Original article

One quarter of total myocardial infarctions are silent manifestation in patients with type 2 diabetes mellitus

Hirofumi Soejima (MD, PhD, FJCC)[a,b,*], Hisao Ogawa (MD, PhD, FJCC)[c], Takeshi Morimoto (MD, PhD)[d], Sadanori Okada (MD, PhD)[e], Mio Sakuma (MD, PhD)[d], Masafumi Nakayama (MD, PhD)[f], Izuru Masuda (MD, PhD)[g], Naofumi Doi (MD, PhD)[h], Shiro Uemura (MD, PhD, FJCC)[i], Hideaki Jinnouchi (MD, PhD)[j], Seigo Sugiyama (MD, PhD, FJCC)[j], Masako Waki (MD, PhD)[k], Yoshihiko Saito (MD, PhD, FJCC)[l] for the JPAD Trial Investigators

[a] Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
[b] Health Care Center, Kumamoto University, Kumamoto, Japan
[c] National Cerebral and Cardiovascular Center, Suita, Japan
[d] Department of Clinical Epidemiology, Hyogo College of Medicine, Nishinomiya, Japan
[e] Department of Diabetology and Department of Cardiovascular Medicine, Nara Medical University, Kashihara, Japan
[f] Nakayama Cardiovascular Clinic, Amakusa, Japan
[g] Takeda Hospital Medical Examination Center, Kyoto, Japan
[h] Department of Cardiovascular Medicine, Nara Prefecture Seiwa Medical Center, Ikoma-gun, Japan
[i] Department of Cardiovascular Medicine, Kawasaki Medical School, Kurashiki, Japan
[j] Department Internal Medicine, Jinnouchi Hospital Diabetes Care Center, Kumamoto, Japan
[k] Department of Internal Medicine, Shizuoka City Shizuoka Hospital, Shizuoka, Japan
[l] Department of Cardiovascular Medicine, Nara Medical University, Kashihara, Japan

A R T I C L E   I N F O

A B S T R A C T

Background: Silent events with newly developed Q waves in electrocardiogram (ECG) [silent myocardial infarction (MI)] in diabetic patients is reported to be independently associated with an increased risk of fatal MI. However, the incidence rate of silent MI in diabetic patients has yet to be clarified. We sought to determine the incidence rate of first symptomatic MI and silent MI in diabetic patients.
Methods: We conducted a prospective cohort study on patients enrolled in the Japanese primary prevention of atherosclerosis with aspirin for diabetes (JPAD) trial which was started in 2002. It is a randomized controlled trial to examine the efficacy of low-dose aspirin therapy for the primary prevention of atherosclerotic events in type 2 diabetic patients. No patients had Q waves in their ECG before entry to the JPAD trial. We followed-up 1825 patients until July 2015 after completion of the JPAD trial in 2008. The median follow-up period was 10.3 years. We collected 1648 patients' ECGs to identify patients with silent MI.
Results: Symptomatic MI occurred in 65 patients and silent MI occurred in 22 patients. The incidence rate of symptomatic MI was 4.26 per 1000 patient-years and 1.44 for silent MI in diabetic patients. Thus, 25% of total MIs were silent. Cause-specific Cox proportional hazard model indicated that age (hazard ratio 1.06, 95% confidence interval; 1.03–1.10, $p = 0.0004$) and long history of diabetes (1.00, 1.01–1.07, $p = 0.01$) were independently associated with symptomatic MI, but these were not associated with silent MI.
Conclusions: We demonstrated that incidence rate of first silent MI and that proportion of silent MI to all MIs was 25% in diabetic patients without a history of atherosclerotic events. Diabetic patients frequently need ECG screening for detection of silent MI.

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* Corresponding author at: Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto City 860-8556, Japan.

Introduction

Cardiovascular disease is a major cause of death in the diabetic population. Patients with diabetes have an estimated two- to four-fold increased risk of developing cardiovascular disease [1]. Adjusting for other risk factors, a 1% increase in HbA1c is associated with an 18% increase in risk of cardiovascular events [2] and a 12% to 14% increased risk of death [3].

It was reported that there were 20% of patients who presented with atypical symptoms and 80% of patients with typical symptoms in patients with symptomatic myocardial infarction (MI) [4].

A resting electrocardiogram (ECG) remains a simple and inexpensive component of recommended routine cardiovascular risk assessment in diabetes mellitus [5]. Silent MI is defined as the presence of pathological Q waves in the absence of a history of typical cardiac symptoms. Silent MI is one of the abnormalities that can be detected through ECG screening. The prevalence of silent MI in patients with diabetes has been recognized for decades. The silent MI was reported in the Framingham study which was based on 34 years of follow-up of 5070 participants [6–10]. In this series, silent MI represented 26% and 34% of all MIs (silent + symptomatic) in men and women, respectively. The proportion of silent MI ranges from 22% to 44% [11]. However, there are few data on the incidence rate of silent MI in patients with type 2 diabetes mellitus.

