

Long-Term Prognosis in Young Patients with Acute Coronary Syndrome Treated with Percutaneous Coronary Intervention

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Background: Acute coronary syndrome (ACS) at a young age is uncommon. Limited data regarding the long-term follow-up and prognosis in this population are available. Our objectives were to evaluate the long-term clinical outcomes of patients presenting with ACS at a young age and to assess factors that predict long-term prognosis.

Methods: A retrospective analysis of consecutive young patients (male below 40 and female below 50 years old) that were admitted with ACS and underwent percutaneous coronary intervention (PCI) between the years 1997 and 2009. Demographics, clinical characteristics, and clinical outcomes including major cardiovascular (CV) events and mortality were analyzed. Multivariable cox proportional hazard model was performed to identify predictors of long-term prognosis.

Results: One-hundred sixty-five patients were included with a mean follow-up of 9.1±4.6 years. Most patients were men (88%), and mean age (years) was 36.8±4.2. During follow-up, 15 (9.1%) died, 98 (59.4%) patients had at least one major CV event, 22 (13.3%) patients had more than two CV events, and the mean number of recurrent CV events was 1.4±1.48 events per patient. In multivariate analysis, the strongest predictors of major CV events and/or mortality were coronary intervention without stent insertion (HR 1.77; 95% CI 1.09–2.9), LAD artery involvement (HR 1.59; 95% CI 1.04–2.44) and hypertension (HR 1.6; 95% CI 1.0–2.6).

Conclusion: Patients with ACS in young age are at high risk for major CV and/or mortality in long-term follow-up with a high rate of recurrent CV events. Close follow-up and risk factor management for secondary prevention have a major role, particularly in this population.

Keywords: acute coronary syndrome, ACS, NSTEMI, STEMI, young population, outcomes

Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide.^{1,2} Several studies have shown that coronary atherosclerosis begins in the second or third decade of life with an increased prevalence with age in both males and females.^{3–5} However, the clinical manifestations of acute coronary syndrome (ACS) in most cases occur later, during the fifth to seventh decade of life^{6,7} and only 2–10% of all patients with ACS, are younger than 40 years old.^{8,9}

Young patients with ACS have unique characteristics with distinct risk factors and clinical manifestations. Prior studies have shown that family history, hypercholesterolemia, sedentary lifestyles, obesity and smoking were common risk factors

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in young patients with ACS compared to older age groups.^{8,10–15} Diabetes and smoking in young patients is a significant risk factor for recurrent coronary events and interventions, as well as mortality.^{14,15} In addition, there is an association between ethnicity and geographical location and the incidence of ACS events at a young age.^{16,17}

When compared to an older population, ST-segment elevation myocardial infarction (STEMI) is more common in young patients compared to non-ST-segment elevation myocardial infarction (NSTEMI).^{12,13,18} Young ACS patients have a lower incidence of multi-vessel (MVD) and left main (LM) disease,^{16,17} whereas involvement of the left anterior descending (LAD) artery is more common.¹⁴

Previous studies in this population mainly focused on risk factors and the unique clinical characteristics of this group,^{11–18} while others focused on in-hospital and short-term outcomes which demonstrated improved outcomes in the young ACS population.^{13,18,19} To date, only a limited number of studies have evaluated the long-term outcomes of this population, most of which were performed prior to the widespread use of the invasive strategy in patients with ACS.^{10,11,20} The goal of this study was to evaluate the long-term clinical outcomes of young patients with ACS who underwent percutaneous coronary intervention (PCI) and to elucidate predictive factors affecting long-term prognosis in this population.

Methods

A retrospective cohort study that was approved by the Institutional Research Ethics Board (IRB) at Hadassah Medical Center approval number 0685-17-HMO). The IRB approved that patients' consent was not required for this historical retrospective study that includes only de-identified data. Our study complied with the Declaration of Helsinki.

Population and Data Collection

We included consecutive patients that were admitted with a diagnosis of first ACS event in young age and underwent PCI at a tertiary medical center between the years 1997–2009. Young patients were defined as ≤ 40 years for males, and ≤ 50 years for females at the time of the presenting coronary event.

Demographic and clinical data were collected from the hospitals' electronic medical files system including hospitalization summary, cardiac catheterization and echocardiography reports as well as outpatient clinic reports.

