

Surviving a Decade or More After Coronary Revascularization in a Middle Eastern Population: The Impact of Diabetes Mellitus.

Imad A Alhaddad (✉ alhaddad63@gmail.com)

Jordan Hospital <https://orcid.org/0000-0002-7723-5479>

Ramzi Tabbalat

Abdali Medical Center

Yousef Khader

Jordan University of Science and Technology

Zaid Elkarmi

Jordan Hospital

Zaid Dahabreh

Jordan Hospital

Ayman Hammoudeh

Istishari Hospital

Research Article

Keywords: Surviving a Decade, Coronary Revascularization, Diabetes Mellitus

Posted Date: February 26th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-242417/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Introduction and aims

There is scarcity of studies that evaluate cardiovascular events and repeat revascularization among Middle Eastern patients who have long-term survival after coronary artery revascularization. In this study, patients who survived at least 10 years after percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) were assessed for the evolution of cardiovascular risk factors, occurrence of acute cardiovascular events and the need for further coronary revascularization procedures after the index coronary revascularization. Patients were classified according to the presence or absence of diabetes mellitus (DM) at baseline.

Methods

The study enrolled consecutive ambulatory or in-patients who had PCI or CABG at least 10 years prior to enrollment. Collected data included cardiovascular risk factors at the time of the index revascularization and evolution of risk factors since then, occurrence of cardiovascular events and the need for coronary revascularization after the index procedure. Events were compared between patients with DM and no DM at baseline.

Results

The study population consisted of 891 consecutive patients with 351 patients (39.4%) had DM and 540 patients (60.6%) had no DM. Of all patients, 123 (13.8%) were females with the DM group had more females compared to no DM group (19.7 vs 10%, $p < 0.001$). Mean age of the study population at baseline was 53.9 ± 8.8 years for DM patients and 53.0 ± 9.8 years for no DM patients ($p = 0.16$). At baseline, the DM group had more hypertension (70.9% vs 27.6%, $p < 0.0001$), more dyslipidemias (12% vs 5.2%, $p = 0.001$) but less smokers compared to no DM group (44.4% vs 58.3%, $p < 0.001$). DM and no DM groups had similar proportion of PCI (65.5% vs 68.3%, $p = 0.42$) and CABG at baseline (34.5% vs 31.7%, $p = 0.43$).

The mean time elapsed since the index coronary revascularization was 13.5 ± 3.5 years for DM patients and 14.4 ± 4.8 years for no DM ($p = 0.02$). Following the index revascularization procedure, ACS events occurred in 40.7% of diabetic patients and in 41.6% in no DM patients ($p = 0.82$). Heart failure and stroke developed in similar proportions in the DM and no DM groups (12.5% vs 13.3%, $p = 0.51$) and (4.6% vs 5.9%, $p = 0.75$) respectively. Repeat revascularization after the index procedure showed that DM group had more PCI compared to no DM group (52.7% vs 45.4%, $p = 0.04$) but proportions of CABG (7.1% vs 9.8%, $p = 0.20$).

Conclusions

In this retrospective observation of Middle Eastern patients who survived at least a decade after coronary revascularization, DM group had more hypertension and dyslipidemias but less smokers compared to no

DM at baseline. During follow up, DM group required more PCI revascularization compared with no DM group.

Introduction

Coronary artery disease (CAD) is the leading cause of death in the Middle East (1–3) and many patients require coronary artery revascularization by either coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI).

Diabetes mellitus (DM) is a major risk factor for the development and progression of CAD and adverse cardiovascular outcomes. The prevalence of DM is high and rapidly increasing among Middle Eastern region (4–7). There is scarcity of studies that addressed the impact of DM on the evolution of risk factors and the need for further coronary revascularization after the initial revascularization procedure in the Middle East.

The current study enrolled Middle Eastern patients who had undergone coronary revascularization at least one decade earlier to determine the impact of DM on the prevalence and evolution of cardiovascular risk factors, the occurrence of cardiovascular events, and the need for further coronary revascularizations.

Methods

We enrolled consecutive Middle Eastern patients who had coronary revascularization by either PCI or CABG at least 10 years prior to enrollment. Patients were included if they were ≥ 18 years old at the time of the index coronary revascularization with available medical records and adequate documentation of patients' events.

