

# Effects of anti-ischaemic drug therapy in silent myocardial ischaemia type I: the Swiss Interventional Study on Silent Ischaemia type I (SWISSI I): a randomized, controlled pilot study

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## KEYWORDS

Silent ischaemia;  
Coronary artery disease;  
Drug therapy;  
Risk factor intervention

**Aims** To determine the effect of anti-ischaemic drug therapy on long-term outcomes of asymptomatic patients without coronary artery disease (CAD) history but silent exercise ST-depression.

**Methods and results** In a randomized multicentre trial, 263 of 522 asymptomatic subjects without CAD but at least one CAD risk factor in whom silent ischaemia by exercise ECG was confirmed by stress imaging were asked to participate. The 54 (21%) consenting patients were randomized to anti-anginal drug therapy in addition to risk factor control (MED,  $n = 26$ ) or risk factor control-only (RFC,  $n = 28$ ). They were followed yearly for  $11.2 \pm 2.2$  years. During 483 patient-years, cardiac death, non-fatal myocardial infarction, or acute coronary syndrome requiring hospitalization or revascularization occurred in 3 (12%) of MED vs. 17 (61%) of RFC patients ( $P < 0.001$ ). In addition, MED patients had consistently lower rates of exercise-induced ischaemia during follow-up, and left ventricular ejection fraction remained unchanged ( $-0.7\%$ ,  $P = 0.597$ ) in contrast to RFC patients in whom it decreased over time ( $-6.0\%$ ,  $P = 0.006$ ).

**Conclusion** Anti-ischaemic drug therapy and aspirin seem to reduce cardiac events in subjects with asymptomatic ischaemia type I. In such patients, exercise-induced ST-segment depression should be verified by stress imaging; if silent ischaemia is documented, anti-ischaemic drug therapy and aspirin should be considered.

## Introduction

Although there is still controversy regarding why ischaemic episodes are symptomatic in some patients and completely asymptomatic in others, it is now widely accepted that silent ischaemia, similar to symptomatic episodes, negatively affects prognosis.<sup>1–3</sup> Silent ischaemia may occur in totally asymptomatic patients without (type I) or with (type II) a history of an ischaemic cardiac event and coexists with symptomatic episodes in many patients (type III).<sup>1–3</sup> In the absence of coronary angiography, most investigations on silent ischaemia relied upon documentation of asymptomatic ST-segment depression on Holter-ECG recordings or during stress testing for diagnostic purposes. However, both test methods have a low sensitivity and a rather high prevalence of false-positive results in clinically healthy men.<sup>4,5</sup> Accordingly, stress echocardiography (stress ECHO), myocardial perfusion scintigraphy (MPS), and

radionuclide ventriculography have been used to investigate the relationship between asymptomatic ST-segment changes and myocardial ischaemia.<sup>6–8</sup>

The prognostic impact of silent ischaemia has been studied in type II and III patients, i.e. in patients with angina pectoris<sup>9</sup> or following myocardial infarction (MI)<sup>10,11</sup> as well as in patients after coronary artery bypass graft surgery<sup>12</sup> or angioplasty.<sup>13</sup> In addition, the prospective Asymptomatic Cardiac Ischemia Pilot study and the Atenolol Silent Ischemia Study have shown benefit of revascularization<sup>14</sup> or drug therapy<sup>14,15</sup> in patients who had silent ischaemic episodes in addition to symptomatic ones. However, there is a lack of data on the prognostic importance of silent ischaemia in totally asymptomatic subjects without history of coronary artery disease (CAD), i.e. silent ischaemia type I, and, particularly, on a possible benefit of medical therapy in such patients. Reasons lie in the difficulty to identify such patients and their expected low event rates implying that large patient populations and/or long follow-up periods would be necessary to come to definite

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conclusions. Thus, specific aims of the Swiss Interventional Study on Silent Ischaemia type I (SWISSI I) were to perform a pilot feasibility study in totally asymptomatic subjects older than 40 years of age without any history of CAD but one cardiovascular risk factor and documented silent ischaemia in order to (i) assess the incidence of silent myocardial ischaemia by an imaging technique, (ii) determine their long-term prognosis, and (iii) assess the impact of anti-ischaemic drug therapy and aspirin plus risk factor control vs. risk factor control-only on outcome.