Demographic variables included age, sex, and ethnic origin. Risk factors variables included hypertension (HTN), diabetes mellitus (DM), dyslipidemia, smoking and family history of ischemic heart disease (IHD) and clinical characteristics included ACS presentation type (unstable angina, NSTEMI, STEMI).

The angiographic and PCI data were retrieved from the procedural report and was reviewed by an expert interventional cardiologist. Procedural variables included location of culprit lesion, presence of MVD and PCI type (stent insertion vs plain old balloon angioplasty (POBA)).

Outcome Variables

Cardiovascular events were collected from the hospital database and from the patient's own medical files. Mortality was determined from hospital chart review and by matching identification numbers of patients with the Israeli National Population Register.

The clinical outcomes were defined as mortality and major CV event that included hospitalization for the following events: myocardial infarction (MI), cerebrovascular accident (CVA), percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG) and exacerbation of congestive heart failure (CHF).

Statistical Analysis

Differences in baseline characteristics were compared using unpaired *t*-test for continuous variables, χ^2 -distribution or Fisher's exact test for categorical variables. Differences between the frequencies of the different events; mortality and major events according to baseline characteristics of population were compared using χ^2 -distribution or Fisher's as appropriate. The event rate over time was displayed using the Kaplan–Meier method, with comparison between groups by Log rank test.

To examine the association between baseline characteristics and outcome, a multivariable cox proportional hazard model was used. For the mortality analysis, we used the total cohort, 165 patients as we have reliable information about the mortality date in all patients with matching identification numbers of patients with the Israeli National Population Register. For time for first CV event analysis and for the number of recurrent events analysis, we excluded patients that were lost to complete long-term follow-up. The final analysis for CV events included a cohort of 145 patients. The association between baseline characteristics and the annual event rate was examined by multivariate linear regression.

For all analyses, we used SAS software version 9.4 (SAS Institute Inc., Cary, NC). A $p < 0.05$ was considered statistically significant.

Results

A total of 165 patients who had ACS and PCI at a young age were included in the study. The mean follow-up was 9.1 ± 4.6 years and median follow-up was 10 years (IQR: 5.67, 10.75). The baseline and clinical characteristics of the study population are summarized in Table 1. Most of the patients (88%) were males and 95% of the patients had at least one risk factor, the most common risk factor in our population was smoking.

Nearly half of the patients (48%) presented with ST-segment elevation myocardial infarction (STEMI) and 52% non-STE-ACS. Surprisingly, the proportion of unstable angina was greater than that of NSTEMI (33% vs 19%, respectively); this may be dependent on the definition of UAP/MI that was not based on the high-sensitive troponin assays which were not available at the years of the study. The most common vessel involved was the LAD (44.2%), while 42% had multi-vessel coronary disease (MVD). Most patients had good left ventricular function (Table 1).

MACCE and Mortality Analysis

Fifteen (9.1%) patients died during follow-up while 98 (59.4%) patients had at least one major CV event and 107 (64.9%) patients had at least one major CV event and/or mortality (Figure 1). Hypertension, family history of ischemic heart disease and PCI without stent insertion were found to be predictors for major CV and/or mortality in the univariate analysis (Table 2). Survival curves of hypertensive versus non-hypertensive patients are presented in Figure 2.

In the multivariate regression analysis, the strongest predictors for MACCE and/or mortality were coronary intervention without stent insertion, LAD artery involvement and hypertension (Table 3).

Recurrent Event Analysis

The recurrent event analysis was performed for 145 patients with complete follow-up at the end of study follow-up (1/2018). Twenty-two patients (13.3%) had three or more events during follow-up, the mean number of events was 1.4 ± 1.48 per patient and the mean event rate per patient per year was 0.3 ± 0.8 . The median number of events per patients was 1 (IQR 0.2) and the median event rate per patient per year was 0.14 (IQR: 0, 0.27). Recurrent events according to baseline characteristics are presented in Appendix Table 1.