Patients were enrollment during routine out-patient evaluation or in-patient settings when they sought medical care for cardiovascular or non-cardiovascular health issues. A case report form for each patient was filled out by the physician assigned by the study steering committee in each participating center. Data were collected from patients, relatives and from medical records according to predefined criteria for each variable. Patients were categorized at the time of the index coronary revascularization as having DM or not having DM. Data were analyzed and compared accordingly for clinical characteristics at baseline, evolution of cardiovascular risk factors, cardiovascular events and further coronary revascularization from the time of the index procedure until the time of enrollment.

Cardiovascular risk factors were defined according to standard definitions published by the American College of Cardiology/American Heart Association (8). Hypertension was defined as having either systolic blood pressure elevated above 140 mm Hg and/or diastolic blood pressure above 90 mm Hg on several occasions during hospital stay, being diagnosed to have hypertension or prescribed anti hypertension medications by a treating physician. DM was defined according to the standard criteria set by the American Diabetes Association, i.e., fasting serum glucose ≥ 126 mg/dl, 2-hour glucose level ≥ 200 mg/dl, or glycosylated hemoglobin (HbA1c) value $\geq 6.5\%$. DM was also diagnosed in patients who

had unequivocal hyperglycemia and classical symptoms of DM (polyuria, polydipsia, and unexplained weight loss) and casual plasma glucose ≥ 200 mg/dL, and those with a prior diagnosis of DM or who were prescribed anti-diabetic medications by a treating physician. Patients who were cigarette smokers at enrollment were considered current smokers. Patients who never smoked, and past smokers who quit at least one month prior to enrollment were considered non-smokers. Family history of premature CVD was defined as MI, coronary revascularization, or sudden death before 55 years of age in father or other male first degree relative, or before 65 years of age in mother or other female first-degree relative.

Hypercholesterolemia was determined by a diagnosis by a physician or/and a lipid lowering agent prescription, serum cholesterol ≥ 240 mg/dL, or low-density lipoprotein cholesterol level ≥ 100 mg/dL.

Cardiovascular events that occurred since the index coronary revascularization included (a) acute coronary syndrome diagnosed by documented typical chest pain, electrocardiographic changes of ST-segment elevation or depression, T-wave inversion, with or without elevated cardiac enzymes, (b) heart failure, diagnosed by a physician based on clinical, radiological and echocardiographic features of left ventricular systolic dysfunction (ejection fraction $< 40\%$), (c) stroke, diagnosed by a neurologist, (d) chronic renal impairment, defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) Less than 60 ml/min/1.73 m² persisting for 3 months or more, irrespective of the cause.

Further coronary revascularization included all documented repeat PCI or CABG after the index procedure. Use of guideline-directed secondary cardiovascular prevention medications was documented. Medications included antiplatelet medications (aspirin, clopidogrel and ticagrelor), beta blockers, renin-angiotensin system blockers (angiotensin converting enzyme inhibitors, angiotensin II blockers and valsartan-sacubitril), lipid-lowering agents (statins, fibrates or ezetimibe).

The study was approved by the Internal Review Board in all participating centers and an informed consent was obtained from all patients.

Statistical Analysis: Patients' characteristics were described using frequency and percentages for categorical variables and in mean \pm SD for continuous variables. The differences in percentages between DM and no DM groups were analyzed using the Chi-square test and the differences in the means between the two groups were analyzed using the two-tailed Student's *t* test. A *p* value of less than 0.05 was considered statistically significant. All *p* values were the results of two-tailed tests.

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Results

Table 1 shows baseline clinical characteristics at the time of the index coronary revascularization according to DM status. Patients in the DM group were more likely to have hypertension and dyslipidemia and were less likely to be smokers compared with patients with no DM group. The no DM group had longer time elapsed since the index revascularization to enrollment compared with DM group and that

mainly driven by more patients in the no DM who had over 20 years elapsed since the index procedure. There were no significant differences in the other characteristics between the two groups.

Table 1
Baseline clinical characteristics at the time of the index coronary revascularization according to diabetes mellitus (DM) status.