## Participants and methods

### Participants

Study participants were recruited from subjects sent for exercise testing to four Swiss medical centres (Lucerne, Chur, Zurich, and Basel) between 1992 and 1996. Subjects with asymptomatic ST-segment depression during bicycle ergometry and with at least one cardiovascular risk factor (i.e. smoking, hypertension, diabetes, hypercholesterolaemia, or a family history of CAD) were considered for study inclusion if they had no history of prior MI or other vascular disease, no anginal chest pain, and no other obvious disease. Most study participants fulfilling these criteria were found among totally asymptomatic subjects sent by their primary care physician for life insurance or other check-up investigations. The study protocol was approved by the institutional review boards of the four participating institutions.

### Silent ischaemia detection

After documentation of a normal 12-lead ECG at rest, bicycle ergometry was started at 50 W and increased by 25 W every 2 min until exhaustion. Asymptomatic ischaemia was defined as a  $\geq 0.1$  mV horizontal or downward sloping ST-shift in more than one of the 12 ECG leads measured 80 ms after the J point without chest pain. Subjects presenting with this finding were asked to undergo stress imaging, i.e. stress ECHO or stress MPS. These imaging tests were performed according to standard techniques and ischaemia was diagnosed only in the presence of unequivocally reversible perfusion defects or new wall motion abnormalities, respectively.

### Randomization and interventions

Study participants with verified silent ischaemia consenting to the study (written informed consent) were randomized to intensive anti-ischaemic drug therapy and risk factor control (MED group,  $n = 26$ ) or to risk factor control-only (RFC group,  $n = 28$ ). MED group patients were given anti-ischaemic drug therapy aiming to reduce or possibly eliminate ischaemia on ergometry consisting of bisoprolol 5–10 mg/day, amlodipine 5–10 mg/day, molsidomine 4–12 mg bid, or combinations thereof. The order of starting anti-ischaemic therapy and the increase of drug dosages or switching to combination therapy were left to the discretion of individuals' primary care physician and follow-up investigations according to the following rules: start with one single drug, increase drug dosage after 1 month if ischaemia persisted, combine with a second drug if ischaemia persisted after 3 months, and so on. Decisions regarding the choice of starting drug were left to the individuals' primary care

physician but increases in drug dosage or a switch to combination therapy during follow-up was allowed only if symptoms occurred. In addition, MED group patients received open-label acetosalicylic acid (100 mg/day). Risk factor control, which was attempted in both patient groups, consisted of counselling on eating habits, weight control, smoking cessation, and physical exercise with specific drug therapy allowed for hypercholesterolaemia (statin), diabetes (oral anti-diabetics, if necessary), or hypertension (an angiotensin-converting enzyme inhibitor, if needed).

### Follow-up and outcomes

All study participants were followed up after 3, 6, and 12 months and yearly thereafter for a pre-specified duration of 10 years. Follow-up examinations included a clinical exam as well as a bicycle ergometry and repeat rest/stress ECHO. Pre-specified outcome events were assessed and included the occurrence of angina pectoris (stable and unstable), symptomatic and silent MI, death (from cardiac and non-cardiac causes), and revascularization therapies (surgery or angioplasty). MI was diagnosed in the presence of typical chest pain, ST-segment elevation in the ECG, and/or a typical rise and fall of cardiac enzymes according to the definitions of the European Society of Cardiology.<sup>16</sup> Silent MI was diagnosed in the presence of new Q-waves in the resting ECG, new distinct wall motion abnormalities in the resting ECHO, and a reduction in the left ventricular ejection fraction of  $>5\%$  (or of  $>10\%$  without regional wall motion abnormalities) between two subsequent ECHO exams. Coronary angiograms were allowed only if symptoms occurred. All outcome events were adjudicated by an independent event committee blinded to the study group (W.K. and M.Z.).

