Progression of Coronary Artery Disease During Long-Term Follow-Up of the Swiss Interventional Study on Silent Ischemia Type II (SWISSI II)

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ABSTRACT

Background: This study evaluates cardiovascular risk factors associated with progression of coronary artery disease (CAD) in patients with silent ischemia following myocardial infarction.

Hypothesis: Coronary artery disease only progresses slowly with comprehensive risk factor intervention.

Methods: A total of 104 of 201 patients (51.7%) of the Swiss Interventional Study on Silent Ischemia Type II (SWISSI II) with baseline and follow-up coronary angiography were included. All patients received comprehensive cardiovascular risk factor intervention according to study protocol. Logistic regression was used to evaluate associations between baseline cardiovascular risk factors and CAD progression.

Results: The mean duration of follow-up was 10.3 ± 2.4 years. At baseline, 77.9% of patients were smokers, 45.2% had hypertension, 73.1% had dyslipidemia, 7.7% had diabetes, and 48.1% had a family history of CAD. At last follow-up, only 27 patients of the initial 81 smokers still smoked, only 2.1% of the patients had uncontrolled hypertension, 10.6% of the patients had uncontrolled dyslipidemia, and 2.1% of the patients had uncontrolled diabetes. Coronary artery disease progression was found in up to 81 (77.9%) patients. Baseline diabetes and younger age were associated with increased odds of CAD progression. The time interval between baseline and follow-up angiography was also associated with CAD progression.

Conclusion: Coronary artery disease progression was highly prevalent in these patients despite comprehensive risk factor intervention. Further research is needed to optimize treatment of known risk factors and to identify other unknown and potentially modifiable risk factors.

Introduction

Myocardial ischemia may occur in totally asymptomatic patients without (silent ischemia type I) or with (silent ischemia type II) a history of an ischemic cardiac event.[1–8] Silent ischemia, like symptomatic ischemia, negatively affects prognosis.[1–8] Recent findings from the Swiss Interventional Study on Silent Ischemia Type II (SWISSI II) have shown a persistent benefit of percutaneous coronary interventions (PCI) compared to anti-ischemic drug therapy on long-term outcomes of asymptomatic patients with silent ischemia type II.[5]

Patients of the SWISSI II trial were followed for more than 10 years, many of whom underwent coronary angiography (hereafter angiography) during follow-up. There are, to the best of the authors' knowledge, no previous studies on the progression of coronary artery disease (CAD) in patients with silent ischemia type II. Furthermore, most previous studies evaluating cardiovascular risk factors associated with CAD progression confirmed by angiography were conducted more than 2 decades ago when cardiovascular risk factor intervention was less effective.[9–13] This study attempts to address this void by evaluating cardiovascular risk factors associated with the progression of CAD among a subset of patients of the SWISSI II trial.

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Methods

Patients

Participants of the SWISSI II trial were recruited from patients treated for a first ST-segment elevation myocardial infarction (MI) or non–ST-segment elevation MI at 3 medical centers in Switzerland (Luzern, Basel, and Chur). A total of 1057 eligible patients underwent bicycle exercise testing and, if asymptomatic ischemia was confirmed, were asked to undergo stress imaging (ie, stress myocardial perfusion scintigraphy, stress echocardiography, or stress radionuclide angiography). In 411 patients willing to participate, exclusive silent ischemia was confirmed. These patients underwent baseline angiography. Finally, 201 were identified with 1-vessel or 2-vessel CAD suitable for inclusion in the SWISSI II trial. According to the study protocol, these patients were randomized to balloon angioplasty (n = 96) or intensive anti-ischemic drug therapy (n = 105). Balloon angioplasty was performed with the aim to attain full revascularization without residual coronary stenoses of more than 75%. It was performed according to standard techniques, but in general, without stents during that period (only 13 patients received a stent). Anti-ischemic drug therapy consisted of either 5 to 10 mg/d of bisoprolol, 5 to 10 mg/d of amlodipine, 4 to 12 mg of molsidomine twice daily, or combinations thereof, aiming to eliminate or maximally reduce silent ischemia during bicycle ergometry.