Table 1 Baseline Characteristics

Variable	N=165
Age (years) mean \pm SD	36.81 \pm 4.24
Male sex, n (%)	145 (88)
Origin, n (%)	
Arabs	83 (50)
Jews	82 (50)
Risk factors, n (%)	
Family history of IHD	76 (46)
Hypertension	33 (20)
Hyperlipidemia	94 (57)
Diabetes mellitus	25 (15)
Smoking	110 (67)
ACS presentation, n (%)	
Unstable angina	54 (33)
NSTEMI	31 (19)
STEMI	80 (48)
LV function^a (assessed by echocardiogram), n (%)	
Normal	49 (46.5)
Mild to moderately reduced	47 (45)
Severely reduced	9 (8.5)
MVD	70 (42)
Culprit lesion (%)	
LM	1 (0.6)
LAD	73 (44)
LCX	27 (16)
RCA	47 (29)
Indeterminate	17 (28)
PCI \geq 1 stent	130 (82)

Note: ^a105 Patients with available data.

Abbreviations: ACS, acute coronary syndrome; IHD, ischemic heart disease; IQR, interquartile; NSTEMI, non-ST elevation segment myocardial infarction; STEMI, ST elevation segment myocardial infarction; LV, left ventricle; LAD, left anterior descending; LCX, left circumflex; LM, left main; MVD, multi-vessel disease; PCI, percutaneous coronary intervention; RCA, right coronary artery.

In a linear multivariate regression model, the strongest predictor for recurrent event was hypertension (Table 4).

Discussion

We present an analysis of 165 young patients with ACS who underwent PCI at a young age, with a long-term mean follow-up of 9.1 ± 4.6 years. The main finding of this study is the remarkably high rate of recurrent CV events in the years following initial ACS. During follow-up, approximately 65% of the patients had at least one endpoint of