Clinical feature	DM (N = 351) (39.4%)	No DM (N = 540) (60.6%)	p-value
Age at first coronary revascularization (years)	53.9 ± 8.75	53.0 ± 9.82	0.164
≤ 45	51 (14.5)	98 (18.1)	0.578
> 45	300 (85.5)	442 (81.9)	0.196
Coronary revascularization at baseline	230 (65.5)	369 (68.3)	0.399
Percutaneous coronary intervention (PCI)	121 (34.5)	171 (31.7)	0.426
Coronary artery bypass graft (CABG) surgery			
Years since first coronary revascularization	13.5 ± 3.5	14.4 ± 4.8	0.025
10 years	105 (29.9)	149 (27.6)	0.689
11–20 years	235 (67)	339 (62.8)	0.301
> 20 years	11 (3.1)	52 (9.6)	< 0.001
Women	69 (19.7)	54 (10)	< 0.001
Hypertension	249 (70.9)	149 (27.6)	< 0.001
Dyslipidemia	42 (12)	28 (5.2)	< 0.001
Cigarette smoking	157(44.4)	315 (58.3)	< 0.001
Family history of premature CAD	30 (8.5)	35 (6.5)	0.252

Table 2 demonstrates the evolution of major risk factors and the development of major adverse events among the two groups from the index procedure till enrollment. The no MD group were more likely to develop hypertension compared to DM group. There were no significant differences in the evolution of other risk factors of clinical events among the two groups.

Table 2

Emerging risk factors and cardiovascular events since the first coronary revascularization

Event	DM	No DM	P-value
	N (%)	N (%)	
Emerging risk factors after the initial procedure	-	167(30.9)	-
- No DM initially developed DM	33 (9.4)	107(19.8)	< 0.001
- Developed hypertension	2 (0.6)	3 (0.6)	1.000
- Became smoker	70 (19.9)	129 (23.9)	0.519
- Quit smoking			
Cardiovascular events after the initial procedure	143 (40.7)	225 (41.7)	0.820
- Acute coronary syndrome	44 (12.5)	72 (13.3)	0.511
- Congestive heart failure	16 (4.6)	32 (5.9)	0.748
- Stroke	7 (2)	19 (3.5)	0.479
- Renal Failure			
DM: Diabetes Mellitus			

Table 3 summarizes the need for further coronary revascularization after the index procedure till enrollment. The DM group was more likely to require PCI procedures compared to no DM group. CABG was required similarly in the two groups.

Table 3

Repeat coronary revascularization after the index procedure

Procedure	DM	No DM	p-value
PCI: Total patients	N (%)	N (%)	0.039
- One occasion	184 (52.4)	246 (45.6)	
- Two occasions	106 (30.2)	152 (28.1)	
- Three or more occasions	45 (12.8)	71 (13.1)	
	33 (9.4)	23 (4.3)	
CABG: Total patients	25 (7.1)	53 (9.8)	0.202
- One occasion	25(7.1)	51(9.4)	
- Two occasions	0	2 (0.4)	
- Three or more occasions	0	0	
PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass graft surgery			

Table 4 shows cardiometabolic medications used in diabetic vs non diabetic patients at the time of enrollment. Generally, there was a high utilization of guideline-directed secondary preventive therapies with no significant difference between the two groups except higher utilization of clopidogrel in the DM group compared to no DM.

Table 4
Utilization of cardiometabolic medications at enrollment

Medication	DM N (%)	No DM N (%)	P-value
Aspirin	295 (92)	449 (89.6)	0.609
Second antiplatelet agent	124 (38.6)	175 (34.9)	0.023
- Clopidogrel	16 (5)	13 (2.6)	0.081
- Ticagrelor			
Beta blocker	257 (80)	383 (76.4)	0.192
ACEI or ARB	190 (54.1)	292 (54)	1.000
Lipid lowering agent	287(89.4)	459 (91.4)	0.355
- Statin	9 (2.8)	23(4.6)	0.327
- Fibrate	3 (0.9)	10 (2)	0.935
- Ezetimibe	3 (0.9)	2 (0.4)	0.948
- Combination			
ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker.			

Discussion

This is the first report, up to our knowledge, that addressed the impact of DM on the prevalence and evolution of cardiovascular risk factors, the occurrence of cardiovascular events, the need for further coronary revascularizations among long-term survivors of coronary revascularization in a Middle Eastern population. Almost 40% of the study population had DM at baseline with close to additional 30% developed DM during the elapsed time between the index procedure and enrollment. This finding speaks to the alarming high prevalence of DM in our region. With the addition of high smoking rate among our population, it is not surprising to see the baseline index revascularization was performed at a very young age compared to western population.