We have sought to determine the incident rate and the proportion of first silent MI to all MIs in type 2 diabetic patients without a history of atherosclerotic events on the basis of resting ECG reading taken routinely throughout the study period.

Methods

This study was a prospective cohort study on patients enrolled from the Japanese primary prevention of atherosclerosis with aspirin for diabetes (JPAD) trial, a randomized controlled trial to examine the efficacy of low-dose aspirin therapy for the primary prevention of atherosclerotic events in type 2 diabetic patients [12]. The JPAD trial was conducted from December 2002 through April 2008 at 163 institutions throughout Japan, which enrolled 2536 patients with type 2 diabetes mellitus without a history of atherosclerotic disease. No patients had Q waves in their ECG. The study protocol was in agreement with the ethics committee guidelines of our institutions and complied with the Declaration of Helsinki. The institutional review board of each participating hospital approved this trial, and written informed consent was obtained from each patient. Because 1825 people agreed to follow-up survey after completion of the JPAD trial in 2008, we continue to follow-up the patients, as a cohort study (Fig. 1). Standard 12-lead ECGs supine at rest were obtained. ECGs were recorded with a calibration mark in millivolts and paper speed was marked on each trace, against which standardized measurements could be made. ECGs performed during the study period were read according to the Minnesota ECG code [13] by physicians of hospital or clinic doing patient care. The follow-up ECG data were collected in 2013 and 2015. A diagnosis of symptomatic MI during the study period required at least two of three criteria: ECG changes, ischemic symptoms, and raised cardiac enzymes. Q waves were defined as present when duration exceeded 0.03 s and in the absence of right or left bundle branch block or ventricular pacing. They were defined as new if absent from baseline or previous ECGs and as diagnostic of silent MI in the absence of a preceding clinical history of MI or unstable angina during the study period. ECGs that were suspected Q waves were forwarded to the independent committee consisting of cardiologists. An independent commit-
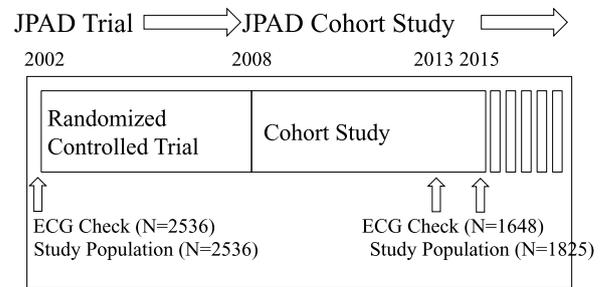

Fig. 1. JPAD trial and JPAD cohort participants sample size. The Japanese primary prevention of atherosclerosis with aspirin for diabetes (JPAD) trial was a randomized controlled trial to examine the efficacy of low-dose aspirin therapy for the primary prevention of atherosclerotic events in type 2 diabetic patients. The JPAD trial was conducted from December 2002 through April 2008 at 163 institutions throughout Japan, which enrolled 2536 patients with type 2 diabetes mellitus without a history of atherosclerotic disease. After completion of the JPAD trial in 2008, we continue to follow-up the patients, as JPAD cohort study consisting of 1825 patients. ECG, electrocardiogram.

tee validated the ECGs whether they had Q wave without knowing patient characteristics.

Statistical analyses

Continuous variables were expressed by means and SD, and compared by ANOVA between groups. Categorical variables were expressed by number and percent, and compared by chi-square test between groups. Patients lost to follow-up were censored at the point of their last hospital visit. Incidence rates were calculated by number of events divided by the patient-years in the cohort. Cumulative incidence curves of MI events were estimated by the Kaplan–Meier method. Cox proportional hazard models were developed to estimate cause-specific hazard ratios (HRs) of potential risk factors along with 95% confidence intervals (CIs). Each model for symptomatic MI or silent MI had the same potential risk factors as independent variables but either symptomatic MI or silent MI was included as dependent variables. We used the data on patients who provided the ECG data during follow-up for both models. If the same patient had both symptomatic and silent MI, the event that occurred first was considered the cause-specific event. Death, opposite event, or loss to follow-up were treated as censor. The potential risk factors included age, hypertension, dyslipidemia, and duration of diabetes before enrollment. We simultaneously included these factors without model selection. Missing data were not imputed and we analyzed all data as they were. A multivariate model was constructed for complete cases without missing variables in the models. All statistical analyses were conducted using JMP version 13.1 (SAS Institute Inc, Cary, NC, USA). Two-tailed *p*-values of less than 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 1648 patients' ECGs were screened by physicians. Overall mean (SD) age was 64 (10) years; 53% of patients were men (Table 1). Duration of diabetes was median 7.1 (25–75%) (3.1–12.5) years and levels of hemoglobin A1c were 7.2 (6.6–8.0) %. The prevalence of hypertension and dyslipidemia was 58% and 53%, respectively. Blood pressure was well controlled: mean (SD) systolic pressure, 135 (15) mmHg; mean (SD) diastolic pressure, 77 (9) mmHg. During the observation periods, the number of all-cause deaths was 173 (10%) and that of cardiac death was 12 (0.7%).

