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Coronary angiography in the very old: impact of diabetes on long-term revascularization and mortality

Elad Shemesh, Barak Zafrir

Department of Cardiovascular Medicine, Lady Davis Carmel Medical Center, Haifa, Israel

Abstract

Background   Diabetes is often associated with coronary artery disease, leading to adverse clinical outcomes. Real-world data is limited regarding the impact of diabetes in very old patients undergoing coronary angiography on the risk for late or repeated coronary revascularization and mortality. **Methods**   Retrospective analysis of 1,353 consecutive patients $\geq$ 80 years who were admitted to the cardiac unit and further underwent coronary angiography. Subsequent revascularization procedures and all-cause mortality were recorded over a median follow-up of 47 months and their relation to diabetic status and presentation with acute coronary syndrome (ACS) was studied. **Results**   Diabetes was present in 31% of the patients undergoing coronary angiography, and was associated with higher rates of obesity, hypertension, hyperlipidemia, chronic kidney disease and female gender. ACS was the presenting diagnosis in 71% of the patients and was associated with worse survival (1-year mortality 20% in ACS *vs*. 6.2% in non-ACS patients, *P* < 0.0001). Increase in long-term mortality rates was seen in diabetic subjects compared to non-diabetic subjects presenting with ACS (log-rank *P* = 0.005), but not in the non-ACS setting (*P* = 0.199). In a multivariable model, additionally adjusting for acuity of presentation, the presence of diabetes was associated with an adjusted hazard ratio of 1.60 (95% confidence interval: 1.12–2.28), *P* = 0.011, for the need of late or repeat coronary revascularization and 1.48 (1.26–1.74), *P* < 0.0001 for all-cause mortality, during long-term follow-up. **Conclusions**   In very old patients undergoing coronary angiography, presentation with ACS was associated with worse survival. Diabetes was an independent predictor of late or repeated revascularization and long-term mortality.

1   Introduction

The population above eighty years of age in developed countries has more than doubled in recent decades. This reflects the increase in life expectancy, reaching 80.7 years in men and 84.6 years in women in Israel.[1] The prevalence of coronary artery disease (CAD) increases with age, and age is an independent predictor of adverse events after acute coronary syndrome (ACS).[2] Persons above the age of eighty are less likely to be treated with evidence-based invasive coronary procedures,[3] due to multiple factors such as: (1) delayed onset of presentation, (2) atypical symptoms making the diagnosis more challenging,[4] (3) the concern from life-limiting adverse events, (4) higher periprocedural complications,[5] (5) existing comorbidities,[6] and (6) perception of lower impact on clinical outcomes and longevity.

One of the most common comorbidities in the older population is type 2 diabetes, which is associated with a more complex and rapidly progressive atherosclerosis,[7] leading to unfavorable clinical outcomes, increased risk for post-procedural complications and need for repeat revascularization.[8,9] Elderly patients are often excluded from clinical trials regarding treatment options for ACS and diabetes.[10] Accordingly, there are limited evidence-based data on the management and outcomes of very old diabetic patients presenting to coronary angiography.

Therefore, in the present study we aimed to further investigate this unique and growing group of very old patients referred for coronary angiography, by assessing whether the presence of diabetes impacts the risk for late or repeated coronary revascularization and all-cause mortality, and by evaluating the impact of acuity of presentation with ACS on these outcomes.

2   Methods

2.1   Study population

The cardiac catheterization laboratory database of Car-

mel Medical Center, Haifa, Israel, was examined retrospectively for patients aged 80 years and older undergoing coronary angiography. Only the first angiography of each patient performed during the years 2000–2016 was included. Patients were classified according to the presence of diabetes mellitus, as was prospectively documented during the presentation at the cardiac catheterization unit. Identification of diabetes mellitus was based on primary care physicians diagnosis, according to clinical judgment and customary definitions. Data regarding age, gender, clinical risk factors and comorbidities were determined retrospectively from patients' electronic files and computerized records of health maintenance organizations. Study outcomes included subsequent coronary revascularization during long-term follow-up [both percutaneous coronary interventions (PCI) and cardiac surgery], as well as all-cause mortality, which were analyzed in relation to the presence of diabetes at baseline evaluation.