The DM group required more repeat PCI compared to the no DM group; however, CABG and adverse cardiovascular outcomes were similar among the two groups. This may be related to the retrospective nature of the current study and longer time elapsed after the index revascularization in no DM group.

Retrospective nature of this study may have downplayed or missed more serious adverse events in the DM group like mortality or major disability that prevents enrollment of such patients. This is partially supported by the longer time elapsed after the index revascularization in the no DM group, thus many adverse events and repeat revascularizations are related to time factor diminishing the impact of DM. Furthermore, extended survival in this report after the index revascularization could be related to a relatively young age of patients at the time of index procedure, adoption of contemporary percutaneous and surgical coronary revascularization strategies, and the high utilization of secondary cardiovascular prevention medications.

The global burden of DM has more than doubled over the last three decades (5) with a greater escalation over the same time span was seen in the Middle East (4–6). The ascending trends of DM prevalence in our region leads to more premature heart disease, stroke and other vascular disorders (9, 10). The cardiovascular diseases (CVD) had become the leading cause of death in the Middle East (1–3, 10), with almost one to two thirds of patients admitted with acute coronary syndrome (ACS) are diabetics (11–13). These alarming trends in the prevalence of DM and premature CVD in the region should be addressed and overturned through national and regional preventive health policies.

Coronary atherosclerosis in patients with DM is usually diffuse and rapidly progressive disease (R). Revascularization in these patients is usually faced with augmented risk related to DM itself, type of treatment and the angiographic complexity of CAD. Thus, it is not surprising to find that revascularization in DM patients is associated with higher rates of major cardiac adverse events (MACE) compared to no DM (14–16).

Limitations

The major limitation of the study is inherited in its retrospective design. Enrollment was limited to patients encountered after at least 10 years after coronary revascularization. The information may be biased by random selection and lack of prospective controlled data collection.

Conclusions

In this retrospective observation of Middle Eastern patients who survived at least a decade after coronary revascularization, the initial revascularization procedure was performed at a younger age compared to western population mostly related to abundance of risk factors. Almost 40% of the population had DM at baseline and an additional 30% acquired DM during the elapsed time. During follow up, DM group required more PCI revascularization compared with no DM group. Preventive strategies targeting Middle East populations are essential to minimize the burden of the disease and its consequences.

Declarations

Competing interests: The authors declare that they have no competing interests.

Funding: None

Authors' contributions:

Imad Alhaddad: Conception, design, acquisition, interpretation of data, drafting and substantial revision

Ramzi Tabbalat: Conception, design and acquisition

Yousef Khader: Acquisition, analysis, interpretation of data and substantial revision

Zaid Alkarmi: Acquisition, interpretation of data and drafting

Ayman Hammoudeh: Conception, design, acquisition, interpretation of data and substantial revision

Acknowledgements

We would like to thank the following physicians for participation in patients' enrollments (alphabetical order): Ahmad Abdulsattar, MD; Ahmad R. Othman, MD; Ahmad Tamari, MD; Akram Saleh, MD; Ala'eddin Jaber, MD; Amr Karmi, MD; Ghufran F. Al-Dloush, MD; Islam Abu Sedo, MD; Lobaba Qabbaa, MD; Mahmoud Izraiq, MD; Moath Alfawara, MD; Mohammad A Al-Jarrah, MD; Murad A. Alkouz, MD; Rashid Ibdah, MD; Sokaina Rawashdeh, MD; Yahia Shahwan, MD; and Zaid Dahabreh, MD.

