ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

The Acute Coronary Syndrome Risk in Medically Managed Subjects with Type 2 Diabetes Mellitus – Is the ASCVD Risk Score Failing Here?

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Abstract

Objectives. The risk of acute coronary syndrome (ACS) is high in subjects with type 2 diabetes mellitus (T2DM). The current management algorithm focuses on atherosclerotic cardiovascular (ASCVD) risk score to stratify this risk. However, in medically managed subjects, this algorithm may not be accurate. The current study compares the ASCVD risk score calculated in a subset of the Indian population with T2DM under medical supervision and the actual incidence of ACS. It also compared the ASCVD risk scores in cases with T2DM who developed ACS to controls who did not and tried to estimate whether ASCVD risk score is different in the two subsets, thereby evaluating the utility of ASCVD risk score in predicting ACS in subjects with T2DM on medical management. The impact of other factors like hypertension, dyslipidaemia, family history of ACS, and duration of T2DM on the development of ACS was also investigated.

Methodology. This is an electronic medical record (EMR) based case-control study. Only records of subjects with T2DM where details of age, sex, body mass index, blood pressure, duration of diabetes, family history of ACS, lipid profile, renal and liver function tests (in those affected with ACS, the details need to be within 6 months prior to the ACS) were included. The incidence of ACS was calculated in the selected records. The records of subjects who developed ACS were compared with age and sex-matched subjects who did not develop ACS. Data are summarized as median and interquartile range (IQR). Wilcoxon rank-sum test was used for checking differences in continuous variables and Pearson's Chi-squared test for categorical data. Univariate and multivariate logistic regression analyses were used to check the effect of ASCVD scores and other variables on the occurrence of ACS.

Statistical data analyses were performed using JASP, version 0.16.4 (JASP Team [2022]) for MS Windows.

Results. Of the 1226 EMRs included in the analysis, 207 had ACS. The actual incidence of ACS was 16.85 percent in 6 years which was more than the mean predicted 10-year incidence of 14.56 percent (p <0.05). The cases were age and sex-matched with controls and the ASCVD incidence was estimated in the two groups. The mean ASCVD score in the cases was 14.565 ± 8.709 (Min: 1.5, Max: 38.3) and controls 13.114 ± 8.247 (Min: 1.4, Max: 45). We conclude that the ASCVD risk score may not accurately predict the ACS risk (may underestimate) and may be similar in those who developed ACS and those who did not. The chance of development of ACS increases with raised systolic blood pressure (per mmHg rise OR: 1.04, 95% CI: 1.03, 1.06; p <0.001), positive family history (OR: 5.70, 95% CI: 3.41, 9.77; p <0.001), statin use (OR: 2.26, 95% CI: 1.46, 3.52; p <0.001), and longer duration of diabetes (for every year increase OR: 1.19, 95% CI: 1.13, 1.25; p <0.001)

Conclusion. The authors conclude that the ASCVD risk score underestimates the ACS risk in subjects with T2DM under medical supervision and may not be different in those who developed and those who did not develop ACS. We also conclude that factors like family history (30% less risk with negative family history), longer duration of diabetes, and higher SBP may be of relevance in those who developed ACS and throw open the need for more objective measures to assess risk in T2DM under medical supervision.

Key words: ASCVD, acute coronary syndrome, family history

eISSN 2308-118x (Online)
Printed in the Philippines

Received: June 26, 2023. Accepted: September 1, 2023.
Published online first: February 5, 2024.
https://doi.org/10.15605/jafes.039.01.15

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is reaching epidemic proportions across the globe with the International Diabetes Federation estimating that close to 537 million people are living with diabetes in 2021. India is home to 74 million people with T2DM. Ischaemic heart disease (IHD) affects almost one-third of people with diabetes and is the leading cause of mortality accounting for close to 9 million deaths per annum. T2DM is a major risk factor for IHD and ACS which is almost 2-3 times common in people with T2DM as compared to controls.[1,2]

