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Evolution of silent myocardial ischaemia prevalence and cardiovascular disease risk factor management in Type 2 diabetes over a 10-year period: an observational study

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Abstract

Aims To assess the evolution of silent myocardial ischaemia prevalence and of cardiovascular disease risk factor management over 10 years in people with Type 2 diabetes.

Methods This repeated cross-sectional study prospectively included 770 people with Type 2 diabetes who presented at our centre in the period 1999–2009. All had at least one additional cardiovascular disease risk factor, no history of coronary disease and were screened for silent myocardial ischaemia using myocardial perfusion imaging. The prevalence of silent myocardial ischaemia, clinical and biological variables and treatments were collected and compared among participants screened in three periods: 1999 to 2002; 2003 to 2005; and 2006 to 2009. We also identified predictive factors for silent myocardial ischaemia.

Results Participants had a mean $\pm$ SD age of 62.3 ± 9.3 years, 57.4% were men and the mean time from diagnosis of diabetes was 13.4 ± 9.3 years. Overall, silent myocardial ischaemia screening was positive in 13.9% of participants. This prevalence decreased sharply over the 10-year study period (22.6% in 1999–2002, 13.7% in 2003–2005 and 5.9% in 2006–2009; $P < 0.0001$). In parallel, diastolic and systolic blood pressure, HbA_{1c} and LDL cholesterol significantly decreased and glitazone and statin use increased (all $P < 0.001$). Male gender, peripheral artery disease, diastolic blood pressure > 80 mmHg and LDL cholesterol > 2.6 mmol/l were independently associated with silent myocardial ischaemia. Further adjustment showed the screening period had a significant effect, which erased the effects of diastolic blood pressure and LDL cholesterol.

Conclusions The prevalence of silent myocardial ischaemia decreased sharply over time, and control of the main cardiovascular disease risk factors improved. Although the causality link cannot be established, the present study supports current recommendations advocating glycaemic control and intensive management of cardiovascular factors instead of systematic screening.

Introduction

In 2013, 382 million people had diabetes worldwide, and this number is expected to reach 592 million by 2035 [1]. The association between diabetes and cardiovascular disease is well established; coronary artery disease is the leading cause of death in diabetes [2]. Importantly, coronary artery disease is also more often silent in people with diabetes [3].

Given the elevated risk of cardiovascular events and the higher prevalence of silent myocardial ischaemia in diabetes, screening asymptomatic people with diabetes for silent myocardial ischaemia was an appealing concept; however, many factors argue against implementing a broad-based screening programme [4–6]. Despite an important number of trials, the usefulness of silent myocardial ischaemia screening in people with Type 2 diabetes remains controversial, especially in the context of intensive therapy with regard to risk factors. Very few data have shown that a prospectively applied screening programme improves outcomes in

What's new?

- The prevalence of silent myocardial ischaemia decreased sharply over 10 years (from 22.6% in 1999–2002 to 5.9% in 2006–2009).
- In parallel, the management of cardiovascular disease risk factors (diastolic and systolic blood pressure, HbA_{1c}, LDL cholesterol) improved, and glitazone and statin use increased.
- Intensive management of cardiovascular factors could be recommended instead of systematic screening for silent myocardial ischaemia in people with Type 2 diabetes at high risk.