Of the 201 patients in the SWISSI II trial, 104 patients had a second angiography over follow-up and formed the study population of this analysis. Follow-up angiography was performed, if recommended by the clinical guidelines, at the time of the study.[14,15] The study protocol was approved by the institutional review boards (ethical committees) of the 3 participating institutions and was consistent with the principles of the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Management of Cardiovascular Risk Factors and Follow-Up

In addition to balloon angioplasty or intensive anti-ischemic drug therapy, all patients received secondary preventive advice regarding weight control, nutrition, smoking cessation, and regular exercise. Pharmacological treatment of hypertension, dyslipidemia, and diabetes was initiated based on clinical guidelines in effect at the time of the study. Pharmacological treatment included β-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors for hypertension, and statins for dyslipidemia. For the treatment of cardiovascular risk factors, the following goals were used: blood pressure <140/90 mm Hg, total cholesterol <234 mg/dL (6.0 mmol/L) low-density lipoprotein cholesterol <117 mg/dL (3.0 mmol/L), and hemoglobin A_{1c} (HbA_{1c}) <7.5%.

Patients received clinical examination, bicycle exercise testing, and stress imaging at baseline. Follow-up examinations at 3, 6, and 12 months and yearly for approximately 10 years thereafter included clinical examination, bicycle exercise testing, and repeat rest/stress echocardiography. Cardiovascular risk factors assessed at every follow-up examination included measurement of body weight and blood pressure, as well as assessment of in-home blood pressure and glucose monitoring diaries. Measurements of cholesterol and HbA_{1c} were left to the discretion of the individuals' primary care physician and follow-up investigators.

Measurements

Baseline and follow-up angiographies were evaluated by 2 independent cardiologists (PJ, MZ) who determined the percentage of stenosis in 6 coronary segments (proximal or distal portion of left anterior descending, left circumflex, or right coronary artery). Coronary artery disease was considered present, if there was a coronary luminal stenosis of 50% or more in at least 1 vessel. Coronary artery disease progression was assessed by comparing results of baseline and follow-up angiography. Coronary artery disease progression was defined in 3 different ways: first, any increase in the coronary luminal stenosis of 25% or more in at least 1 coronary vessel; second, an increase in the number of vessels with luminal stenosis of 50% or more; and third, the development of new coronary lesions with luminal obstruction of 50% or more.

Statistical Analysis

Descriptive statistics were expressed as count, percentage, and mean ± standard deviation (SD). Continuous variables with normal distributions were compared using Student *t* tests and non-normal distributions by Wilcoxon rank sum test. Dichotomous variables were compared by the χ^2 test or Fisher exact test when cell counts were <5. Multivariable logistic regression models were calculated using odds ratios (OR) and 95% confidence intervals (CI) to evaluate associations between CAD progression, CAD regression, new coronary lesions, and baseline cardiovascular risk factors, as well as, for sensitivity analyses. All models were evaluated with and without adjustment for variables that may have influenced potential associations (ie, age, sex, cardiovascular risk factors, the number of coronary stenosis at baseline, PCI at baseline, and time between baseline and follow-up angiography). All statistical analyses were performed using STATA software (version 11.0, Stata Corporation, College Station, TX).

Results

Baseline characteristics are summarized in Table 1. All patients were followed up for a mean duration of 10.3 ± 2.4 years after randomization.

Changes in Cardiovascular Risk Factors

Smoking and dyslipidemia were the most prevalent cardiovascular risk factors at baseline (Table 1). Changes in

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Table 1. Baseline Characteristics

Characteristic	n = 104
Age, mean ± SD (range), in yrs	54.3 ± 9.0 (25.5–74.6)
Female sex, No. (%)	15 (14.4)
Height, mean ± SD, in cm	170.8 ± 6.7
Weight, mean ± SD, in kg	75.1 ± 11.6
Blood pressure, mean ± SD, mm Hg	
Systolic	128.6 ± 22.4
Diastolic	76.6 ± 14.6
Risk factors for CAD, No. (%)	
Hypertension	47 (45.2)
Dyslipidemia	76 (73.1)
Smoking	81 (77.9)
Diabetes	8 (7.7)
Family history of CAD	50 (48.1)
Maximal workload during bicycle exercise testing in watts	146.8 ± 32.2
Percent ejection fraction, mean ± SD	56.5 ± 10.0
LVEDP, mean ± SD, in mm Hg	14.2 ± 4.2
Received PCI, No. (%)	55 (52.9)