T2DM is ironically a silent disease existing long before it is symptomatic. It also remains the main reason responsible for the leading cause of mortality that is atherosclerotic cardiovascular disease (ASCVD). The existence of metabolic derangements like dysglycaemia, hypertension and dyslipidaemia precede the development of ASCVD. These remain undiagnosed for a long time before ASCVD manifests. Many attempts have been made in the past to do risk stratification for ASCVD. Most of these were based on the existence of risk factors like age, sex, smoking, diabetes, hypertension, dyslipidaemia, etc.[2-4]

The main utility of these risk engines has been for the identification of individuals who are to be targeted for therapies, most notably statins, for the prevention of ASCVD. However, time and again, some limitations of these risk engines have been realised like the non-incorporation of family history of ASCVD as well as the omission of factors like obesity. This may be responsible for the fact that even in countries with better health coverage, the residual risk of ASCVD remains to be addressed. The utility of these risk engines, in particular, ASCVD risk score in the assessment of risk in T2DM is not yet proven. Also, in those subjects with T2DM who are in regular follow-up with their physicians as well as on medical management for diabetes, hypertension, and dyslipidaemia, the utility of ASCVD risk score to predict ACS risk is not well studied.[4]

The target study population for the generation of these risk engines has been Caucasians and so, the validity of these in other races is doubtful. Indian or Southeast Asian population is different in that the onset of ASCVD is quite early as compared with Caucasians.[5] Also, the pattern of obesity in Indians is predominantly central with metabolically unhealthy abdominal fat which exists even despite body mass indices that may fall within the normal range as per Caucasian standards.[5,6]

The most common risk score used to predict future cardiovascular risk is the Atherosclerotic Cardiovascular Disease (ASCVD) risk score 2013 by the American Heart Association. Data from diverse racial populations were used to get the ASCVD risk score. This score estimates the cardiovascular risk based on variables like age, sex, race, total cholesterol levels, HDL levels, blood pressure, history of diabetes and hypertension, addictions like smoking and chewing tobacco and use of medications like aspirin and statin. Patients are categorized as high (>20%), intermediate (7.5-20%), borderline (5-7.5%) or low (<5%) risk depending on the score calculated. ASCVD risk score is the maximally used risk score to estimate the possible cardiovascular event risk in clinical practice and is used to make management decisions based on the risk obtained.[7]

However, the ASCVD risk score validity has not been studied in a population which is under regular medical follow-up. This population is different because they are regularly on medications for diabetes, hypertension, and dyslipidaemia as well as other comorbidities. The main objective of this study was, therefore, to look at the performance of ASCVD risk score in people with T2DM on medical management as well as to compare the ASCVD risk score in people with T2DM who developed ACS with those age- and sex-matched T2DM who did not. The secondary objective of the study was to look at the impact of factors like blood pressure, lipid levels, family history of diabetes, duration of diabetes and smoking status on the development of ACS.

OBJECTIVES

Primary objectives

The primary objective was to assess whether the ASCVD risk calculator accurately estimates the ACS risk in people with T2DM under medical supervision. The study aimed to look at whether the ASCVD risk scores are different in those who developed ACS versus those who did not develop ACS.

Secondary objective

The secondary objective was to look at the impact of variables like hypertension, lipid profile parameters, family history of ACS and duration of diabetes on the development of ACS.

METHODS

Study design

This is an electronic medical record (EMR) based case-control study to understand the utility of the ASCVD risk calculator in predicting ACS as well as look at other risk factors that can predict ACS in T2DM.

Inclusion criteria

EMRs of people with T2DM who visited the outpatient clinic between 1st January 2016 to 31st December 2022 were analysed. Only those EMRs with complete details of age, sex, and body mass index, diagnosis of diabetes including timing of onset, family history of diabetes, blood pressure, lipid profile, renal and liver function tests (in those affected with ACS, the details need to be within 6 months prior to ACS) were included.

Exclusion criteria

EMRs of people with diabetes other than confirmed T2DM were excluded. Those with no documented visit within 6 months before developing an ACS, or subjects with chronic liver disease (transaminases more than 2 times the upper limit of normal or Child-Pugh class B and C), chronic kidney disease (eGFR<60 ml/min), known previous cardiovascular disease, cerebrovascular disease, or peripheral vascular disease, hyperhomocystinaemia, known familial hypercholesterolaemia, valvular heart disease or cardiac arrythmias, retroviral disease, pulmonary tuberculosis and severe chronic obstructive airway disease.