Table 1
Baseline characteristics in symptomatic MI, silent MI, and no-MI groups.

Characteristics	Symptomatic MI patients ($n=65$)	Silent MI patients ($n=22$)	No-MI patients ($n=1561$)	p-Value	No. missing data
Age, mean ± SD, yrs	69 ± 10	66 ± 9	64 ± 10	0.001	0
Male (%)	41 (63)	15 (68)	840 (54)	0.1	0
Current smoker or past smoker (%)	36 (55)	13 (59)	646 (41)	0.02	0
Body mass index, mean ± SD, kg/m^2	24 ± 3	26 ± 4	24 ± 4	0.09	3
Hypertension (%)	38 (58)	17 (77)	899 (58)	0.2	0
Dyslipidemia	40 (62)	10 (45)	825 (53)	0.3	0
Systolic blood pressure, mean ± SD, mmHg	137 ± 16	138 ± 15	135 ± 15	0.4	0
Diastolic blood pressure, mean ± SD, mmHg	75 ± 9	79 ± 10	77 ± 9	0.3	0
Duration of diabetes (IQR), yrs	8.9 (4.9–15.8)	8.2 (2.7–10.2)	7.0 (3.0–12.4)	0.047	137
Hemoglobin A1c (IQR), %	7.5 (6.8–8.6)	7.0 (6.5–7.5)	7.2 (6.6–8.0)	0.1	0
Total cholesterol, mg/dl	205 (40)	197 (30)	201 (33)	0.6	0
Triglyceride, mg/dl	149 (82)	160 (65)	130 (79)	0.007	88
High density lipoprotein cholesterol, mg/dl	53 (13)	46 (10)	56 (15)	0.004	130
Creatinine, mg/dl	0.8 (0.7–1.0)	0.8 (0.6–1.0)	0.7 (0.6–0.9)	0.0004	12
Estimated glomerular filtration rate, ml/min/1.73 m^2	64.9 (54.6–73.3)	72.7 (53.3–82.3)	72.9 (60.5–87.6)	0.002	12
Diabetic microvascular complication					
Diabetic retinopathy (%)	7 (11)	6 (27)	233 (15)	0.2	0
Diabetic nephropathy (%)	7 (11)	4 (18)	182 (12)	0.6	0
Proteinuria (%)	14 (23)	4 (18)	258 (17)	0.4	25
Diabetic neuropathy (%)	13 (20)	4 (18)	176 (11)	0.06	0
Dermal ulcer (%)	1 (1.5)	0 (0)	9 (0.6)	0.6	0
Diabetes treatment					
Sulfonylureas (%)	39 (60)	10 (45)	859 (55)	0.5	0
α-Glucosidase inhibitors (%)	24 (37)	4 (18)	538 (34)	0.3	0
Biguanides (%)	6 (9)	2 (9)	211 (14)	0.5	0
Insulin (%)	14 (22)	3 (14)	211 (14)	0.2	0
Thiazolidines (%)	4 (6)	0 (0)	75 (5)	0.5	0
Treatment for hypertension					
Calcium channel blockers (%)	29 (45)	13 (59)	538 (34)	0.02	0
Angiotensin-II receptor blockers (%)	7 (11)	4 (18)	337 (22)	0.1	0
Angiotensin-converting enzyme inhibitors (%)	11 (17)	6 (27)	226 (14)	0.2	0
β-Blockers (%)	6 (9)	1 (5)	105 (7)	0.7	0
α-Blockers (%)	2 (3)	1 (5)	56 (4)	0.9	0
Statins (%)	22 (34)	4 (18)	410 (26)	0.3	0
Nitrate (%)	1 (1.5)	1 (5)	15 (0.96)	0.2	0
Family history					
Type 2 diabetes mellitus (%)	22 (34)	8 (36)	652 (42)	0.4	0
Ischemic heart disease (%)	8 (12)	1 (5)	179 (11)	0.6	0
Stroke (%)	15 (23)	6 (27)	340 (22)	0.8	0

MI, myocardial infarction.

