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REVIEW

Prevalence, incidence, predictive factors and prognosis of silent myocardial infarction: A review of the literature

Prévalence, incidence, facteurs prédictifs, et pronostic de l'infarctus du myocarde silencieux: revue de la littérature

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Summary The prevalence, incidence, risk factors and prognosis of silent myocardial infarction are less well known than those of silent myocardial ischaemia. The aims of this article are to evaluate the prevalence and incidence of silent myocardial infarction in subjects with or without a history of cardiovascular disease and in diabetic patients, and to identify potential risk factors and estimate prognosis through a review of the literature. A Medline search identified studies that provided data on the prevalence, incidence, potential risk factors and/or prognosis of silent myocardial infarction, among cohorts from the general population and large clinical studies of at-risk patients (with hypertension or a history of cardiovascular disease or diabetes). The search identified 15 studies in subjects from the general population, five in hypertensive patients, six in patients with a history of cardiovascular disease, and 10 in diabetic patients. The prevalence and incidence of silent myocardial infarction appear highly variable depending on the population studied, the patients' ages, and the method used to detect silent myocardial infarction. In the general population, the prevalence of silent myocardial infarction increased markedly with increasing age (up to > 5% in elderly subjects). Hypertension causes only a moderate increase in prevalence, whereas underlying cardiovascular diseases and diabetes are associated with marked increases in prevalence. The incidence of silent myocardial infarction changes in the same way. The main predictive factors of silent myocardial infarction are hypertension, history

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of cardiovascular diseases and diabetes duration. Silent myocardial infarction is associated with as poor a prognosis as clinical myocardial infarction. The frequency of silent myocardial infarction and the poor prognosis in at-risk patients amply justify its systematic early detection and active management.

MOTS CLÉS
Infarctus du myocarde ;
Prévalence ;
Incidence ;
Hypertension ;
Maladie cardiovasculaire ;
Diabète

Résumé Comparativement à l'ischémie myocardique silencieuse, la prévalence et l'incidence de l'infarctus du myocarde silencieux (IDMs), ses facteurs de risque et son pronostic sont mal connus. Évaluer la prévalence et l'incidence de l'IDMs chez des sujets avec/sans antécédents cardiovasculaires et chez des diabétiques, identifier ses facteurs de risque et estimer son pronostic, à partir des données de la littérature. La recherche a été effectuée dans Medline pour identifier, parmi les cohortes de sujets de population générale et les grandes études de patients à risque (hypertension, maladies cardio-vasculaires, diabète), celles évaluant la prévalence et l'incidence de l'IDMs, ses facteurs de risque et son pronostic. La recherche a identifié 15 études en population générale, cinq chez des patients hypertendus, six chez des patients avec antécédents cardiovasculaires et dix chez des patients diabétiques. La prévalence et l'incidence de l'IDMs apparaissent très variables selon la population étudiée, l'âge des patients et la méthode de détection. En population générale, la prévalence de l'IDMs augmente nettement avec l'âge (jusqu'à > 5 % chez les sujets âgés). L'hypertension augmente modérément la prévalence, tandis que les maladies cardiovasculaires sous-jacentes et le diabète induisent une nette augmentation de la prévalence de l'IDMs. L'incidence de l'IDMs varie parallèlement. Les principaux facteurs pronostiques sont l'hypertension, les maladies cardiovasculaires et la durée du diabète. Enfin, le pronostic de l'IDMs est aussi péjoratif que celui de l'IDMs clinique. La fréquence et le mauvais pronostic de l'IDMs chez les patients à risque justifient son diagnostic systématique précoce et une prise en charge active.

Background

A substantial number of myocardial infarctions (MIs) are asymptomatic or associated with minor and atypical symptoms, and are found accidentally during routine electrocardiogram (ECG) examinations that reveal the existence of abnormal Q waves. The possible causes of blunted MI perception in some patients remain ill defined, but there may be some impairment of the stimulation of cardiac receptors, impulse initiation, or conduction, or of cerebral pain perception [1]. Symptoms are often atypical or even absent, especially in diabetic patients — a population particularly at risk for coronary artery disease (CAD) [2].