asymptomatic people with diabetes. Indeed, the Detection of Ischaemia in Asymptomatic Diabetics (DIAD) study is a randomized multicentre trial of silent myocardial ischaemia screening in asymptomatic adults with diabetes mellitus. A total of 522 people were allocated to systematic silent myocardial ischaemia screening, while 562 people were assigned to regular follow-up. At 5 years, the overall cardiac event rate was not significantly different between the groups, arguing against systematic silent myocardial ischaemia screening [6]. More recently, the Factor-64 randomized clinical trial was carried out in people with asymptomatic Type 1 or Type 2 diabetes [7]. It also reported that systematic coronary artery disease screening did not reduce the composite rate of all-cause mortality, non-fatal myocardial infarction, or unstable angina requiring hospitalization. The DYNAMIT randomized trial attempted to assess the effect of silent myocardial ischaemia screening on cardiovascular events [8], although it was stopped prematurely after 631 inclusions because of recruitment difficulties. A meta-analysis of DYNAMIT and DIAD studies showed no significant benefit of systematic screening [8]. Further, a commonly admitted rationale for systematic research of silent myocardial ischaemia in asymptomatic patients in general is to intensify treatment of risk factors. This might not apply to treatment of risk factors in people with diabetes. Indeed, since 2001, the National Cholesterol Education Program recommended more aggressive treatment for high lipid levels and hypertension simply on the basis of diabetes status [5]. More recently, the American Diabetes Association did not recommend routine screening for silent myocardial ischaemia in asymptomatic people as it does not improve outcomes as long as cardiovascular disease risk factors are treated [4]. Similarly, European guidelines recommend the screening of only patients at particularly high risk, such as those with evidence of peripheral artery disease, high coronary artery calcium scores or proteinuria [9].

We have routinely screened for silent myocardial ischaemia in all patients with high-risk Type 2 diabetes referred to our institution since 1999, according to French guidelines

[10]. In the context of the controversy over the usefulness of this screening, to the aim of the present study was to evaluate the evolution of the prevalence of silent myocardial ischaemia and the evolution of cardiovascular disease risk factor management in the period from 1999 to 2009.

Materials and methods

We carried out a repeated cross-sectional study from a previously described cohort [11] of participants with Type 2 diabetes, screened for silent myocardial ischaemia. All asymptomatic people with Type 2 diabetes referred to our diabetes clinic (either new referrals or those returning for routine follow-up) at an academic university hospital in Montpellier, France between 1999 and December 2009 were prospectively assessed for eligibility. People admitted thereafter were not included because at that point our team considered that systematic screening was no longer useful, and since January 2010, screening has only been performed in specific patients at our centre. Diabetes was diagnosed according to American Diabetes Association criteria available at that time (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 1997). Participants were considered to have Type 2 diabetes if they had no history of ketosis and if they did not initiate insulin treatment either in the 2 years after the diagnosis or before the age of 40 years.

At inclusion, participants were considered for silent myocardial ischaemia screening according to the French-speaking diabetes association (formerly ALFEDIAM) guidelines currently available at that time [10]. Included participants, therefore, had at least one of the following cardiovascular disease risk factors: age ≥ 60 years; active smoking habit; albuminuria; hypertension (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 80 mmHg); dyslipidaemia (LDL cholesterol ≥ 3.4 mmol/l and/or HDL cholesterol < 1.0 mmol/l or triglycerides ≥ 1.7 mmol/l or lipid-lowering therapy); family history of premature coronary artery disease (i.e. occurring before age 55 years in a male first-degree relative or before age 65 years in a female first-degree relative); and peripheral artery disease (considered when one or more peripheral arterial pulse was absent at clinical examination and/or when intermittent claudication and/or a history of revascularization of the lower limbs was present). Atherogenic dyslipidaemia was defined as triglycerides ≥ 2.26 mmol/l and HDL cholesterol ≤ 0.88 mmol/l [12]. Retinopathy was assessed by ophthalmoscopy. People with albumin excretion rate > 30 mg/day and/or macroproteinuria and/or renal failure were considered to have diabetic nephropathy.

Exclusion criteria included: known ischaemic heart disease; electrocardiographic evidence of Q-wave myocardial infarction, ischaemic ST-segment or T-wave changes; critical illness or unstable haemodynamics; surgery within the previous 3 months; age ≥ 80 years; contraindication to dipyrindamole (such

as history of severe bronchospasm); and previous silent myocardial ischaemia screening in the last 5 years.

Cardiovascular disease risk factors, family history of stroke or coronary disease, current medications and concomitant illnesses were recorded. Participants were considered to be active smokers if they currently smoked or had stopped smoking in the preceding 3 years. Blood pressure was measured with an automatic blood pressure monitor that was set to report the average of six blood pressure measurements, taken 5 min apart, after lying down for 15 min.