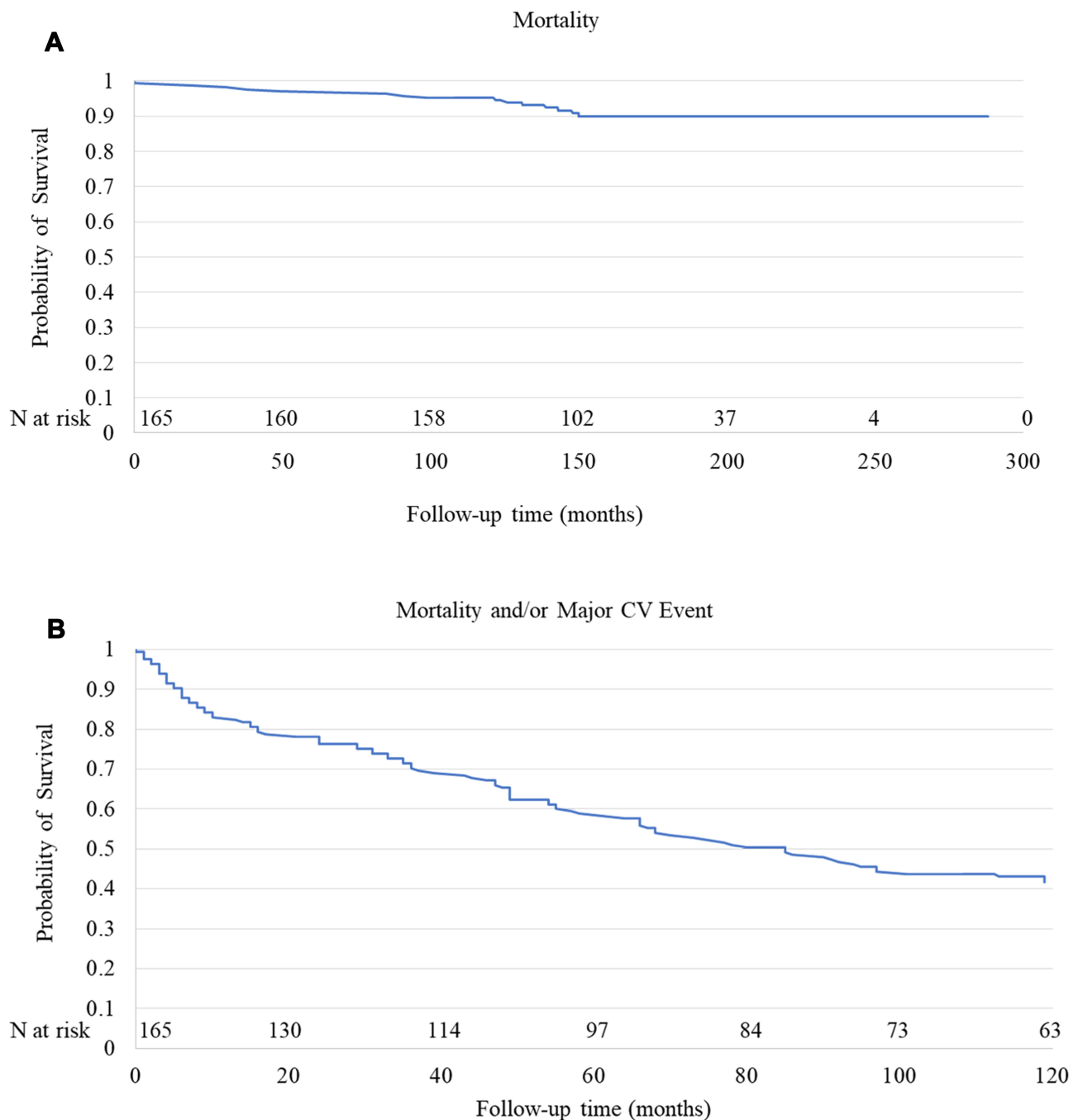


Figure 1 Kaplan–Meier survival curve showing cumulative survival free from mortality event (**A**) and from mortality and/or major CV event (**B**).

mortality or major CV event. The average number of recurrent events per patient was 1.85, with an event rate of 0.3 per patient per year. These percentages are higher than previously published studies, in which the percentage of recurrent events was less than 30%.²¹ Moreover, in a more recent study with shorter follow-up of 3–5 years, only 11.2% patients younger than 45 years old had recurrent events with mortality rate of only 0.9%.¹⁴

The longer follow-up in our study and better recoding of events may explain the differences between our findings and prior studies. Another possible explanation is that our population may have lower compliance to optimal medical treatments and lifestyle modifications and thus a relatively high recurrent event rate.

It may be expected that in a more contemporary revascularization era the prognosis of young ACS patients will

Table 2 Predictors for Mortality and/or Major CV Events (Univariate Analysis)

Parameter	Hazard Ratio (95% CI)	P-value
Sex	1.55 (0.81–2.97)	0.19
Race	1.26 (0.86–1.85)	0.23
HTN	1.84 (1.18–2.85)	0.007
DM	1.08 (0.65–1.80)	0.76
Smoking	1.05 (0.70–1.57)	0.83
Family history of IHD	0.63 (0.43–0.94)	0.02
LAD lesion	1.38 (0.94–2.01)	0.09
MVD	1.17 (0.79–1.72)	0.42
Stent; none vs ≥ 1	2.00 (1.26–3.18)	0.003

Abbreviations: CV, cardiovascular; DM, diabetes mellitus; HLP, hyperlipidemia, HTN, hypertension; LAD, left anterior descending; MVD, multi-vessel disease; STEMI, ST-segment elevation myocardial infarction.

be better. However, our results do not support this assumption. One explanation is that the invasive approach influences mainly the short-term outcome, up to 1 year but thereafter factors such as lifestyle and compliance are more dominant for long-term prognosis. Furthermore, an invasive approach may be harmful in patients with poor compliance due to late stent thrombosis. Young patients who experience coronary events may have trouble to adhere with medications and risk factors' management and thus are exposed to recurrent adverse events.²² Hypertension prevalence in the first event was found only in 20% of the patients. However, in patients who died during follow-up or experienced MACCE, the

percentages were much higher. We found that patients with hypertension had significantly shorter time to recurrent event (Figure 2). We found that hypertension was the strongest risk factor for recurrent CV events. This may be because hypertension is a less controlled among young patients who in many cases do not compliant with anti-hypertensive medications.²² We postulate that early intervention focusing on treatment of hypertension may reduce the risk for recurrent events.