Incidence of myocardial infarction

Fifty-one patients' ECGs that were suspected to have Q waves were forwarded to the independent committee, then 22 patients' ECGs were judged to have Q waves. The 29 patients were excluded from the silent MI patients by various reasons. Seventeen cases did not meet the criteria of Q wave. Five cases were diagnosed as symptomatic MI. Three cases' ECG recorded complete right or left bundle branch block or pacemaker rhythm. Four cases' ECGs were not sent to the committee. Silent MI occurred in 22 patients (1.3%) and symptomatic MI occurred in 65 patients (3.9%) during the study period. On the other hand, MI did not occur in 1561 patients (no-MI patients). The incidence rate of symptomatic MI was 4.26 per 1000 patient-years while that of silent MI was 1.44 ($p < 0.0001$). Thus, 25% of total MIs were silent [$1.44/(1.44 + 4.26) = 0.25$].

Cumulative incidence of myocardial infarction

During the study period, symptomatic MI occurred with a constant frequency (Fig. 2, Left). On the other hand, incidence of silent MI is increasing in the latter half (Fig. 2, Right). Cumulative incidences at 12 years were 0.0512 in symptomatic MI and 0.0302 in silent MI.
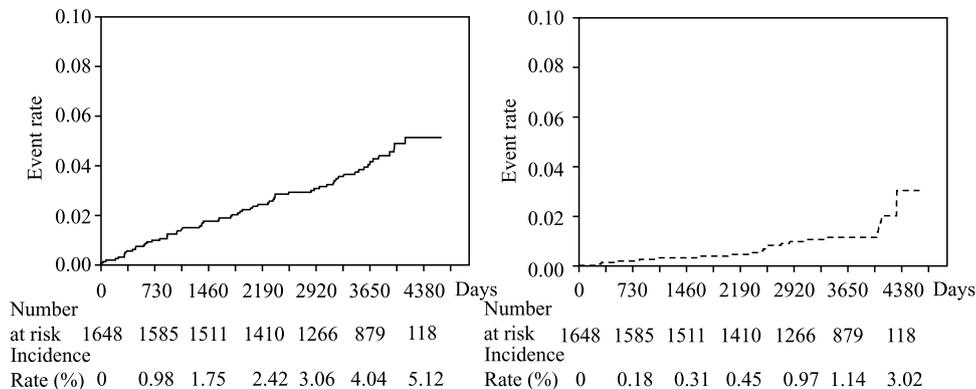

Fig. 2. The incidence rate of MI. Left: The incidence rate of symptomatic MI Right: The incidence rate of silent MI. Cumulative incidences at 12 years were 0.0512 in symptomatic MI and 0.0302 in silent MI. MI, myocardial infarction.

Table 2
Potential risk factors for symptomatic and silent myocardial infarction.

Factor	Symptomatic MI		Silent MI	
	Hazard ratio (95%CI)	p-Value	Hazard ratio (95%CI)	p-Value
Age	1.06 (1.03–1.10)	0.0004	1.02 (0.97–1.07)	0.48
Hypertension	0.91 (0.54–1.57)	0.74	2.39 (0.91–7.46)	0.10
Dyslipidemia	1.39(0.83–2.36)	0.21	0.70 (0.29–1.68)	0.42
Duration of diabetes	1.04 (1.01–1.07)	0.01	0.99 (0.93–1.05)	0.86
MI, myocardial infarction.				

Characteristics of patients with symptomatic and silent myocardial infarction

The baseline characteristics of symptomatic MI patients, silent MI patients, and no-MI patients are shown in Table 1. Mean age was higher in symptomatic MI patients than silent MI patients and no-MI patients. The frequency of smoking habits and calcium channel blocker usage were highest in silent MI patients. The duration of diabetes was longest in symptomatic MI patients. The other clinical characteristics such as the gender, body mass index, blood pressure, frequency of dyslipidemia, diabetic microvascular complications, and usage of drugs for diabetes were similar among the 3 groups.

Risk factors for symptomatic and silent myocardial infarction

Hazard ratios for MI compared with no-MI for general characteristics among those having a first symptomatic or silent MI are shown in Table 2. Cause-specific Cox proportional hazard model demonstrated that age and duration of diabetes were independently associated with symptomatic MI, but not with silent MI.