Each participant enrolled in the present study had given oral informed consent in accordance with the European directives as edited in 2001, which require no approval from an ethical committee for a study design as described herein.

Treatments

All participants had been receiving long-term treatment for atherosclerotic risk factors since 1999 according to recommendations available at that time, with stepwise implementation of behaviour modification and pharmacological therapy targeting hyperglycaemia, hypertension and dyslipidaemia. Medications were categorized as biguanide, sulfonylureas, α -glucosidase inhibitors, glitazone, insulin, renin-angiotensin system blockers (either angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists), antiplatelet drugs and lipid-lowering drugs.

Myocardial perfusion imaging

Stress tests and myocardial perfusion imaging were performed as previously described [11]. Briefly, all participants underwent a combined dipyridamole (0.75 mg/kg) exercise stress test, followed by a same-day stress–rest imaging protocol using ^{99m}Tc -sestamibi (1 mCi/10 kg body weight with a minimum of 7 mCi; 259 MBq). Stress and rest images were acquired, with the participant in prone position, 1 h after injection of ^{99m}Tc -sestamibi. Acquisition was performed using a double-headed gamma camera (GE-SMV DST-XL; GE Healthcare, Little Chalfont, UK) with low-energy, high-resolution, parallel-hole collimators. Stress and rest acquisitions were ECG-gated (10% R-R interval acceptance window, eight gated intervals). Silent myocardial ischaemia was defined as positive myocardial perfusion imaging (mean activity <70% of the maximum myocardium activity in three of 20 segments). Two experienced nuclear medicine physicians, blinded to the clinical data, reviewed the scintigraphic images.

Laboratory procedures

Biological variables were evaluated in fasting conditions on the same day as silent myocardial ischaemia screening took place. Serum total cholesterol, HDL cholesterol and

triglyceride levels were measured using routine enzymatic methods (Architect C8000; Abbott, Rungis France). LDL cholesterol was calculated using the Friedewald formula. HbA_{1c} was measured by a routine HPLC-based ion-exchange procedure (HA-8140; Menarini, Rungis, France). Enzymatic creatinine (Randox reagent, Mauguio, France) was measured and creatinine clearance was calculated using the Modification of Diet in Renal Disease equation. Urinary albumin excretion and proteinuria were measured via 24-h urine collections by immunoturbidimetry (Roche Cobasc502; Roche, Meylan, France). Microalbuminuria was defined as urinary albumin excretion values between 30 and 300 mg/24h. When urinary albumin excretion was >300 mg/24h, proteinuria was measured and defined as values above 0.3g/24 h.

Statistical analysis

A descriptive analysis was performed on all cardiovascular disease risk factors for people with and without silent myocardial ischaemia. Quantitative variables were described using mean values and standard deviations. As they were non-normally distributed, these variables were compared between people with and without silent myocardial ischaemia using the Mann–Whitney test. Qualitative variables were described using numbers and percentages and were compared using the Fisher's test. The level of statistical significance was set at 0.05.

The cohort was then divided into groups based on the date of silent myocardial ischaemia screening. Group 1 included participants screened between July 1999 and December 2002, group 2 included those screened between January 2003 and December 2005 and group 3 included those screened between January 2006 and December 2009. Differences between these three periods of time were analysed using the chi-squared test for qualitative variables or the Kruskal–Wallis test for quantitative variables. Missing data were not imputed. Multivariate analyses were implemented using unconditional logistic models. Variables were selected using a stepwise procedure, with an α -to-enter value of 0.15 and α -to-exit value of 0.05. A first model was carried out using variables associated with silent myocardial ischaemia. In addition to those variables, screening period was introduced in a second model. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics according to silent myocardial ischaemia status

A total of 770 people with Type 2 diabetes were screened between 1999 and 2009, all of whom were included and analysed. Population characteristics at inclusion are presented in Table 1. Participants were aged 62.3 ± 9.2 years,