Another finding in this study was that PCI without stent insertion was found to be an independent predictive factor for worse outcomes. Possible explanation may be the fact that patients who had complex or diffuse ectatic disease not suitable for stent implantation, have worse prognosis.²³

Our study indicates that patients who had a coronary event at a young age are in a remarkably high risk for recurrent event during long-term follow-up. While the short-term prognosis of these young patients is relatively good as they have less comorbidities, the long-term prognosis might be unfavorable. It seems that health systems should put more focus on the population of young ACS patients in order to improve compliance and potentially, prognosis.

The present study has several limitations. First, the study based on a retrospective administrative database that contains discharge-level records and as such is susceptible to reporting errors and missing data. In order to minimize those errors, we have crosschecked our data in several major databases and we believe that we were able to obtain high-quality long-term data which allowed a consistent analysis. Another limitation is the lack of a control group of older patients, these data were not

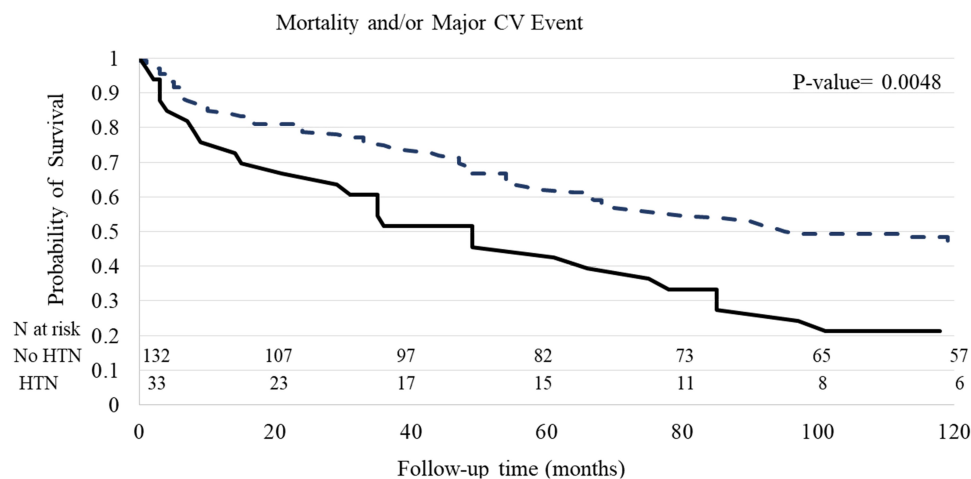
**Figure 2** Kaplan–Meier survival curve showing cumulative survival free from mortality and major CV event in patient with and without hypertension.

Table 3 Multivariable Cox Proportional Hazard Model for Major CV Event and/or Mortality

Parameter	Hazard Ratio (95% CI)	P-value
Sex	1.18 (0.57–2.42)	0.65
Race	1.13 (0.74–1.73)	0.58
HTN	1.61 (1.0–2.6)	0.05
DM	0.75 (0.44–1.30)	0.31
Smoking	0.77 (0.49–1.23)	0.27
Family history of IHD	0.67 (0.45–1.02)	0.06
LAD lesion	1.59 (1.04–2.44)	0.03
MVD	1.26 (0.83–1.91)	0.28
Stent; none vs ≥1	1.77 (1.09–2.9)	0.02

Abbreviations: CC, cardiovascular; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; LAD, left anterior descending; MVD, multi-vessel disease.

Table 4 Linear Model for Recurrent Annual Event (N=145)

Variable	Parameter	Standard Error	P-value
Sex	−0.090	0.14	0.51
Race	−0.043	0.09	0.62
HTN	0.310	0.11	0.004
DM	0.062	0.12	0.59
Family history of IHD	−0.144	0.08	0.09
Smoking	−0.028	0.10	0.77
LAD involvement	0.072	0.09	0.41
Stent insertion ≥ 1	0.038	0.10	0.72

Abbreviations: DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; LAD, left anterior descending.

available in this cohort. However, data on the expected outcome of general ACS populations both old and young are abundant and we used it for reference as discussed.

In conclusion, the rate of mortality and recurrent CV events in patients who presented with ACS at a young age is relatively high during long-term follow-up. Hypertension, LAD disease and coronary intervention without stenting are important negative prognostic factors in this population. Early interventions to reduce risk factors and to improve compliance, particularly for hypertensive patients may lead to a better prognosis in this unique population.

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Disclosures

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