Endpoints

The current study looks at the comparison of ASCVD risk score calculated based on parameters prior to actual development of ACS in subjects with T2DM who developed ACS and age and sex-matched controls who did not develop ACS thereby testing the utility of ASCVD risk score in predicting ACS in subjects with T2DM on medical management. The individual impact of these factors on the development of ACS was also analysed.

Data parameters

Details of age (in years), sex, duration of diabetes (as available from patients' clinical records), family history of ACS (as recalled by the patient in first-degree relatives), blood pressure (measured and documented in EMR in mm hg), HbA1c and lipid profile (from the laboratory reports of the patient) were extracted from the EMRs for the cases and controls. The uniqueness of this population was the documented medical visit within the last 6 months before the occurrence of ACS with a qualified medical practitioner. As a result, most of the subjects were already on statins, taking antihypertensives and all were taking oral anti-diabetic medications ± insulin. ASCVD risk score for possible 10-year risk of ACS was calculated using the online ASCVD risk calculator.

Sample size

The EMRs of 4248 individuals with diabetes who visited a single outpatient practice (total of 15567 visits) between 1st January 2016 to 31st December 2022 were reviewed. Of these, 1226 EMRs matched the inclusion criteria, of which 207 people with T2DM had an ACS (documented fatal myocardial infarction, nonfatal myocardial infarction or unstable angina leading to hospitalisation and revascularisation from 1 January 2016 to 31 December 2022). The required sample size based on adverse cardiovascular event incidence in the CVD-REAL study (2.25 percent per patient year translating to 13.5 percent for six patient years) was found to be 180. With the sample size of 1226, the margin of error at a 95% confidence interval was found to be 2.1% and for a 99% confidence interval, it was 2.76%.[8] With a population size of 1226 and an ACS incidence rate of 16.88%, a sample size of 184 was found to be sufficient (5% margin of error, 95% confidence interval). At a sample size of 207, the margin of error with 95% confidence interval was 4.65%. The records of these 207 subjects who developed ACS were compared with 207 age and sex-matched controls. The controls were identified among the remaining 1019 EMRs. The ratio of cases to controls was 1:1.

Statistical analysis

Data are summarized as median and IQR. Wilcoxon rank-sum test was used for checking differences in continuous variables and Pearson's Chi-squared test for categorical data. The chi-square test was used to check differences in ordinal variables. To examine the relationship between these variables and the occurrence of acute coronary syndrome (ACS) beyond that explained by the ASCVD score, we conducted univariate and multivariate logistic regression analysis. The model utilised the forced entry method to assess the effect of variables other than the ASCVD score to predict the occurrence of ACS. The dependent variable is the occurrence of ACS.

Statistical data analysis is performed using JASP, version 0.16.4 (JASP Team [2022]) for MS Windows.

RESULTS

Of the 1226 EMRs of patients with T2DM under medical follow-up, 207 had ACS in the last 6 years. This gives an incidence rate of 16.88% over 6 years. This is more than the 10-year incidence predicted by the ASCVD risk calculator for 1226 people (13.85 ± 8.21) (p <0.05).

Furthermore, a case-control study conducted on 207 cases and 207 controls (adequate sample size estimated to be 184 assuming a population of 1226 and proportion of 16.88%) to understand the utility of ASCVD risk calculator in predicting atherosclerotic cardiovascular events among subjects with T2DM, as well as the impact of other variables like lipid profile, blood pressure, family history of diabetes, duration of diabetes, smoking status, and statin use on the development of ACS. The cases with ASCVD had a mean age of 56.8 ± 6.403 (Min: 34, Max: 65) while the controls without ASCVD had a mean age of 56.8 ± 6.430 (Min: 34, Max: 65). The mean ASCVD score was 14.565 ± 8.709 (Min: 1.5, Max: 38.3) for the cases and 13.114 ± 8.247 (Min: 1.4, Max: 45) for the controls, with no significant difference between the groups (p = 0.083). Breaking down the scores into Low (<5%), Borderline (5-7.5%), Intermediate (7.5-20%) and High (>20%), there were no significant differences between the two groups as well, with an equal and varied range of scores in both groups (Figure 1).