The primary endpoint was defined as a combination of cardiac death, non-fatal MI (symptomatic or silent), or unstable angina pectoris leading to hospitalization or revascularization (surgery or angioplasty). The secondary endpoint included the occurrence of chronic stable angina in addition to outcome events of the primary endpoint. If patients experienced more than one event of the primary or secondary endpoint, only the first event was counted. In addition, the time course of physical performance and left ventricular function, the appearance or disappearance of objective signs of ischaemia, blood pressure control, as well as drug adherence during follow-up were assessed as further measures of outcome. In order to increase the validity of these additional findings, patients who experienced the primary endpoint were excluded in this analysis at the time of the primary endpoint.

### Statistical analysis

Software used for statistical analysis was STATA 8.2 (Stata-Corp, College Station, TX, USA). Data are expressed as percentages and mean  $\pm$  standard deviation. Continuous variables were compared by the use of the Student *t*-test assuming normal distributions or by the Wilcoxon rank sum test for variables with non-normal distributions. Dichotomous variables were compared by the  $\chi^2$  test or the Fisher exact test when cell counts were less than five. Cox proportional hazards models<sup>17</sup> were used to calculate hazard ratios and 95 percent confidence intervals for the comparison of event rates in the MED and RFC groups without and

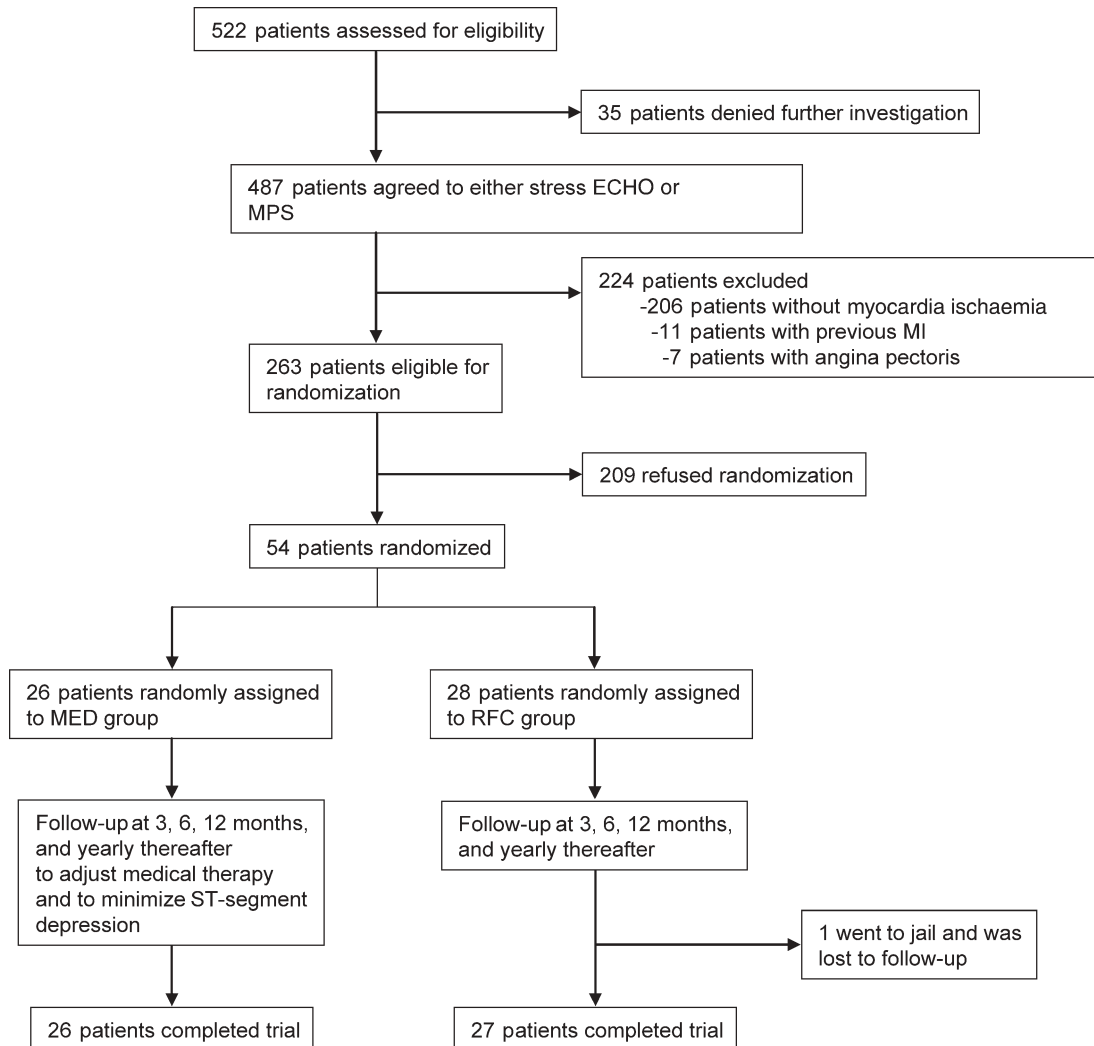


Figure 1 Patient selection and flow chart.

with adjustment for age, gender, and other assignments which revealed possible influences on outcome in univariable analysis (including hypertension, diabetes, dyslipidaemia, and left anterior descending coronary artery ischaemia). Deviations from the proportional hazards assumption were tested by examining the global test of the Schoenfeld residuals. The times to event were depicted with the Kaplan–Meier estimates of the survival function. In all tests, values of  $P \leq 0.05$  were considered significant. Analyses of the primary and secondary endpoints were performed according to the intention-to-treat principle.