Compared with the frequency of silent myocardial ischaemia, which is defined as evidence of myocardial ischaemia in the absence of signs of angina [3—5], the frequency of silent MI, which is unequivocal objective signs of infarction accompanied by unrecognized minimal, atypical symptoms or no symptoms at all, is less well known. Data may be collected, however, from studies that followed subjects from the general population or subjects at risk for CAD, such as those with hypertension or a history of cardiovascular disease, and also from large clinical studies that have been conducted for the evaluation of antidiabetic or hypolipidaemic therapies.

The aim of the present study was to retrieve information on the prevalence, incidence, and predictive/prognostic factors of silent MI, and to assess the influence of potential factors such as age, hypertension, other cardiovascular disorders, and diabetes that may promote the occurrence of silent MI.

Methods

Articles meeting the study objectives were identified by searching the MEDLINE database. Only relatively recent studies (from 1980 onwards) were retained for analysis, given that the detection and management of infarction may have changed considerably over time. Furthermore, studies essentially focused on the treatment of coronary heart disease were excluded.

A general search was first performed using the following keywords: ''silent myocardial infarction'' and ''unrecognized myocardial infarction''. Furthermore, a manual search was conducted from the bibliographic references quoted in the selected publications, and also from the ''related citations'' in PubMed. The information gathered was then analysed to estimate the prevalence of silent MI in the populations considered and the incidence over the follow-up period in each study.

Hereafter, the prevalence of silent MI is expressed as the proportion of patients with silent MI detected by the presence of a Q wave on the ECG or of abnormalities at stress echocardiography, delayed gadolinium-enhanced cardiac magnetic resonance imaging (DGE-MRI), or scintigraphy in the absence of a previous history or obvious clinical symptoms of MI. The prevalence of silent MI is also expressed as the proportion relative to all clinical MIs or all non-fatal MIs. The incidence of silent MI is either reported as the number of incident cases per 1000 patient-years, or estimated from the cumulative number of cases observed referred to the duration of the follow-up period and expressed as the number of cases per 1000 patient-years.

Results of the bibliographic search

The search in MEDLINE allowed the initial identification and selection of:

- 23 general publications on silent MI;
- 134 articles on studies conducted in patients with hypertension;
- nine articles on studies conducted in patients with CAD (five studies), thrombosis (two studies), or cardiac dyskinesia (two studies);
- 73 articles on clinical studies conducted in diabetic patients;
- eight articles in patients with diabetic neuropathy;
- 24 articles on clinical studies conducted in patients with dyslipidaemia;
- 14 articles on studies conducted in patients with nephropathy.

In addition to these 285 publications, 16 articles were identified by the manual search. Analysis of all these articles finally allowed the selection of 36 articles reporting data on silent MI: 15 in healthy subjects from the general population, five in hypertensive patients, six in patients with a history of cardiovascular disease, and 10 in diabetic patients.

Methods of silent MI diagnosis

In most studies, diagnosis of silent MI was based on the existence of a Q wave on ECG, and in some cases on R-wave reduction or abnormalities of the ST segment and/or T wave as coded according to the Minnesota classification [6,7]. In some studies, silent MI was detected by stress echocardiography (one study), dipyridamole/exercise stress scintigraphy (two studies) or delayed DGE-MRI (three studies) which in addition detected non-Q-wave silent MIs.

The choice of the detection method may have had an impact on silent MI diagnosis, as there may be a relationship between the knowledge of a patient's medical history at the time of examination, the choice of the detection method, and the accuracy of the diagnosis. An ECG is indeed the preferred detection method for patients with no obvious sign of MI, but may show low sensitivity, whereas more sophisticated methods used in patients with a stronger suspicion of MI may show greater sensitivity (e.g. DGE-MRI), possibly at the cost of lower selectivity (e.g. stress methods may erroneously detect reversible ischaemia).