Abbreviations: CAD, coronary artery disease; LVEDP, left ventricular end-diastolic pressure; PCI, percutaneous coronary intervention; SD, standard deviation.

cardiovascular risk factor control and the use of antihypertensive or lipid-lowering therapies are summarized in Table 2. All modifiable cardiovascular risk factors (hypertension, dyslipidemia, smoking, and diabetes) were controlled in more than two-thirds of the patients after 4 years. The proportion of patients with controlled cardiovascular risk factors further increased until the last follow-up after 10 years. At 10-years follow-up, only 27 of the initial 81 smokers still smoked, only 2.1% of the patients had uncontrolled hypertension, 10.6% of the patients had uncontrolled dyslipidemia, and 2.1% of the patients had uncontrolled diabetes. Mean body weight increased ($P = 0.014$) from 75.1 ± 11.6 kg at baseline to 79.1 ± 11.8 kg over follow-up.

Angiographic Follow-Up

Mean time between baseline and follow-up angiography was 5.1 ± 4.4 years (range, 14 d–14.5 yrs). Follow-up angiography was performed for the following reasons: evaluation of symptomatic stable angina in 46 patients (44.2%), unstable angina in 2 patients (1.9%), symptomatic MI in 21 patients (20.2%), and silent MI in 6 patients (5.8%). In the remaining 29 patients (27.9%), follow-up angiography was performed in the absence of symptoms, mainly for evaluation of persistent silent ischemia, for documentation of extent and relevance of CAD, before valvular or other surgery, or for evaluation in the context of rhythm disturbances or syncopes.

Table 3 displays results from baseline and follow-up angiography for the study population. There were more patients with 2-vessel and 3-vessel disease at follow-up angiography compared to baseline. The mean number of vessels involved in CAD increased ($P < 0.001$) from baseline to follow-up angiography (Table 3). Coronary artery disease extent measured by the number of vessels with coronary luminal stenoses of 50% or more increased in 48 patients (46.1%), remained stable in 40 patients (38.5%), and decreased in 16 patients (15.4%). The proportion of patients with progression increased to 77.9%, when an increase of stenosis severity by ≥25% was considered in addition to an increase in the number of vessels involved. New coronary lesions were observed in 46 patients (44.2%), restenosis of a previously stenotic lesion in 18 patients (17.3%), and new lesions as well as restenosis in 19 patients (18.3%).

Associations With Changes in Coronary Artery Disease

An overview of baseline factors associated with CAD progression is presented in Table 4. In multivariable regression analysis, the time interval between baseline and follow-up angiography was significantly associated with a progression of coronary luminal stenosis of 25% or more in at least 1 coronary artery (OR per year increase in time: 1.20, 95% CI: 1.04–1.37). Baseline diabetes was the strongest significant cardiovascular risk factor, whereas use of a PCI at baseline and increasing age were significantly associated with less CAD progression in the same model. When considering CAD progression in terms of an increase in the number of coronary vessels with luminal stenosis of 50% or more, the time interval between baseline and follow-up angiography (OR per year increase in time: 1.14, 95% CI: 1.02–1.27) was the only significant factor associated with CAD progression. The time interval between baseline and follow-up angiography was also the only variable significantly associated (OR: 1.30, 95% CI: 1.12–1.51) with new coronary lesions. In multivariable analysis, there were no significant associations of baseline variables with the measured increase in the number of coronary vessels with luminal stenosis ≥50% or with new coronary lesions. In bivariable regression analysis, use of a PCI at baseline was significantly associated with CAD regression ($P = 0.008$). However, there were no significant associations in multivariable logistic regression analysis of baseline variables with CAD regression. Similar results were found in a sensitivity analysis restricted to patients

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Table 2. Cardiovascular Risk Factor Control