The cases had a median total cholesterol of 174 mg/dL (IQR: 148 to 197 mg/dL), while the controls had a median cholesterol level of 186 mg/dL (IQR: 175 to 191 mg/dL) (p = 0.007). The cases had a median systolic blood pressure

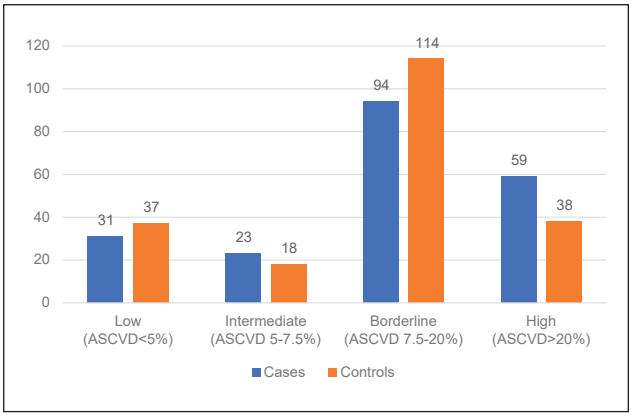

Figure 1. Number of subjects among cases and controls with ASCVD risk scores in the low, borderline, intermediate and high categories.

of 140 mmHg (IQR: 124 to 154 mmHg), while the controls averaged 125 mmHg (IQR: 120 to 135 mmHg). Statin use was more prevalent in the cases, with 79% (n = 164) taking the drug compared to 63% (n = 130) in the control group (p <0.001). Family history of diabetes was notably different between the groups. While 34% (n = 141) of the entire cohort reported family history, it was significantly more common in cases (50%) than in controls (18%) with p <0.001. Overall, the median duration of diabetes was 8 years. Cases had a notably longer diabetes duration with a median of 12 years (IQR: 8 to 15 years) compared to controls with a median of 5 years (IQR: 3 to 9 years), which was statistically significant with p <0.001 (Table 1).

We found significant correlations between the ASCVD score and several health indicators (LDL, HDL, SBP, diastolic blood pressure, cholesterol, hypertension, smoking). Similarly, several factors were significantly and positively correlated with the occurrence of atherosclerotic cardiovascular events, including SBP, duration of diabetes, statin use, and family history.

In the univariate analysis, every unit increase in HbA1c was associated with 16% increased odds of the outcome, which bordered on statistical significance (OR: 1.16, 95% CI: 0.99, 1.36; p = 0.068). The multivariate analysis indicated a 17% increase in odds (OR: 1.17, 95% CI: 0.96, 1.44; p = 0.12). Every unit increase in systolic blood pressure was associated with a 3% and 4% increase in odds in the univariate (OR: 1.03, 95% CI: 1.02, 1.05; p <0.001) and multivariate (OR: 1.04, 95% CI: 1.03, 1.06; p <0.001) analyses, respectively. The use of statins was associated with a significant 126% increase in odds of the outcome in univariate analysis (OR: 2.26, 95% CI: 1.46, 3.52; p <0.001). A positive family history was strongly associated with the outcome. The univariate analysis demonstrated a 364% increase in odds (OR: 4.64, 95% CI: 2.99, 7.33; p <0.001), and the multivariate analysis showed a 470% increase (OR: 5.70, 95% CI: 3.41, 9.77; p <0.001). Every unit increase in the duration of diabetes was associated with a 17% increase in the univariate analysis (OR: 1.17, 95% CI: 1.13, 1.23; p <0.001) and a 19% increase in the multivariate analysis (OR: 1.19, 95% CI: 1.13, 1.25; p <0.001). The results of the regression analysis are summarized in Table 2.

The multivariate regression analysis showed that the probability of development of ACS was higher with raised systolic blood pressure (OR: 1.04, 95% CI: 1.03, 1.06; p <0.001), positive family history (OR: 5.7, 95% CI: 3.41,9.77; p <0.001), and longer duration of diabetes (OR: 1.19, 95% CI: 1.13, 1.25; p <0.001). Raised HbA1c also showed a trend towards increased risk but did not reach statistical significance in the multivariate analysis (OR: 1.17, 95% CI: 0.96, 1.44; p = 0.12) though it was significant in the univariate analysis. Thus, the risk of ACS was increased by 4% per mmHg increase in systolic pressure, 19 percent per year of increase in the duration of T2DM, and with a positive family history of ACS. One percent (1 %) change in HbA1c increased ACS risk by 17 % but did not reach statistical significance.