Results

Prevalence of silent MI in the general population

Data on the prevalence of silent MI were obtained from 10 studies conducted in Europe, North America and India in healthy subjects from the general population, either adults (eight studies) [8—15] or elderly subjects (two studies) [16,17] (Table 1). In all these studies, silent MI was detected by ECG (Q wave and/or ST-T abnormalities in two studies) (Table 1). The patient populations comprised only low proportions of diabetic patients (0—7.6% of subjects aged < 65 years; 9.8—12.4% of those aged > 65 years).

These data suggest a strong relationship between subjects' age and prevalence of silent MI. The prevalence of silent MI was lowest (0.3—0.5%) in the studies that included young subjects (Rochester cohort and Reykjavik male cohort) [10,14] and highest (3.4—6.4%) in those that included older subjects (Rotterdam, Olmsted, Cardiovascular Health Study [CHS], and Bronx Aging Study [AS] cohorts) [8,9,16,17]. The prevalence of silent MI was also high among the young subjects included in the Northern Sweden Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) cohort (4.8%) [11]. This is probably because this particular ethnic group is more likely to develop CAD (8.6% of subjects had impaired glucose tolerance). The direct relationship between age and the prevalence of silent MI was well assessed in the two Reykjavik cohorts: in middle age (~ 60 years), the prevalence of silent MI was estimated at 1—1.5% in men and women, but this was much higher (> 5%) in men aged > 75 years [13,14]. Geographic location does not seem to exert a notable influence. In the studies in relatively young people, silent MIs accounted for 42—64% of all MIs [8—15], whereas this proportion was lower (22—35%) in older subjects (CHS and Bronx AS cohorts) [16,17] (Table 1).

Prevalence of silent MI in high-risk populations: patients with hypertension or a history of CAD

The two studies [18,19] of hypertensive subjects that provided prevalence data reported somewhat conflicting results. In the Medical Research Council (MRC) trial, which included mildly hypertensive patients [18], hypertension did not seem to be associated with increased prevalence of silent MI, whereas in the International Prospective Primary Prevention Study in Hypertension (IPPPSH)-Italia study [19], the prevalence of silent MI appeared moderately elevated compared with that in normotensive subjects of similar age (except for the MONICA study [11] and the Olmsted study [9]; see above) from the general population (Table 2).

The four studies in patients with a history of cardiovascular disease [20—23] showed a notably higher prevalence of silent MI (Table 2). In patients with a history of cardiovascular disease, including those with a clinical suspicion of CAD or with non-cardiac vascular surgery, the observed prevalence of silent MI reached 23% in both a European and a North American study where silent MI was detected by stress echocardiography or DGE-MRI [21,23]. The prevalence of silent MI was similar (27%) in a study of patients with suspected CAD in whom silent MI was detected by DGE-MRI (compared with only 8.1% by ECG) [20]. It was found to be lower, however, in a study that included a high proportion of diabetic patients in whom silent MI was detected by exercise stress scintigraphy [22]. In two studies where both types of data were available, the proportion of silent MI patients was notably higher amongst diabetic patients compared with their non-diabetic counterparts [21,22].

Prevalence of silent MI in diabetic patients

Data on the prevalence of silent MI in diabetic patients were retrieved from four articles (Table 3) [24—27]. One of them concerned the Australian Fremantle cohort, which included

Table 1 Prevalence of silent MI in the general population.