## Results

### Patient selection and characteristics

Figure 1 shows the patient screening, selection, and randomization processes. Between 1992 and 1996, 522 subjects with asymptomatic ST-segment depression during bicycle ergometry, with at least one cardiovascular risk factor, and without a history of vascular disease were identified. Of them, 487 consented to a stress imaging test to verify silent ischaemia. In 263 subjects, silent ischaemia was verified by stress imaging for a positive predictive value of 54% of the bicycle ergometry for this finding. A total of 224

subjects had to be excluded because ischaemia could not be verified with imaging techniques ( $n = 206$ ) or a prior silent MI was found at stress imaging ( $n = 11$ ) or angina appeared during stress imaging ( $n = 7$ ). The 263 subjects with verified silent ischaemia were asked to participate. Only 54 subjects (21%) consented. The high percentage of refusals was related to the possible need of drug therapy and the frequent control examinations necessary for this study in otherwise healthy asymptomatic subjects.

Baseline characteristics of study participants are shown in Table 1. The age range was 41.8–75.4 years without any significant differences between the two treatment groups in risk factor prevalence, work load achieved, severity of ST-segment depression during exercise, or resting ejection fraction.

### Adherence to treatment

Risk factor control resulted in similar discontinuation rates for smoking in both patient groups during follow-up (Table 2). Elevated cholesterol levels, hypertension, and diabetes, if present, were treated in similar rates too; however, body weight did not change significantly during the study period (Table 2). Drug treatment consisted mainly in beta-blocking agents and/or calcium antagonists

**Table 1** Baseline characteristics by treatment group

	MED group (n = 26)	RFC group (n = 28)	P-value
Age, years	59.5 ± 9.0	59.2 ± 8.5	0.9
Female sex, n (%)	8 (31)	9 (32)	1
Blood pressure at rest, mmHg			
Systolic	140 ± 17	143 ± 19	0.55
Diastolic	85 ± 8	86 ± 11	0.57
Risk factors for CAD			
Smoking, n (%)	12 (46)	15 (54)	0.93
Pack-years	18 ± 21	17 ± 18	0.85
Hypertension, n (%)	15 (58)	9 (32)	0.75
Dyslipidaemia, n (%)	13 (50)	12 (43)	0.33
Diabetes, n (%)	1 (4)	4 (14)	1
Family history of CAD, n (%)	10 (38)	10 (36)	0.82
Two or more risk factors, n (%)	17 (65)	16 (57)	0.54
Bicycle ergometry			
Maximal workload, W	169 ± 38	175 ± 44	0.58
ST-segment depression, mm	2.2 ± 0.9	1.9 ± 0.6	0.18
Ejection fraction, %	61.8 ± 3.7	61.3 ± 4.5	0.63
Ischaemic region			
Anteroseptal, n (%)	9 (35)	9 (32)	0.7
Posterolateral, n (%)	6 (23)	9 (32)	1
Inferior, n (%)	11 (42)	11 (39)	0.48

Data are presented as mean ± standard deviation or as number of patients (percentages).