Hypertension[b]	Baseline (n = 104)	At 4-year Follow-Up (n = 101)[a]	At 10-year Follow-Up (n = 94)[a]
Patients with blood pressure <140/90 mm Hg, No. (%)	57 (54.8)	73 (72.3)	92 (97.9)
Systolic blood pressure, mean ± SD, mm Hg	128.6 ± 22.4	129.6 ± 18.1	127.0 ± 14.7
Diastolic blood pressure, mean ± SD, mm Hg	76.6 ± 14.6	81.7 ± 10.8	80.8 ± 9.3
Use of β-blocker, No. (%)	51 (49.0)	68 (67.3)	52 (55.3)
Use of calcium channel blocker, No. (%)	30 (28.9)	42 (41.6)	20 (21.3)
Use of ACE inhibitor, No. (%)	34 (32.7)	38 (37.6)	39 (41.5)
Dyslipidemia[c]			
Patients with total cholesterol <234 mg/dL and LDL cholesterol <117 mg/dL, No. (%)	28 (26.9)	79 (78.2)	84 (89.4)
No. of patients having a statin, No. (%)	34 (32.7)	67 (66.3)	68 (72.3)
Smoking			
Patients who did not smoke, No. (%)	23 (22.1)	69 (68.3)	67 (71.3)
Diabetes[d]			
Patients with HbA_{1c} <7.5%, No. (%)	96 (92.3)	95 (94.1)	92 (97.9)

Abbreviations: ACE = angiotensin-converting enzyme; HbA_{1c} = hemoglobin A_{1c}; LDL = low-density lipoprotein.
[a] Patients who died before date of follow-up were censored.
[b] Hypertension was defined as a repeatedly elevated blood pressure >140/90 mm Hg.
[c] Dyslipidemia was defined as total cholesterol >234 mg/dL (6.0 mmol/L) or low-density lipoprotein cholesterol >117 mg/dL (3.0 mmol/L).
[d] Diabetes was diagnosed, if fasting plasma glucose level was twice >126 mg/dL (7.0 mmol/L).

Table 3. Comparison of Baseline and Follow-Up Coronary Angiography

	Baseline Coronary Angiography (n = 104)	Angiographic Follow-Up (n = 104)	*P* Value[c]
CAD[a]			
No CAD, No. (%)	0 (0.0)	4 (3.8)	0.008
1-vessel CAD, No. (%)	44 (42.3)	31 (29.8)	
2-vessel CAD, No. (%)	60 (57.7)	35 (33.7)	
3-vessel CAD, No. (%)	0 (0.0)	34 (32.7)	
Number of vessels, mean ± SD	1.6 ± 0.5	2.0 ± 0.9	<0.001
Coronary vessel[b]			
LAD, No. (%)	67 (64.4)	78 (76.0)	0.041
CX, No. (%)	44 (42.3)	63 (60.6)	0.002
RCA, No. (%)	53 (51.0)	62 (59.6)	0.106

Abbreviations: CAD = coronary artery disease; CX = left circumflex artery; LAD = left anterior descending artery; RCA = right coronary artery; SD = standard deviation.
[a] Coronary artery disease defined as coronary luminal stenosis of 50% or more in at least 1 vessel.
[b] Coronary luminal stenosis of 50% or more in the specified coronary vessel.
[c] *P* value for the comparison of baseline and follow-up angiographic findings.

Table 4. Factors Associated with Progression of Coronary Artery Disease

Definition of CAD Progression	CAD Progression			
	Increase in the Coronary Luminal Stenosis of ≥25% in ≥1 Coronary Vessel		Increase in the Number of Coronary Vessels With Luminal Stenosis of ≥50%	
Factor	OR (95% CI)[a]	*P* Value	OR (95% CI)[a]	*P* Value
Age at baseline (OR per yr increase)	0.94 (0.89–0.99)	0.047	1.02 (0.97–1.07)	0.449
Sex (OR for female sex)	1.17 (0.23–6.06)	0.848	2.08 (0.52–8.28)	0.299
Smoking at baseline	1.87 (0.37–9.46)	0.450	1.46 (0.36–5.91)	0.600
Hypertension at baseline	2.05 (0.68–6.16)	0.202	1.25 (0.51–3.08)	0.624
Dyslipidemia at baseline	1.71 (0.47–6.18)	0.414	1.12 (0.41–3.07)	0.830
Diabetes at baseline	19.01 (1.42–254.64)	0.026	5.21 (0.84–32.32)	0.076
Family history of CAD	2.13 (0.71–6.36)	0.178	1.32 (0.53–3.31)	0.553
Number of stenoses at baseline coronary angiography (OR per stenosis)	1.19 (0.74–1.90)	0.470	0.94 (0.64–1.40)	0.778
Use of a PCI at baseline	0.10 (0.03–0.35)	<0.001	0.98 (0.39–2.51)	0.975
Time interval between baseline and follow-up angiography (OR per year increase)	1.20 (1.04–1.37)	0.010	1.14 (1.02–1.27)	0.022