Table 1. Differences in the characteristics among diabetic subjects with (cases) and without (controls) ACS

Characteristic	Overall, N = 414*	Controls, N = 207*	Cases, N = 207*	p†
Sex				>0.9
Female	164 (40%)	82 (40%)	82 (40%)	
Male	250 (60%)	125 (60%)	125 (60%)	
Age in years	59 (54, 62)	59 (54, 62)	59 (54, 62)	>0.9
HbA1c in %	7.60 (7.00, 8.30)	7.60 (7.00, 8.10)	7.60 (7.00, 8.50)	0.6
LDL in mg/dl	86 (70, 96)	86 (78, 95)	84 (66, 100)	0.3
HDL in mg/dl	44 (38, 47)	44 (40, 48)	43 (35, 46)	0.10
Cholesterol in mg/dl	184 (160, 194)	186 (175, 191)	174 (148, 197)	0.007
Systolic BP in mmHg	133 (123, 145)	125 (120, 135)	140 (124, 154)	<0.001
Diastolic BP in mmHg	80 (78, 88)	82 (78, 88)	80 (80, 90)	0.052
Smoker	18 (4.3%)	9 (4.3%)	9 (4.3%)	>0.9
Hypertension	282 (68%)	132 (64%)	150 (72%)	0.058
Statin	294 (71%)	130 (63%)	164 (79%)	<0.001
Aspirin	132 (32%)	58 (28%)	74 (36%)	0.092
ASCVD	12 (7, 19)	12 (7, 18)	13 (7, 22)	0.092
Family history of diabetes	141 (34%)	37 (18%)	104 (50%)	<0.001
Duration of diabetes	8 (4, 12)	5 (3, 9)	12 (8, 15)	<0.001

*n (%); Median (IQR)
†Pearson's Chi-squared test; Wilcoxon rank sum test

Table 2. Results of univariate and multivariate logistic regression analyses for the variables with occurrence of ACS

Characteristic	Univariate				Multivariate		
	N	OR	95% CI	*p*-value	OR	95% CI	*p*
Sex	414						
Female		—	—		—	—	
Male		1.00	0.67, 1.48	>0.9	1.20	0.60, 2.44	0.6
Age	414	1.00	0.97, 1.03	>0.9	1.01	0.95, 1.08	0.7
HbA1c	414	1.16	0.99, 1.36	0.068	1.17	0.96, 1.44	0.12
LDL	414	1.00	0.99, 1.01	0.5			
HDL	414	1.00	0.97, 1.02	0.7			
Cholesterol	414	1.00	0.99, 1.00	0.5	1.00	0.99, 1.01	0.7
Systolic BP	414	1.03	1.02, 1.05	<0.001	1.04	1.03, 1.06	<0.001
Diastolic BP	414	1.02	0.99, 1.04	0.2	0.99	0.96, 1.02	0.5
Smoker	414	1.00	0.38, 2.61	>0.9			
Hypertension	414	1.50	0.99, 2.27	0.058			
Statin	414	2.26	1.46, 3.52	<0.001			
Aspirin	414	1.43	0.94, 2.17	0.092			
ASCVD	414	1.02	1.00, 1.04	0.083	0.97	0.92, 1.03	0.4
Family history of diabetes	414	4.64	2.99, 7.33	<0.001	5.70	3.41, 9.77	<0.001
Duration of diabetes	414	1.17	1.13, 1.23	<0.001	1.19	1.13, 1.25	<0.001