Table 1 Baseline characteristics of the study cohort

	Missing values	Whole cohort N=770	Patients with silent myocardial ischaemia n=107	Patients without silent myocardial ischaemia n=663	P
Men, n (%)	0	442 (57.4)	90 (84.1)	352 (53.1)	<0.0001
Age, years	0	62.3 ± 9.3	62.3 ± 8.8	62.3 ± 9.3	0.96
BMI, kg/m ²	13	30.3 ± 5.7	30.2 ± 5.4	30.4 ± 5.8	0.80
Time from diagnosis of diabetes, years	12	13.4 ± 9.3	12.6 ± 9.6	13.5 ± 9.2	0.24
Smoking, n (%)	0	183 (23.8)	27 (25.2)	153 (23.5)	0.71
Systolic blood pressure, mmHg	1	132.0 ± 18.1	137.8 ± 19.3	131.0 ± 17.7	0.002
Systolic blood pressure >130 mmHg, n (%)	1	445 (57.9)	70 (65.4)	375 (56.7)	0.09
Diastolic blood pressure, mmHg	1	72.8 ± 10.7	74.9 ± 11.6	72.4 ± 10.5	0.04
Diastolic blood pressure > 80 mmHg, n (%)	1	256 (33.3)	46 (43.0)	210 (31.7)	0.03
Hypertension, n (%)	1	467 (60.7)	73 (68.2)	364 (59.5)	0.09
HbA _{1c} , mmol/mol	16	68 ± 13	69 ± 15	67 ± 12	0.86
HbA _{1c} , %		8.4 ± 1.6	8.5 ± 1.9	8.3 ± 1.5	
LDL cholesterol, mmol/l	46	2.9 ± 0.9	3.0 ± 0.8	2.8 ± 0.9	0.03
LDL >2.6 mmol/l, n (%)	46	433 (59.8)	69 (70.4)	364 (58.2)	0.02
HDL cholesterol, mmol/l	34	1.4 ± 0.4	1.3 ± 0.3	1.4 ± 0.4	0.03
HDL >1 mmol, n (%)	34	587 (79.8)	79 (79)	508 (79.9)	0.84
Triglycerides, mmol/l	10	1.9 ± 1.9	2.2 ± 1.8	1.9 ± 1.9	0.07
Triglycerides > 1.7 mmol/l	10	303 (39.9)	48 (44.9)	255 (39.1)	0.29
Atherogenic dyslipidaemia, n (%)	34	32 (4.4)	5 (5.0)	27 (4.3)	0.79
Creatinine clearance, ml/min	2	89.9 ± 31.9	87.4 ± 32.8	90.2 ± 31.8	0.34
Diabetic nephropathy, n (%)	41	299 (41.0)	52 (50.5)	247 (39.5)	0.04
Peripheral artery disease, n (%)	16	91 (12.1)	30 (28.0)	61 (9.4)	<0.0001
Retinopathy, n (%)	32	219 (29.7)	38 (37.6)	181 (28.4)	0.06
Biguanide, n (%)	0	478 (62.1)	71 (66.4)	407 (61.4)	0.34
Sulphonylureas, n (%)	0	345 (44.8)	53 (49.5)	292 (44.0)	0.30
α-glucosidase inhibitors, n (%)	0	81 (10.5)	14 (13.1)	67 (10.1)	0.39
Glitazone, n (%)	0	96 (12.5)	6 (5.6)	90 (13.6)	0.02
Insulin, n (%)	0	356 (46.2)	49 (45.8)	307 (46.3)	1
Antiplatelet drug, n (%)	12	237 (31.3)	43 (40.2)	194 (29.8)	0.04
Statins, n (%)	13	333 (44.0)	45 (42.1)	288 (44.3)	0.68
Renin-angiotensin system blockers, n (%)	13	447 (59.0)	67 (62.6)	380 (58.5)	0.46

Values are mean ± sd for quantitative variables or frequency for qualitative variables.
P values indicate the significance of the difference between groups analysed using the Mann–Whitney test for quantitative variables and the Fisher’s test for qualitative variables.