**Table 2** Risk factor control in MED and RFC patients

	MED group (n = 26)	RFC group (n = 28)
Stopped smoking	8/14 (57)	10/17 (71)
High cholesterol treated	16/18 (89)	10/16 (63)
Hypertension treated	16/18 (90)	9/11 (82)
Diabetes treated	1/2 (50)	4/6 (67)
Weight change (0–10 years)	−3.1	0.5

Numbers are number of patients treated/number of patients with risk factor (percentages) or as indicated. P-values are not significant between groups for all comparisons.

and to a much lesser extent in long-acting nitrates (*Figure 2*). According to protocol, these drugs were given significantly more often in MED compared with RFC patients although the differences diminished over time, which, if anything, would tend to underestimate the full effect of MED therapy. This was also true for aspirin, which was given in 100% of MED compared with 12% and up to 55% (at 1 and 10 years, respectively) of RFC patients.

### Outcome events

Follow-up was completed after 10 years in all patients, except in those patients who died and in one patient who went to jail and was lost after 5.5 years. A summary of

outcome events is shown in *Table 3*. Cardiac death, non-fatal MI as well as chronic angina, and revascularizations occurred consistently less frequently in the MED group compared with the RFC group. During a total of 483 person-years of observation, 20 patients had at least one outcome event of the primary endpoint, of whom three were assigned to the MED group and 17 to the RFC group (12 vs. 61%). This corresponds to a hazard ratio of 0.12 (95% CI 0.03–0.43;  $P = 0.001$ ). *Figure 3* shows the event-free survival for the primary endpoint. The event rate per year for the primary endpoint was 1.1% in MED patients, significantly lower than that in RFC patients (8.0%); this difference translated into an absolute risk reduction of 6.9% per year (95% CI 2.9–10.9;  $P < 0.001$ ). It is of note that 16 of the 17 primary endpoint events in the RFC group were due to MI, of which five were silent. The exclusion of silent MI from the endpoint definition still resulted in a hazard ratio of 0.18 in favour of MED patients (95% CI 0.05–0.66;  $P = 0.01$ ). If on the other hand chronic stable angina was considered an additional event of the endpoint definition in these initially asymptomatic patients (secondary endpoint), the absolute risk reduction was even larger: from 79 to 15% in RFC vs. MED patients for an absolute risk reduction of 11.1% per year (95% CI 5.6–16.5%;  $P < 0.001$ ). There was no baseline variable, including age, gender, hypertension, diabetes, dyslipidaemia, or ischaemia in the left anterior descendent territory, which significantly influenced the treatment effect in Cox proportional hazard analysis.

### Ischaemia, left ventricular function, and other observations during follow-up

Data on ischaemia, left ventricular function, blood pressure, and exercise performance in relation to treatment group during follow-up are shown in *Table 4*. During follow-up, patients of the MED group had significantly lower rates of exercise-induced ischaemia than patients of the RFC group. At the 1 year follow-up, exercise-induced ST-segment depression was significantly lower in the MED group [1.0 mm (SD 1.3 mm)] compared with the RFC group [1.8 mm (SD 0.5 mm);  $P = 0.009$ ]. The difference in exercise-induced ischaemia between MED and RFC group gradually decreased over time, maybe partly due to a certain increase in anti-ischaemic drug use in the RFC group (*Figure 2*). In addition, global left ventricular ejection fraction decreased significantly over time in patients of the RFC group (−6.0%,  $P = 0.006$ ), contrasting to a nearly constant ejection fraction in the MED group (−0.7%,  $P = 0.597$ ), resulting in significantly lower values at final examination after 10 years. This is remarkable since these data relate only to patients without intercurrent infarction. Exercise performance and blood pressure control were similar in both treatment groups throughout follow-up except for a lower blood pressure in the MED group at the 1 year follow-up. At the final follow-up, systolic/diastolic blood pressures at rest were (129 ± 17)/(80 ± 11) mmHg in the MED group and (133 ± 9)/(82 ± 7) mmHg in the RFC group (differences not significant).