Discussion

Our data demonstrated that symptomatic MI occurred in 65 diabetic patients and silent MI occurred in 22 diabetic patients without a history of atherosclerotic events in the long-term follow-up study of median 10.3 years. We demonstrated for the first time that the incidence rate was 4.26 in symptomatic MI and 1.44 in silent MI per 1000 patient-years and the proportion of silent MI was 25% of total MIs in diabetic patients without a history of atherosclerotic events.

In the Cardiovascular Health Study database, which is based in four US field centers and is confined to persons 65 years of age or older (mean age 72.2 years, men 42.1%), 22% of all prevalent Q-wave infarctions was undetected until entry to the study [14]. The rate of silent MI and Q-wave infarctions was 3.4% and 15.3% of study population. The Fremantle Diabetes Study detected silent MI in 3.9% of patients, 43.9% of all MIs from the data of 1269 patients (mean age 64.1 years, men 49.2%) with type 2 diabetes mellitus from a community-based observational study [15]. Silent MI occurred in 16.6% patients of 1967 diabetic patients (mean age 52 years, men 60%) included in the United Kingdom prospective diabetes study (UKPDS) [16]. In the action to control cardiovascular risk in diabetes (ACCORD) cohort that was limited to patients without history of cardiovascular events and with diabetic patients as in the JPAD study, ECGs at the time of study entry were analyzed in the subjects. This study showed that men have higher prevalence of silent MI on baseline ECG than women (6% vs 4%) [17]. In the JPAD study, there were no significant differences between men and women although the incidence rate of silent MI was 1.4 times higher in men than in women. The rate of silent MI varies widely for these four studies by the difference of study population. These data showed the rate of silent MI to study population at the time of study entry, however, the incidence rate of silent MI was not able to be detected.

The fenofibrate intervention and event lowering in diabetes (FIELD) study detected silent MI in 2.5% of patients, 38.3% of all MIs over 5 years [18]. The incidence rate of both silent MI and symptomatic MI were much higher than that in the JPAD study. This seems to be due to FIELD study involving 21.8% of patients with a history of cardiovascular disease. In the Reykjavik study, men living in the Reykjavik area who were born between 1907 and 1934 were selected, and 4 to 20-year follow-up was performed [19]. This study showed that incidence rate of silent MI was almost zero up to age 40 years, then increased steeply to more than 3 cases per 1000 patient-years at age 60 years, and decreased with age after age 65 years. In the JPAD study, a long-term follow-up study of median 10.3 years, silent MI was found at a frequency of 1.44 per 1000 patient-years. These two studies were able to detect the incidence rate of silent MI because of follow-up study, however, their study populations mainly included non-diabetic patients. To our knowledge, there are no reports on the incidence rate of silent MI in patients with diabetes without a history of cardiovascular events.

Cumulative incidence rate of symptomatic MI occurred with a constant frequency. On the other hand, incidence of silent MI increased in the latter half. The increased detection of the Q wave in the latter half is due to the request for screening ECG in 2013 and 2015 unless recently taken. This fact indicates that verification of silent MI will be delayed with the current ECG screening frequency.

The risk profile of silent MI patients was not significantly different from that of symptomatic MI patients in the JPAD study. In the JPAD study, there were no factors that were independently associated with the incidence of silent MI. It seems because there was a small number of incidence of silent MI. Cox proportional hazards model demonstrated that age and duration of diabetes were significant predictors for symptomatic MI. It was also shown that age was independently associated with incidence of symptomatic MI in the FIELD study [18].

This study has several limitations. First, the occurrence of silent MI was confirmed by the ECG. ECGs were taken regularly at the discretion of each primary physician. In 2013 and 2015, we collected and examined the ECGs which were taken in the past. Patients who did not receive ECG examination recently were recommended to have one taken, therefore, the incidence of silent MI increased since around 2013. The timing of occurrence of silent MI depends on the timing of ECG measurement, so there is a possibility of ascertainment bias with respect to timing. Second, chronic kidney disease was a factor for development of silent MI [20]. It was, however, not included in the multivariate model because the number of events was small. Third, following past papers, the new appearance of Q wave was regarded as asymptomatic MI in this study, but there are myocardial infarctions without Q wave [21], and not all asymptomatic MIs can be detected.

In conclusion, this study demonstrated for the first time that incidence rate of first silent MI and that proportion of silent MI to all MIs was 25% in diabetic patients without a history of atherosclerotic events. It is suggested that diabetic patients frequently need ECG screening for detection of silent MIs to understand the risk of cardiovascular events.

Conflict of interest

Dr Soejima reports research grant from Boehringer Ingelheim; and lecturer's fee from Boehringer Ingelheim, Sumitomo Dainippon,

Acknowledgments

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jjcc.2018.05.017.

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