The study database was approved by Carmel Medical Center Ethics Committee with waiving of the need for individual patient consent.

2.2   Data analysis

Continuous data are presented as means ± SD or medians and interquartile range (IQR). Categorical variables are presented as numbers and percentages. Independent samples *t*-test was used to compare continuous variables, and Chi-square was used to compare categorical variables. Long-term revascularization rates and all-cause mortality in relation to diabetes status and presentation with ACS were calculated using the Kaplan-Meier method, and statistical comparison performed using the log-rank test. Multivariable analysis of the association of diabetes with long-term outcomes was performed using the Cox proportional hazards model with forward stepwise selection of covariates, calculating hazard ratios (HR) and 95% confidence intervals (CI). The model was adjusted for age and gender alone, or with further adjustment to relevant clinical variables as well as presentation with ACS and whether a baseline revascularization procedure was performed.

Results were considered statistically significant when the 2-sided *P*-value was < 0.05. SPSS statistical software version 25 was used to perform all statistical analyses.

3   Results

Study population included 1353 consecutive patients aged ≥ 80 years undergoing coronary angiography during the study period. Mean age was 83.4 ± 3.3 years and 40% were females. Age distribution according to gender is pre-

sented in Figure 1. Diabetes was present in 420 of the patients undergoing coronary angiography (31%). Baseline characteristics of the study population according to the presence or absence of diabetes is presented in Table 1. Compared to non-diabetics, diabetes was associated with higher rates of obesity, hypertension, hyperlipidemia, chronic kidney disease and female gender, but similar rates of smoking. In addition, diabetics presented more often with ACS, in particular unstable angina or non ST-segment elevation myocardial infarction (NSTEMI).
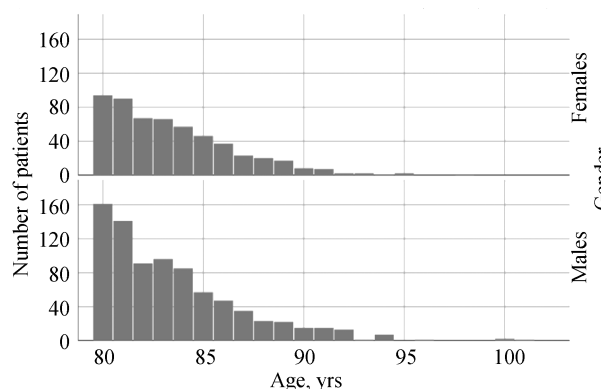

Figure 1.   Age distribution of study population, stratified by gender.

Table 1.   Baseline characteristics according to the presence of diabetes.

Variable	Total (*n* = 1353)	No diabetes (*n* = 933)	Diabetes (*n* = 420)	*P* value
Age, yrs	83.4 ± 3.3	83.6 ± 3.5	83.0 ± 2.7	0.001
Gender, Female	540 (40%)	353 (38%)	187 (44.5%)	0.023
BMI, kg/m²	26.4 ± 4.0	26.1 ± 3.9	27.2 ± 4.1	< 0.001
Obesity	238 (17.6%)	138 (14.8%)	100 (23.8%)	< 0.001
Hypertension	1126 (83%)	739 (79%)	387 (92%)	< 0.001
Hyperlipidemia	897 (66%)	565 (61%)	332 (79%)	< 0.001
Active smoking	56 (4.1%)	39 (4.2%)	17 (4.0%)	0.910
Past smoking	176 (13%)	117 (13%)	59 (14%)	0.485
Chronic kidney disease	144 (10.6%)	72 (7.7%)	72 (17.1%)	< 0.001
Hemoglobin, g/dL	12.6 ± 1.6	12.8 ± 1.6	12.1 ± 1.5	< 0.001
Peripheral artery disease	56 (4.1%)	36 (3.9%)	20 (4.8%)	0.462
Presentation with ACS	964 (71.2%)	646 (69.2%)	318 (75.7%)	0.015
UAP/NSTEMI	757 (55.9%)	492 (52.7%)	265 (63.1%)	0.002
STEMI	207 (15.3%)	154 (16.5%)	53 (12.6%)	