### Discussion

SWISS I is the first prospective randomized study suggesting a beneficial effect of anti-ischaemic drug therapy and aspirin in addition to standard risk factor control on long-term outcome in otherwise healthy asymptomatic

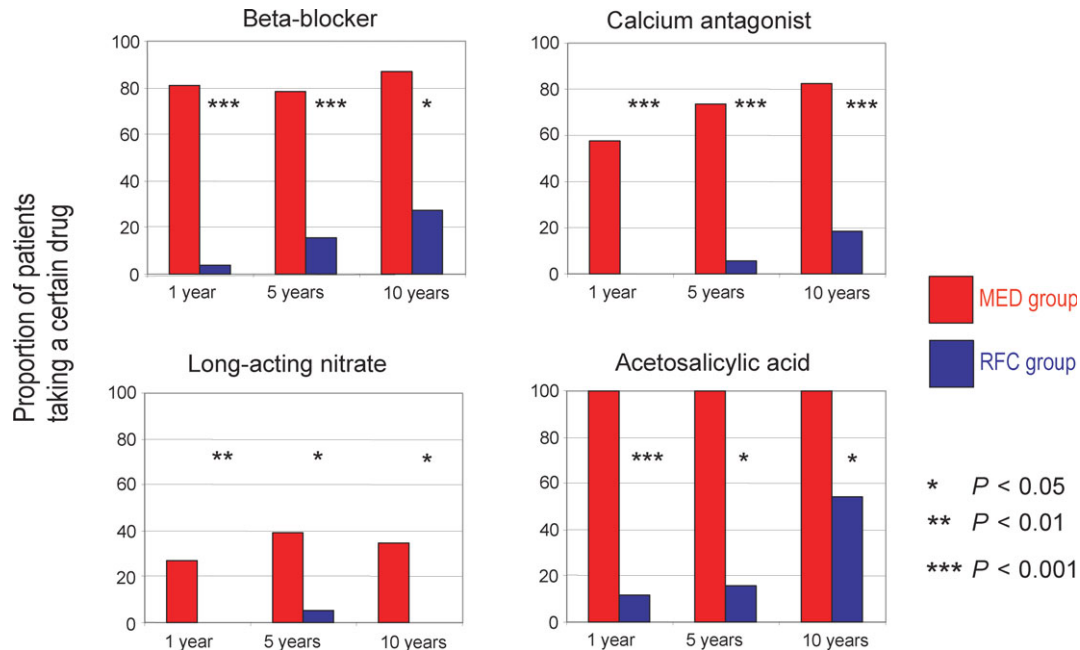


Figure 2 Drug therapy during follow-up.

Table 3 Occurrence of outcome events according to treatment group

	MED group (n = 26)	RFC group (n = 28)	Hazard ratio (95% CI)		P-value
			Unadjusted	Adjusted <sup>a</sup>	
<b>Outcome events<sup>b</sup></b>					
Cardiac death, n (%)	0 (0)	3 (10.7)			
Non-fatal MI <sup>c</sup> , n (%)	1 (3.8)	16 (57.1)	0.05 (0.01–0.35)	0.03 (0.01–0.23)	0.001
Unstable angina, n (%)	2 (7.7)	0 (0)			
Coronary artery bypass graft, n (%)	4 (15.4)	6 (21.4)			
Percutaneous coronary intervention, n (%)	0 (0)	8 (28.6)			
Stable angina not leading to revascularization, n (%)	1 (3.8)	10 (35.7)	0.09 (0.01–0.70)	0.09 (0.01–0.71)	0.02
Death from non-cardiac causes, n (%)	0 (0)	1 (3.6)			
<b>Combined endpoints<sup>d</sup></b>					
Cardiac death, non-fatal MI <sup>c</sup> , or unstable angina, n (%)	3 (11.5)	17 (60.7)	0.14 (0.04–0.49)	0.12 (0.03–0.43)	0.001
Cardiac death, non-fatal MI <sup>c</sup> , or stable/unstable angina, n (%)	4 (15.4)	22 (78.6)	0.13 (0.04–0.37)	0.08 (0.02–0.26)	<0.001