Cohort name and/or year	Region	*n*	Sex	Mean or range age (years)	Method of diagnosis	Prevalence (%)	Proportion of all MIs (%)
Bronx AS 1990 [17]	USA	390	M/F	79	ECG Q wave	6.4	35
1992 [15]	India	5621	M/F	25—64	ECG Q wave	1.4	—
Reykjavik 1995 [14]	Europe	9141	M	33—60 at entry	ECG	0.5 at age 50 to > 5 at age 75	54
Reykjavik 1998 [13]	Europe	9773	F	32—59 at entry	ECG	< 1 at age 60 to 1.9% at age 75	42
BRHS 2000 [12]	Europe	7735	M	50	ECG	1.7	46
CHS 2000 [16]	USA	5888	M/F	72	ECG Q wave[a]	3.4	22
MONICA 2003 [11]	Europe	771	M/F	45	ECG Q wave	4.8	64
Olmsted 2005 [9]	USA	2042	M/F	62	ECG Q wave[a]	3.9	44
Rochester 2005 [10]	USA	603	M/F	58	ECG	0.3	—
Rotterdam 2008 [8]	Europe	6347	M/F	69	ECG Q wave	5.4	45

AS: Aging Study; BRHS: British Regional Heart Study; CHS: Cardiovascular Health Study; ECG: electrocardiogram; F: female; M: male; MI: myocardial infarction; MONICA: monitoring of trends and determinants in cardiovascular disease.
[a] And ST-T abnormalities.

Table 2 Prevalence of silent MI in at-risk subjects.

Cohort name and/or year	Region	*n*	Sex	Mean or range age (years)	Method of diagnosis	Prevalence (%)
Patients with arterial hypertension						
MRC trial 1988 [18]	Europe	17 354	M/F	35—64	ECG Q wave	M/F 1.3/1.5
IPPPSH 1988 [19]	Europe	746	M/F	40—64	ECG Q wave	M/F 2.4/3.3
Patients with a history of cardiovascular disease						
2006 [22]	USA	579	M/F	—	Exercise stress scintigraphy	7.1 (diabetics 18.4)
2006 [23]	USA	195	M/F[a]	59	DGE-MRI	22.6
2007 [21]	Europe	1092	M/F[b]	64	Stress echocardiography	23.4 (diabetics 34)
2009 [20]	USA	185	M/F[a]	60	ECG Q wave/DGE-MRI	ECG/MRI 8.1/27.0

DGE-MRI: delayed-gadolinium enhanced-magnetic resonance imaging; ECG: electrocardiogram; F: female; IPPPSH: International Prospective Primary Prevention Study in Hypertension; M: male; MI: myocardial infarction; MRC: medical research council.
[a] Subjects with suspected or known CAD.
[b] Patients undergoing non-cardiac vascular surgery.

Table 3 Prevalence of silent MI in diabetic patients.

Cohort name and/or year	Region	Number of subjects	Sex	Mean or range age (years)	Method of diagnosis	Prevalence (%)	Proportion of all MIs (%)
1986 [27]	USA	73[a]	M/F	50	ECG	10	70
1990 [26]	USA	30[b]	M/F	66	DTS	37	–
Fremantle 2004 [24]	Australia	1269[c]	M/F	64	ECG Q wave	3.9	44
2008 [25]	USA	107[d]	M/F	61	DGE-MRI	28	29

DGE-MRI: delayed gadolinium enhanced-magnetic resonance imaging; DTS: dipyridamole thallium scintigraphy; ECG: electrocardiogram; F: female; M: male; MI: myocardial infarction.
[a] Subjects with type 1 or 2 diabetes and peripheral or cardiac neuropathy.
[b] Subjects with type 1 or 2 diabetes without evidence of CAD, but with peripheral artery disease.
[c] Subjects with recent type 2 diabetes, mainly (75%) without history of CAD.
[d] Subjects with suspicion of CAD.

1269 patients with type 2 diabetes of median 4-year duration [24]. The three other studies were smaller series of 30–107 diabetic patients that were carried out in North America. In addition to diabetes, patients included in two studies had a cardiovascular disease (suspicion of CAD based on recent suggestive symptoms [25] or peripheral artery disease [26]) or, in another study, peripheral or cardiac neuropathy characterized by the Valsalva test [27]. Some patients (25%) of the Fremantle cohort also had CAD [24].