Data are presented as mean ± SD or *n* (%). ACS: acute coronary syndrome; BMI: body mass index; NSTEMI: non ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; UAP: unstable angina pectoris.

Coronary angiography was performed in the setting of ACS in 964 patients (71%); of them, 67% had undergone a baseline revascularization procedure. Over a median follow-up of 47 months (interquartile range (IQR): 17–79 months), 735 patients (53%) have died. ACS was associated with significantly worse survival rates (crude 1-year mortality rate of 20% in ACS versus 6.2% in non-ACS patients, $P <$ 0.0001). ACS patients in whom PCI was performed at baseline presentation had lower 1-year mortality rates (17.6% *vs.* 23.3%, $P = 0.028$).

During follow-up period, late or repeat coronary revascularization was performed in 128 patients (9.5%). Cumulative rates of coronary revascularization (Figure 2A) and all-cause mortality (Figure 2B) were significantly higher in diabetics compared to non-diabetics (log-rank $P = 0.0018$ and $P = 0.0006$, respectively). In patients presenting with ACS, diabetes was associated with significantly higher cumulative rates of mortality compared to non-diabetes (log-rank $P = 0.005$), a relationship which was not seen in those presenting in the non-ACS setting (log-rank $P = 0.199$) (Figure 3).

Unadjusted, age- and gender-adjusted, and multivariable adjusted hazard ratios for long-term mortality and need for late or repeat coronary revascularization, associated with the presence of diabetes, are presented in Table 2. In a multivariable model adjusting for age, gender, body mass index, hypertension, hyperlipidemia, active smoking, renal failure,
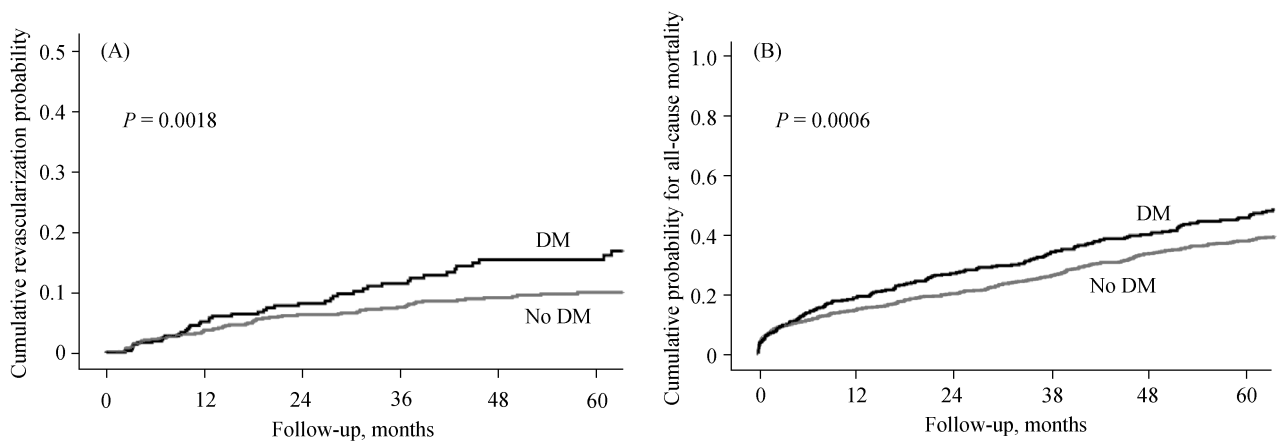