OR = Odds Ratio, CI = Confidence Interval

DISCUSSION

T2DM is a major risk factor for ASCVD which is the leading cause of mortality. With better screening programmes and access to care, a good number of patients with T2DM are in optimum medical management. The recent guidelines in the last few years focused on end-organ protection in addition to blood glucose control. Those who have established cardiovascular disease are subclassified separately and are recommended to be given cardioprotective treatment. However, a large section of people with diabetes has subclinical cardiovascular disease and are deserving candidates for cardioprotective treatment but get deprived. One way of identifying those at risk is the use of the ASCVD risk score. However, its predictive value in patients on treatment is uncertain and it is important to identify those at risk.[3,4]

Asian Indians are an ethnic group with a higher risk of developing IHD and ACS. This can be one of the limitations of applying the ASCVD risk score in Asian Indians. The present study confirms this by noting a higher incidence of ACS (in 6 years only) than predicted by the ASCVD risk score (which predicts a 10-year probability).[5,6]

The risk engines have always underestimated the value of family history which is one of the most important determinants of ACS and ASCVD. This study highlights the relevance of family history. Those with a negative family history had a 30 % less likelihood of getting ACS. This has been seen even in previous studies looking at the relevance of family history in ACS. It also highlights the relevance of raised SBP in the development of ACS. This calls for more proactive and aggressive control of blood pressure especially in those who are vulnerable.[7,9,10]

It is a known fact that the duration of diabetes is relevant in the development of diabetic complications and this study highlights its relevance in the development of ACS. This also substantiates the fact that those who get T2DM early should be more aggressively treated to target.[11]

Participants who are on statins have odds of having an ACS that is 2.26 times higher than those without statins, indicating that these are higher-risk individuals. It is proven beyond doubt that statin use is the mainstay of protection against ASCVD. Also, the current population is under medical supervision. This reflects more baseline dyslipidaemia in the cases and favourable baseline lipid profile in controls since the LDL levels are not different in the two groups. Because the LDL and total cholesterol levels were not different in the two groups but the number using statins was more in the ACS group implied that baseline dyslipidaemia for a duration pre-existed in this population which undermined the fact that early treatment of dyslipidaemia may also have a legacy effect in the prevention of ASCVD.

The study represents the presence of unaddressed residual risk in a population managed as per guidelines. It also stresses the felt need for the usage of methods other than the ASCVD risk calculator which is a decade old now. This calls for better risk stratification using more objective tools like biomarkers (hsCRP, NT-pro BNP) or radiological non-invasive modalities (e.g., coronary calcium scoring, carotid intima-media thickness, etc.) in a vulnerable population (the authors believe Southeast Asians fall in this group), especially with T2DM and positive family history of ASCVD. This is extremely important because the guidelines of T2DM care are now based on cardiac risk stratification and a large population base who are at risk of heart disease may be deprived of cardioprotective medications.[12-14]

The study also highlights the factors to be looked at in those who are under supervised care for T2DM as per current standards and may help clinicians identify people who need more attention notably those with positive family history, longer duration of diabetes, and uncontrolled SBP.

Limitations of the study

This being an EMR-based single centre and retrospective study, the observations need to be verified in a prospective study. Also, the subjects may not represent the general population since they were already diagnosed and in follow-up with their physicians. Most of the people in the study are also residing within a specific geographic area, and so, the conclusions may not be generalizable. The study excluded patients with chronic liver and kidney diseases, known previous cardiovascular and cerebrovascular diseases, and other conditions, which may also affect the generalizability of the findings. The study did not consider the effect of lifestyle factors, such as diet and exercise, as well as compliance with medications which may affect the occurrence of ACS.

CONCLUSION

The study highlights the presence of residual risk in a population treated as per standards of care. Most of the risk engines including the ASCVD risk scoring are well-validated and continue to remain relevant but still have limitations. One of these is the lack of validation of these risk engines in patients already on treatment. The study emphasizes the importance of family history and longer duration of diabetes as non-modifiable risk factors needing additional vigilance and consideration beyond risk engines and blood pressure control as a modifiable risk factor that stands out despite being part of the risk engines too. It also calls for exploring other options for early diagnosis of ASCVD for better risk stratification and optimising medical management.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
AJ: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing - review and editing, Visualization, Supervision, Project administration, Funding acquisition; **HS:** Conceptualization, Validation, Formal analysis, Investigation, Writing – review and editing; **SK:** Conceptualization, Formal analysis, Writing – review and editing.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

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