Abbreviations: CAD = coronary artery disease; CI = confidence interval; OR = odds ratio; PCI = percutaneous coronary intervention.
[a] OR based on multivariable logistic regression analyses included all variables listed.

with follow-up angiography due to symptomatic angina and/or MI.

Discussion

Coronary artery disease progression was observed in this study of patients with silent ischemia following MI despite optimal risk factor management during follow-up resulting in well controlled cardiovascular risk factors. Diabetes and younger age were associated with more severe CAD progression, while no measurable effect on CAD progression was found for other cardiovascular risk factors. A longer time interval between baseline and follow-up angiography was consistently found to be an important factor associated with CAD progression.

The analysis showed that baseline diabetes was the only cardiovascular risk factor associated with CAD progression. Diabetes was shown in previous studies to accelerate CAD progression despite intensive diabetic interventions.[16–18] Apart from diabetes, no other cardiovascular risk factors were associated with CAD progression. This might be a consequence of good risk factor control or of a sample size too small to detect the association.

Few previous studies on the associations of risk factors with CAD progression assessed longer follow-ups than 5 years, whether they used clinical data only and/or serial angiography.[9–13] One study, similar to our study but in a younger population, also found CAD progression to be associated with increasing time intervals between angiography.[10] The association of time interval between angiographies and CAD progression is an expected finding as atherosclerosis progresses with time. However, the statistical importance of the time interval between angiographies in our study was surprising. The former study was conducted nearly 30 years ago when cardiovascular risk factor intervention was less effective. Still, CAD progresses with time despite current day risk factor intervention. This progression points to the fact that a residual cardiovascular risk may be noted despite smoking cessation and optimally reduced blood pressure, cholesterol, and glucose.

Use of a PCI at baseline was associated with less CAD progression. Use of a PCI at baseline was 1 of 2 interventions in the SWISSI II protocol. Therefore, its association with CAD regression was explained by its direct influence on the outcome of this study.

There are several research implications. Previous studies have shown that comprehensive interventions to reduce cardiovascular risk factors can lead to a reduction in concomitant cardiovascular risk factors and to regression of coronary lesions.[19,20] Previous studies have also shown that despite guideline recommendations many patients still do not reach treatment goals.[21–24] These studies, together with ours, therefore raise some important questions: is there a

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collective failure in preventing CAD and its progression? Are there any obstacles such as guideline implementation, patient compliance, or lack of reimbursement for counseling? Or is time an inevitable and unchangeable factor contributing to the progression of atherosclerosis? Future research should explore methods to improve cardiovascular risk factor control and further investigate the possibility of other potentially modifiable risk factors of CAD progression, for example, gene polymorphisms.[25]

Several limitations of this study should be considered. First, the participants of this study were selected for silent ischemia type II thus potentially limiting generalizability to other populations of patients. However, a previous study in another patient population found similar results.[10] Second, follow-up angiography was performed in 51.7% of SWISSI II patients potentially resulting in selection bias for this study. Coronary artery disease progression may be overestimated if patients with CAD progression were more likely to receive angiography over follow-up. However, there were no significant differences in baseline characteristics between study participants and patients without angiographic follow-up, except for dyslipidemia (data available from the authors upon request). Third, target levels for blood pressure and lipid intervention have been lowered since the beginning of this study. Rates of progression might therefore be lower with modern guideline recommendations.

Conclusions

The results of this study show that CAD progresses over time despite current-day cardiovascular risk factor interventions. Coronary artery disease regression was only found in a few patients. It remains to be shown whether and how much even more intense risk factor management may slow or even stop progression of CAD in patients with prior MI as studied in SWISSI II.

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