57.4% of them were men and the mean time from diagnosis of diabetes was 13.4 ± 9.3 years. Regarding risk factors for cardiovascular disease, 12.0% had peripheral artery disease and 41.0% had diabetic nephropathy. The mean HbA_{1c} concentration was 68 ± 13 mmol/mol (8.4 ± 1.6%), mean LDL cholesterol was 2.8 ± 0.8 mmol/l, 23.7% of participants were current smokers and 61.0% had hypertension. Regarding medication use, 54.0% were on lipid-lowering drugs (44.0% used statins), 31.3% were on antiplatelet drugs and 59.0% were on renin-angiotensin system blockers. Insulin-treated participants represented 46.3% of the cohort.

Of the 770 participants with diabetes, 107 (13.9%) were found to be positive for silent myocardial ischaemia after screening. Men were four times more likely to be screened positive than women (20.4% vs 5.2%; *P*<0.0001). Mean age and BMI did not differ significantly between patients with and without SMI (Table 1). Peripheral artery disease and nephropathy were significantly more prevalent in people with

silent myocardial ischaemia than in people without (28.0% vs 9.4%, *P*<0.0001 and 50.5% vs 39.5%, *P*=0.04, respectively). Those with silent myocardial ischaemia also had significantly higher systolic and diastolic blood pressure. Regarding biological variables, people with silent myocardial ischaemia had significantly lower HDL cholesterol and significantly higher LDL cholesterol levels; there was no difference in mean HbA_{1c} concentrations. Regarding medication use, people with silent myocardial ischaemia were more often treated with antiplatelet therapy (40.2% vs 29.8%; *P*=0.04), whereas use of statins, insulin and blockers of the renin-angiotensin system did not differ (Table 1).

Patients’ characteristics according to the screening period

The characteristics and a comparison of the three groups, defined according to inclusion period, are shown in Table 2. The prevalence of silent myocardial ischaemia was 22.6% in

Table 2 Baseline characteristics of patients according to screening period*

	Screening period 1 (n=257)	Screening period 2 (n=241)	Screening period 3 (n=272)	P
Silent myocardial ischaemia, <i>n</i> (%)	58 (22.6)	33 (13.7)	16 (5.9)	<0.0001
Men, <i>n</i> (%)	147 (57.2)	147 (61.0)	148 (54.4)	0.32
Age, years	62.3 ± 9.3	61.5 ± 8.6	62.9 ± 9.7	0.29
BMI, kg/m ²	29.2 ± 5.4	30.8 ± 5.3	31.0 ± 6.3	0.0005
Time from diagnosis of diabetes, years	13.6 ± 9.0	12.5 ± 9.1	14.0 ± 9.7	0.14
Smoking, <i>n</i> (%)	62 (24.1)	57 (23.4)	64 (23.5)	0.99
Systolic blood pressure, mmHg	137.8 ± 19.7	129.9 ± 16.3	128.5 ± 16.7	<0.0001
Diastolic blood pressure, mmHg	76.3 ± 11.2	71.9 ± 9.7	70.2 ± 10.3	<0.0001
Hypertension, <i>n</i> (%)	198 (77.3)	137 (56.9)	132 (48.5)	0.45
HbA _{1c} , mmol/mol	73 ± 15	67 ± 12	64 ± 10	<0.0001
HbA _{1c} , %	8.8 ± 1.8	8.3 ± 1.5	8.0 ± 1.3	
LDL cholesterol, mmol/l	3.2 ± 0.9	2.8 ± 0.9	2.6 ± 0.9	<0.0001
HDL cholesterol, mmol/l	1.3 ± 0.4	1.4 ± 0.5	1.4 ± 0.4	0.007
Triglycerides, mmol/l	2.0 ± 2.1	1.9 ± 1.8	1.7 ± 1.7	0.41
Atherogenic dyslipidemia, <i>n</i> (%)	11 (4.4)	13 (5.7)	8 (3.1)	0.38
Creatinine clearance, ml/min	90.0 ± 30.7	91.2 ± 30.4	88.5 ± 34.4	0.28
Diabetic nephropathy, <i>n</i> (%)	103 (42.9)	95 (40.8)	101 (39.5)	0.73
Peripheral artery disease, <i>n</i> (%)	28 (11.0)	33 (13.8)	30 (11.6)	0.61
Retinopathy, <i>n</i> (%)	98 (39.0)	62 (27.3)	59 (22.7)	0.0002
Biguanides, <i>n</i> (%)	150 (58.4)	153 (63.5)	175 (64.3)	0.32
Sulfonylureas, <i>n</i> (%)	125 (48.6)	111 (46.1)	109 (40.0)	0.13
α-glucosidase inhibitors, <i>n</i> (%)	46 (17.9)	19 (7.9)	16 (5.9)	<0.0001
Glitazone, <i>n</i> (%)	1 (0.39)	35 (14.5)	60 (22.1)	<0.0001
Insulin, <i>n</i> (%)	119 (46.3)	107 (44.4)	130 (47.8)	0.75
Antiplatelet drug	72 (28.2)	70 (29.1)	95 (36.3)	0.10
Statins, <i>n</i> (%)	88 (34.7)	92 (38.2)	153 (58.4)	<0.0001
Renin-angiotensin system blockers, <i>n</i> (%)	146 (57.0)	149 (62.3)	152 (58.0)	0.45

