

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Tables

Due to technical limitations, all Table(s) are only available as a download in the supplemental files section.

Figures

Figure 1

Adjusted Cox regression survival curve for recurrent CVD events by sex

Supplementary Files

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