<sup>a</sup>Adjustment for age, gender, hypertension, diabetes, dyslipidaemia, and ischaemia in the anteroseptal region.

<sup>b</sup>More than one type of outcome event (initial and subsequent events) allowed per patient.

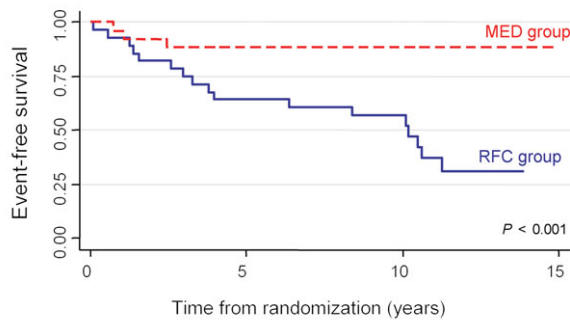
<sup>c</sup>Symptomatic and silent MI.

<sup>d</sup>If a patient experienced more than one outcome event of the endpoint, only the first event was counted.

middle-aged subjects with silent exercise-induced ischaemia verified by stress imaging and at least one risk factor of CAD. The low rate of otherwise healthy asymptomatic patients agreeing to participate in such a pilot study documents the difficulty to perform a large-scale randomized trial to this question and is an obvious reason for the lack thereof. Selection of eligible patients for this study also underscored the low positive predictive value (around 50%) of the bicycle ergometry for the detection of 'true' silent ischaemia in such a low disease-prevalent population. The low disease prevalence is underscored by the excellent 10 year survival even of RFC patients with a mortality of only 1.1%/year. Still, combined anti-ischaemic drug

therapy and aspirin not only reduced combined major cardiac events during follow-up, but also resulted in a persistently lower rate of exercise-induced ischaemia and prevented a gradual decline of left ventricular function noted in patients with risk factor control-only. Of note is the relatively high rate of silent MI detected in these patients with silent ischaemia as previously noted;<sup>18,19</sup> but even without these silent events, the difference in outcome events remained significant in favour of the MED treatment strategy. These results were observed in the presence of a remarkable impact of risk factor control measures in both treatment groups.

Primary endpoint



Number of patients at risk	26	23	23
MED group			
RFC group	28	18	15

**Figure 3** Kaplan–Meier survival function of the primary endpoint (cardiac death, non-fatal myocardial infarction, and unstable angina pectoris).

Previous studies in patients with silent ischaemia showed the prognostic importance of this finding in patients with additional angina,<sup>9,14</sup> previous MI,<sup>10,11</sup> coronary artery bypass graft surgery,<sup>12</sup> or angioplasty.<sup>13</sup> The prognostic importance of silent ischaemia type I documented by stress MPS was also described in asymptomatic volunteers and elderly subjects.<sup>9,20</sup> The prevalence of and the association between silent myocardial ischaemia and new coronary events were found to be true for both older men and women and both with and without cardiovascular disease.<sup>21,22</sup> The risk of coronary events in a 10 year follow-up of patients with silent myocardial ischaemia was reported to depend on the presence of cardiovascular risk factors,<sup>23</sup> and it was found that patients with silent ischaemia type I have a better prognosis than patients with symptomatic stable angina.<sup>24</sup>

There is, however, a debate as to whether silent ischaemia type I should be treated since, in absence of symptoms, such treatment can only be directed towards an improvement of prognosis.<sup>25,26</sup> The Asymptomatic Cardiac Ischemia Pilot study and the Atenolol Silent Ischemia Study showed a benefit of either revascularization<sup>14</sup> or drug therapy<sup>14,15</sup> in patients who had silent ischaemic episodes in addition to symptomatic ones.<sup>1</sup> SWISSI I is the first study which attempted to extend these findings to totally asymptomatic patients with silent ischaemia type I, i.e. without any history of prior CAD disease.