*Period 1: July 1999 to December 2002; period 2: January 2003 to December 2005; period 3: January 2006 to December 2009.

Values are mean ± sd for quantitative variables or frequency for qualitative variables.

P values indicate the significance of the differences among these three periods of time, analysed with the Kruskal–Wallis test for quantitative variables and the chi-squared test for qualitative variables.

period 1 (1999–2002) and had significantly declined to 13.7% in period 2 (2003–2005) and to 5.9% in period 3 (2006–2009; $P<0.0001$). The proportion of men, mean age, time from diagnosis of diabetes, prevalence of smoking and prevalence of peripheral artery disease did not differ significantly among the three groups. By contrast, a decrease over time was observed for mean systolic blood pressure and mean diastolic blood pressure; however, no associated increase in the use of renin-angiotensin system blockers was observed. Furthermore, mean HbA_{1c} significantly fell from 8.8% (73 ± 15 mmol/mol) in period 1 to 8.0% (64 ± 10 mmol/mol) in period 3 ($P<0.0001$). Regarding medications for diabetes, only glitazone use significantly increased over time. No differences in biguanide or insulin use were observed. Mean LDL cholesterol levels significantly declined, while statin use increased. Lastly, antiplatelet drugs tended to be used more often in period 3 than in period 1, although this difference did not reach significance.

Prevalence of risk factors for silent myocardial ischaemia

When considering all factors associated with silent myocardial ischaemia overall, male gender, presence of peripheral artery disease, high diastolic blood pressure and high LDL

cholesterol were associated with an increased risk (Table 3, multivariate model 1). After further adjustment for the screening period, we found that male gender, peripheral arterial disease and the screening period (period 2 vs period 1 only) were significantly associated with silent myocardial ischaemia, but the effects of diastolic blood pressure and LDL cholesterol were no longer significant (Table 3, multivariate model 2). When comparing the first period and the second and third periods considered together, we observed a decrease in the proportion of participants with diastolic blood pressure >80 mmHg (from 52.5% to 23.6%; $P<0.0001$) or LDL cholesterol > 2.6 mmol/l (from 77.4% to 51.1%; $P<0.0001$).

Discussion

In this repeated cross-sectional study in asymptomatic people with Type 2 diabetes at high risk of coronary artery disease, we observed a highly significant decrease in the prevalence of silent myocardial ischaemia over the 10-year study period. In parallel, control of the main cardiovascular disease risk factors improved over time, after an update in recommendations, with an increase in cardiovascular medications used. To our knowledge, only few studies have investigated silent