Figure 2.   Cumulative 5-year rates of (A) coronary revascularization and (B) all-cause mortality, according to the presence of diabetes. DM: diabetes mellitus.
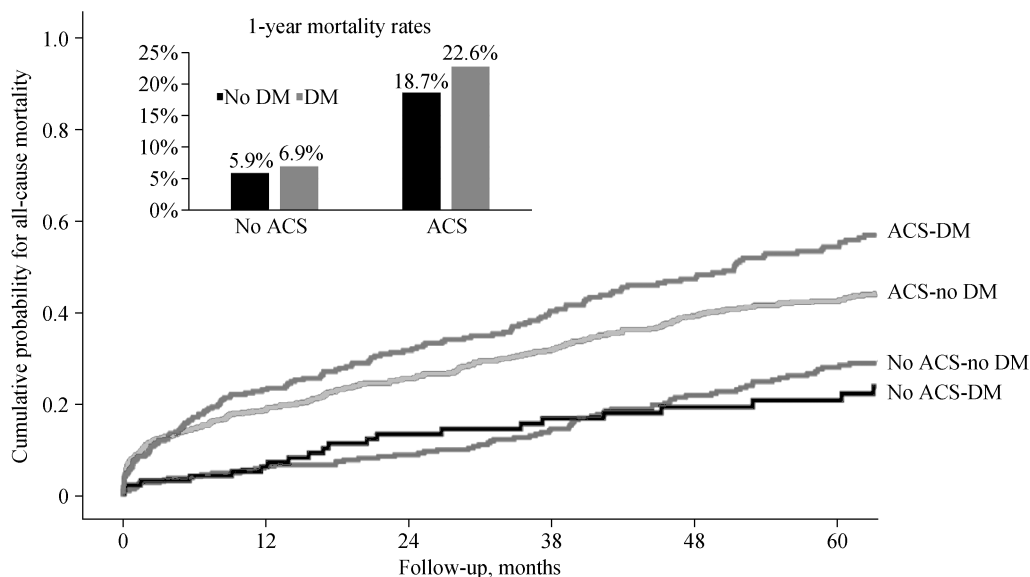

Figure 3.   Cumulative 5-year mortality rates, according presentation with acute coronary syndrome and the presence of diabetes. Log rank $P = 0.005$ for ACS comparison and 0.199 for no-ACS comparison. ACS: acute coronary syndrome; DM: diabetes mellitus.

Table 2.   Unadjusted and adjusted hazard ratios for long-term mortality or need for coronary revascularization, associated with the presence of diabetes.

Outcome	Unadjusted	Age and gender adjustment	Mulitvariable* adjustment
All-cause mortality	1.31 (1.12–1.53)	1.38 (1.18–1.61)	1.48 (1.26–1.74)
	$P = 0.001$	$P < 0.0001$	$P < 0.0001$
Coronary revascularization	1.75 (1.23–2.49)	1.82 (1.27–2.59)	1.60 (1.12–2.28)
	$P = 0.002$	$P = 0.001$	$P = 0.011$

*Adjusted for age, gender, body mass index, hypertension, hyperlipidemia, active smoking, renal failure, presentation with acute coronary syndrome and index revascularization.

as well as presentation with ACS and index revascularization, the presence of diabetes was associated with an adjusted HR of 1.60 (95% CI: 1.12–2.28), $P = 0.011$ for the need of future coronary revascularization and 1.48 (95% CI: 1.26–1.74), $P < 0.0001$ for all-cause mortality, during follow-up.

4   Discussion

In patients above eighty years of age undergoing coronary angiography, presentation with ACS was associated with worse survival, in particular when PCI was not performed, and the presence of diabetes was an independent predictor of the need for late or repeat coronary revascularization and long-term mortality.