**Limitations**

There are certain special aspects and limitations of the present study. First, an unexpectedly low rate of subjects consenting to study inclusion was observed, which makes the estimates of effect size unstable. This low number of patients was due to the inclusion of a low-risk CAD population, mainly asymptomatic middle-aged men sent for life insurance check-up examinations, which required verification of silent ischaemia by stress imaging. Furthermore, these asymptomatic subjects had to be willing to participate in a drug study with repeated examinations over a prolonged period of time. Despite the small sample size, results achieved statistical significance because of a large effect size. The impact of the small sample size was partially mitigated by the remarkably long length of follow-up achieved (483 patient years). In addition, Cox proportional hazards model showed similar results for adjusted and unadjusted

**Table 4** Findings during follow-up according to treatment group

	At 1 year		At 5 years		At 10 years		P-value
	MED group	RFC group	MED group	RFC group	MED group	RFC group	
Number of patients at risk <sup>a</sup>	26	26	23	19	23	11	
Ischaemia present, n (%) <sup>b</sup>	12 (46.2)	26 (100)	9 (39.1)	17 (89.5)	5 (21.7)	7 (63.6)	0.019
Ejection fraction, %	60.3 ± 3.3	60.4 ± 4.7	60.8 ± 4.1	57.1 ± 7.2	61.1 ± 5.7	55.3 ± 8.1	0.021
Blood pressure at rest, mmHg							
Systolic	125 ± 6	140 ± 12	136 ± 16	132 ± 13	129 ± 17	133 ± 9	0.452
Diastolic	80 ± 6	84 ± 8	85 ± 8	88 ± 8	80 ± 11	82 ± 7	0.596
Work load during bicycle ergometry, W	161 ± 36	173 ± 43	170 ± 48	174 ± 47	163 ± 42	170 ± 38	0.635

Data are presented as mean ± standard deviation or as number of patients (percentages).  
<sup>a</sup>Patients with an event of the primary endpoint were excluded at the time of the event.  
<sup>b</sup>As assessed by either bicycle ergometry or stress ECHO or <sup>201</sup>Tl scintigraphy.

analyses, suggesting the results were robust. This is supported by the fact that overall findings were not overly dependent on one component of outcome. The open design of the study treatment is another limitation, but it was impossible to conduct such a long-term study with a placebo control arm in these difficult-to-motivate patients. Thus, this study also does not show that a certain drug or drug class is effective, but rather it provides a proof of principle that anti-ischaemic drug therapy has beneficial effects on outcome in these patients. The difference between study groups in aspirin use may have added to this effect although aspirin is primarily known to improve survival and not to reduce rates of ischaemic symptoms, objective signs of ischaemia, nor to preserve left ventricular function, although a reduced rate of episodes of ST-depression on Holter monitoring has been noted.<sup>27</sup> Finally, the significant treatment effect found in SWISS I parallels that recently found in the medical treatment arm of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial in stable coronary patients, although most of those patients were mildly to moderately symptomatic.<sup>28</sup>

## Conclusions

In conclusion, these data in asymptomatic subjects with silent ischaemia but no history of CAD suggest that anti-ischaemic drug therapy and aspirin may reduce subsequent cardiac events, reduce ischaemia, and preserve left ventricular function. The results of this study indicate that asymptomatic subjects with exercise-induced ST-segment depression at a check-up examination should have this finding verified by stress imaging; if silent ischaemia can be documented, physicians should consider prophylactic anti-ischaemic drug therapy and aspirin in addition to risk factor management. Further research is indicated to confirm these findings in a large population, identify the effective intervention, isolate the population most likely to benefit from it, and clarify the underlying mechanisms.

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**Conflict of interest:** none of the granting institutions had any influence on the study design, data collection, analysis, and interpretation.

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