Table 3 Predictive factors for silent myocardial ischaemia in the whole cohort

	Multivariate model 1 Adjusted odds ratio (95% CI)	Multivariate model 2 Adjusted odds ratio (95% CI)
Sex (men vs women)	5.7 (3.0–10.7)	5.8 (3.1–10.8)
Peripheral artery disease	4.2 (2.3–7.4)	4.5 (2.5–8.0)
Diastolic blood pressure > 80 mmHg	1.8 (1.1–2.9)	–
LDL cholesterol > 2.6 mmol/l	2.0 (1.2–3.4)	–
Screening period 2 vs 1	–	0.38 (0.22–0.68)
Screening period 3 vs 2	–	0.57 (0.29–1.14)

Multivariate model 1: variables associated with silent myocardial ischaemia overall with $P < 0.15$ were entered in the model in a stepwise manner: sex (men vs women), systolic blood pressure (< 130 or > 130 mmHg), diastolic blood pressure (< 80 or > 80 mmHg), hypertension, LDL (< 2.6 or > 2.6 mmol/l), HDL cholesterol, triglycerides, creatinine clearance (< 80 or > 80 ml/min), diabetic nephropathy, peripheral artery disease, retinopathy.

Multivariate model 2: the screening period (1,2,3) was introduced into the model in addition to variables entered in model 1.

Screening periods: period 1, July 1999 to December 2002; period 2, January 2003 to December 2005; period 3, January 2006 to December 2009.

myocardial ischaemia prevalence and cardiovascular disease risk factor management concomitantly, although screening for silent myocardial ischaemia is frequently discussed.

Data on silent myocardial ischaemia prevalence are not consistent in the literature, with values in people with diabetes varying from 12% to 62%. This discrepancy was notably explained in part by differences in patient selection and choice of stress test [13]. For example, in the large Milan Study on Atherosclerosis and Diabetes (MiSAD), enrolling 925 asymptomatic participants with Type 2 diabetes, the prevalence of silent myocardial ischaemia assessed by a stress ECG treadmill test was as low as 12%, but the screened population was at very low risk, with no requirement for additional risk factors for enrolment [14]. In a similar population, Cosson *et al.* [15] reported a 33% prevalence of silent myocardial ischaemia using single-photon emission computed tomography. Ten years ago, we reported a 31% prevalence using stress ECG, coupled with myocardial perfusion imaging, in high-risk Type 2 diabetes [16]. Recent studies, however, report a lower prevalence [3,17].

Regarding the threshold for cardiovascular risk factor control, management of cardiovascular disease risk factors in the present cohort improved over time but cannot be considered as optimal, as also reported by two recent large studies [18,19]. Indeed, in the present study population, the lowest prevalence of silent myocardial ischaemia was associated with an average HbA_{1c} of 8% (64 mmol/mol), which

does not reflect tight glycaemic control; however, this finding should be considered together with the results of the ACCORD, VADT and ADVANCE studies [20–22]. These three major studies in people with high risk Type 2 diabetes showed no significant benefit of tight glycaemic control in terms of reduction in macrovascular complications in people with diabetes with high cardiovascular risk. Nevertheless, the 10-year follow-up UK Prospective Diabetes Study showed that intensive glucose control was associated with a significantly decreased risk of myocardial infarction and death from any cause in the longer term [23]. Furthermore, the results from the ACCORD study suggest that very tight control (HbA_{1c} $< 6.0\%$) might actually be detrimental to those with pre-existing cardiovascular disease and long duration of diabetes [21].

The mean LDL concentration in the present population at the end of the study had decreased from 3.1 to 2.6 mmol/l, which was probably attributable to an increase in statin use; however, once again, this does not reflect tight control with regard to this cardiovascular risk factor. As stated in current guidelines, decreasing LDL concentration to an even greater extent should be beneficial in term of cardiovascular risk, with an LDL cholesterol target of < 1.8 mmol/l [24]. Tight control of lipid levels may therefore be associated with a greater reduction in silent myocardial ischaemia prevalence. By contrast, optimum blood pressure control appears to have been achieved, given the values observed in the present study. No argument is put forward in the literature in defence of a lower target [25], and too great a decrease in blood pressure may even be detrimental [26].