Age is a major non-modifiable cardiovascular risk factor, and CAD significantly contributes to morbidity and mortality at older age. In recent years, there has been a marked increase in the frequency of interventional coronary procedures performed in very elderly patients, and less patients presenting with ACS are now managed conservatively with medical treatment alone.[11] This beneficial effect of invasive strategy was also reported in several clinical trials.[12,13] Despite the emergence of such clinical trials assessing this unique and growing group of patients and the formation of designated guidelines, practice patterns continue to show less use of pharmaceutical and interventional care, even in elderly individuals who are likely to benefit.[14]

In the non-ACS setting, elective PCI in elderly patients was shown to have high procedural success rates with relatively low morbidity, suggesting that PCI is safe and effective in stable CAD among the very elderly patients.[15] However, the prognosis of patients presenting to coronary angiography with ACS requiring hospitalization is much worse, which might be explained by a tendency of late arrival, presentation with more atypical symptoms, the lower chance of having timely reperfusion, and mechanistically as elderly patients often have more calcified lesions with multi-vessel involvement, requiring more complex coronary interventions. Similar patterns were observed in the current

study, showing a significantly reduced survival in patients presenting with ACS than those who underwent coronary angiography in a non-ACS setting. In STEMI-ACS, higher rates of arrhythmias, heart failure and mechanical complications are reported in the elderly population, impacting mortality.[16] Nevertheless, primary PCI improves cardiovascular well-being in the very elderly presenting with STEMI, and is associated with a favorable prognosis compared to medical management alone.[17] In non-STEMI ACS, a benefit from revascularization is also reported, with better in-hospital and 6-months outcomes than those who receive medical management alone.[18] In the current study, performing revascularization at index event was associated with better survival, though one-year mortality rates were still significant in those undergoing PCI, in line with other cohorts in which mortality after PCI was shown to increase with age.[19] This may be explained by non-cardiac causes that may develop in the post-procedural period,[20] such as stroke, major bleeding episodes and renal failure requiring dialysis,[21] as well as additional reasons associated with the high comorbidity rate at older age.

The ageing population has multiple coexisting chronic conditions and diabetes mellitus is increasingly prevalent in very old adults. Different lifestyle factors contribute to the rise in incidence of diabetes with age.[22,23] Previous retrospective studies showed a complex relationship between glucose levels, revascularization and mortality in the elderly.[24] Nevertheless, the evidence regarding adverse cardiovascular outcomes in very old diabetics with CAD is limited, as elderly patients are commonly excluded from clinical trials. Regardless of the diagnosis of ACS in our study, diabetes was noted as an independent predictor of the need for late or repeat coronary revascularization and long-term mortality in the very old population undergoing coronary angiography. Although this finding was more apparent in diabetics presenting with ACS, diabetes remained an independent predictor of morbidity and mortality after multivariate adjustment. Diabetes is both a risk marker and treatment target in elderly patients with CAD. In addition to glycemic control, cardiovascular risk reduction in diabetics

may be achieved from the control of concurrent risk factors such as hypertension and dyslipidemia.[25]

4.1   Limitations

Several issues limit the interpretation of the current study. The cohort of patients enrolled was established through the course of several years, thereby introducing potential heterogeneity. For example, during the years the type of revascularization being performed, and the type of stents used have changed. Furthermore, the diagnosis of diabetes was made through assessing the patient files, and not by directly measuring glucose levels, making sensitivity analyses based on glucose levels, exclusion of patients who suffered from hypoglycemic events, or restricted to those with new-onset diabetes, not feasible. In addition, no data regarding cognitive disorders, physical disabilities or frailty of the patients was available. Finally, the association between diabetes and adverse outcomes after coronary angiography does not prove causation.

4.2   Conclusions

The presence of diabetes in very old patients undergoing coronary angiography was an independent predictor of late or repeat revascularization and long-term mortality, in particular when presenting with ACS which was associated with worse survival. With the ageing of the population and the increase in the prevalence of the metabolic syndrome, diabetes may significantly impact on the incidence and outcomes of ACS in the very old population.

Acknowledgments

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