References

1. Alsheikh-Ali AA, Omar MI, Raal FJ, Rashed W, Hamoui O, Kane A, Alami M, Abreu P, Mashhoud WM. Cardiovascular risk factor burden in Africa and the Middle East: the Africa Middle East Cardiovascular Epidemiological (ACE) study. *PloS One*. 2014 Aug 4;9(8):e102830. Doi: 10.1371/journal.pone.0102830. eCollection 2014.
2. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanans F, McQueen M, Budaj A, Pais P, Varigosx J, Lisheng L; on behalf of the INTERHEART Study Investigatorsx. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;364:937-52.
3. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ. Selected major risk factors and global and regional burden of disease. *Lancet* 2002; 360:1347-60.
4. Majeed A., El-Sayed A. A., Khoja T., Alshamsan R., Millett C., Rawaf S. (2014). Diabetes in the middle-East and North Africa: An update. *Diabetes Research Clinical Practice*, 103(2), 218–222.
5. Global Report on Diabetes [Database on the Internet], WHO, 2016, Available from: <http://www.who.int>
6. Kalan Farmanfarma KH, Ansari-Moghaddamb A, Zarebanc I, Adineh HA. Prevalence of type 2 diabetes in Middle–East: Systematic review& meta-analysis. *Primary Care Diabetes* 2020;14:297-304.
7. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: Systematic analysis of health

- examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 2011;378:31–40.
8. Cannon CP, Brindis RG, Chaitman BR, Cohen DJ, Cross Jr JT, Drozda Jr JP, Fesmire FM, Fintel DJ, Fonarow GC, Fox KA, Gray DT, Harrington RA, Hicks KA, Hollander JE, Krumholz H, Labarthe DR, Long JB, Mascette AM, Meyer C, Peterson ED, Radford MJ, Roe MT, Richmann JB, Selker HP, Shahian DM, Shaw RE, Sprenger S, Swor R, Underberg JA, Van de Werf F, Weiner BH, Weintraub WS. 2013 ACCF/AHA Key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Acute Coronary Syndromes and Coronary Artery Disease Clinical Data Standards). *Crit Pathw Cardiol*. 2013;12:65-105.
 9. Danaei G, Singh GM, Paciorek CJ, Lin JK, Cowan MJ, Finucane MM, et al. The global cardiovascular risk transition: Associations of four metabolic risk factors with national income, urbanization, and Western diet in 1980 and 2008. 2013;127:1493–502. 15021.
 10. Gehani AA, Al-Hinai AT, Zubaid M, Almahmeed W, Hasani MR, Yusufali AH, Hassan MO, Lewis BS, Islam S, Rangarajan S, Yusuf S, for the INTERHEART Investigators in Middle East. Association of risk factors with acute myocardial infarction in Middle Eastern countries: the INTERHEART Middle East study. *Eur J Prev Cardiol* 2014;21:400-410.
 11. Saleh A, Hammoudeh AJ, Hamam I, Khader YS, Alhaddad I, Nammas A, Tarawneh H, Tabbalat R, Harassis A, Bakri M, Alnaquib A, Izraiq M, Al-Mousa E. Prevalence and impact on prognosis of glucometabolic states in acute coronary syndrome in a Middle Eastern country: The GLucometabolic abnOrmalities in patients with acute coronaRY syndrome in Jordan (GLORY) study. *Inter J Diab Develop Countries* 2012; 32:37-43.
 12. Hammoudeh AJ, Izraiq M, Hamdan H, Tarawneh H, Harassis A, Tabbalat R, Al-Mousa E, Yahya I, Shobaki N, Alhaddad I. High-sensitivity C-reactive protein is an independent predictor of future cardiovascular events in Middle Eastern patients with acute coronary syndrome. CRP and prognosis in acute coronary syndrome. *Inter J Atheroscl* 2008;3:50-55.
 13. Hammoudeh AJ, Alhaddad IA, Khader Y, Tabbalat R, Al-Mousa E, Saleh A, Jarrah M, Nammas A, Izraiq M. Cardiovascular risk factors in Middle Eastern patients undergoing percutaneous coronary intervention: Results from the first Jordanian percutaneous coronary intervention study. *J Saudi Heart Assoc* 2017;29:195–202.
 14. Bartorelli AL, Assenza GE, Abizaid A, et al. e-SELECT investigators. One-year clinical outcomes after sirolimus-eluting coronary stent implantation in diabetics enrolled in the worldwide e-SELECT registry. *Catheter Cardiovasc Interv* 2016; 87:52–62.
 15. Koskinas KC, Siontis GC, Piccolo R, et al. Impact of diabetic status on outcomes after revascularization with drug-eluting stents in relation to coronary artery disease complexity: patient-level pooled analysis of 6081 patients. *Circ Cardiovasc Interv* 2016; 9:e003255.

16. Kappetein AP, Head SJ, Morice MC, et al. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J CardiothoracSurg* 2013;43:1006-13.