In the present study, high LDL cholesterol and high diastolic blood pressure were risk factors for silent myocardial ischaemia; however, such associations were no longer significant after adjustment for the period of inclusion. We can therefore hypothesize that the decrease in silent myocardial ischaemia prevalence observed throughout the study can be explained by an improvement in management of cardiovascular risk factors, such as diastolic blood pressure or LDL cholesterol level, even though definitive conclusions cannot be drawn from the present study. Nevertheless, the results are in accordance with Barthelemy *et al.* [27], who reported a much lower prevalence of silent myocardial ischaemia (16%) in people receiving intensive cardiovascular risk factor therapy than that reported previously in people receiving conventional care for cardiovascular risk factors [27]. Indeed, the 122 participants in their observational study benefited from long-term intensive therapy with better control of cardiovascular risk factors (blood pressure: 133/73 vs 139/76 mmHg; LDL cholesterol: 2.6 vs 3.1 mmol/l; and glycaemia: HbA_{1c} 60.7 mmol/mol vs 79.2 mmol/mol). Although the study was small, to our knowledge, no other publication has reported such an association. In the DIAD study, all screened participants who had not experienced cardiac events or revascularization were also invited to return for stress myocardial perfusion imaging 3 years after

entry; repeat tests performed in 358 participants overall showed significant improvement in myocardial perfusion imaging defects [6]. The significant increase in primary medical prevention observed across the study was thought to explain such improvements. In the BARI 2D trial, which included people with Type 2 diabetes and angiographically documented stable coronary heart disease, the number of risk factors controlled during the trial was strongly related to death and cardiovascular events [28]. Moreover, the decrease in silent myocardial ischaemia prevalence may also be attributable to the marked increase in glitazone use over the study period, although this causality link cannot be established from the present results. Indeed, glitazone use has been associated with decreased risks of heart failure, cardiovascular disease and all-cause mortality [29]. However, glitazones were withdrawn in France in 2011.

The present study has some limitations, in particular, the risk of bias inherent to its observational design. The enrolment of all eligible participants during the study period may have limited selection bias, as supported by the very similar number of participants enrolled during each interval. However, we cannot exclude the possibility that an increasing number of people were screened prior to entry into this study because of increased awareness of the presence of silent myocardial ischaemia among primary care physicians which may have contributed to the decreased prevalence observed in our study. Moreover, during the course of the study, Type 2 diabetes may have been diagnosed at earlier stages of the disease; physicians were more aware of the condition and may have screened for it earlier. In addition, the present study was conducted in only one hospital; however, most of the complicated patients in the region are likely to be referred to our centre, limiting selection bias. Moreover, we cannot exclude the possibility that routine clinical management of patients could have evolved through time, as the inclusion period is rather long. Nevertheless, the single-photon emission computed tomography method used may have been increasingly sensitive because of increasing experience among specialists, reinforcing our observation. Better specificity of screening technique, however, may have induced a decrease in the false-positive rate for silent myocardial ischaemia and therefore may have contributed to the observed decrease in the prevalence of the disease. Lastly, the observational study design does not allow conclusions to be drawn regarding causality link between decreasing prevalence of silent myocardial ischaemia and optimized cardiovascular risk factors or drug use.

In conclusion, positive screening for silent myocardial ischaemia affects a lower proportion of people with diabetes than it did a few years ago. Given the dynamic nature of myocardial ischaemia, the prohibitive cost of screening all asymptomatic patients, and the proven efficacy of primary preventive strategies, we recommend implementation of better clinical risk stratification strategies to identify very high-risk individuals. Indeed, European guidelines

recommend the screening of only those at particularly high risk, such as people with evidence of peripheral artery disease, a high coronary artery calcium score or proteinuria [9]. Several questions remain unclear: (1) what is the best strategy to allow proper patient selection through logical stepwise approaches to screening? and (2) would rigorously implemented primary preventive measures alter patient outcomes?

The results of the present study are consistent with current recommendations that advocate glycaemic control and intensive management of cardiovascular risk factors instead of systematic screening for silent myocardial ischaemia.

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Competing interests

None declared.

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