Prevalence data from these four studies in diabetic patients revealed various proportions of silent MI patients, depending on the characteristics of the patients included and the detection method used. In diabetic patients from the general population (Fremantle cohort), the prevalence of silent MI evaluated by ECG was about 4% [24]. The prevalence of silent MI increased to 10% when diabetes was associated with peripheral neuropathy [27], to 28% when there was clinical suspicion of CAD and silent MI was detected by DGE-MRI [25], and to 37% in patients with peripheral artery disease with silent MI detection by dipyridamole thallium scintigraphy [26] (Table 3). The proportion of silent MI among all MI varied from 29 to 70% depending on the study, and was particularly high in patients with cardiac autonomic neuropathy.

Incidence of silent MI in the general population

The incidence of silent MI in studies performed in the general population was assessed in nine studies (five in North America, three in Europe and one in Oceania), in which the duration of follow-up varied from 6 to 34 years (Table 4) [10,13,14,17,28–32]. One of them included very old subjects [17]. The influence of age on the incidence of silent MI was examined in the Reykjavik [13,14] and Honolulu [31] cohorts. In all cases, silent MI was detected by ECG (Q wave, and ST-T abnormalities in the Atherosclerosis Risk in Communities [ARIC] study [29]).

Results generally showed relatively narrow between-study variations, except for the Bronx AS study in very old subjects [17] in which the incidence of silent MI was around 10 times higher (about 1/4 of these patients had a history of angina) (Table 4). In the Reykjavik and Honolulu cohorts, a direct relationship was found between age and the incidence of silent MI [13,14,31]. Comparison of data from the Reykjavik male and female cohorts indicated higher incidence rates in relatively young male subjects than in their female counterparts [13,14]. Two studies [14,31] found an inverted-U relationship between age and the incidence of silent MI in male subjects, but this may have been due, at least partly, to a higher mortality rate among old patients who had experienced a first silent MI. However, in the Reykjavik female cohort, there was an exponential relationship with age [13]. The ARIC cohort (North America) [29] and the Reykjavik female cohort (Iceland) [13] reported similar incidence rates (0.8–0.9/1000 patient-years) for middle-aged subjects (~60 years old). Slightly higher incidence rates (~1.5/1000 patient-years) were reported in two studies (Rochester and Honolulu cohorts) of subjects without obvious risk factors [10,31], while two studies (Rotterdam and Multiple Risk Factor Intervention Trial [MRFIT] cohorts [28,32]) reported higher incidence rates (~4/1000 patient-years) in populations of subjects at a higher risk for coronary heart disease or including a proportion of hypertensive patients (Table 4).

Incidence of silent MI in the high-risk population: patients with hypertension or history of CAD

Four studies conducted in Europe, America and Asia included hypertensive patients (Table 5) [18,33–35]. The oldest ones (MRC trial, 1988 [18]; Metoprolol Atherosclerosis Prevention in Hypertensives [MAPHY] study, 1991 [35]) reported the highest rates of silent MI prevalence (~5–8/1000 patient-years), while the rates were notably lower (~1–2/1000 patient-years) in the more recent ones (Hypertension Optimal Treatment [HOT] study, 1998 [34]; Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm [ASCOT-BPLA], 2005 [33]). Duration of follow-up was 3.8–5.5 years.

Two studies carried out in Europe or North America included patients with a history of cardiovascular disease (angina, MI, revascularization, etc.) (Table 5) [36,37]. These

Table 4 Incidence of silent MI in the general population.

Cohort name and/or year	Region	*n*	Sex	Mean or range age (years)	Method of diagnosis	Follow-up duration (years)	Incidence (per 1000 patient-years)
MRFIT 1987 [32]	USA	12 866	M	35—57 at entry	ECG Q wave	6	4.4
Honolulu 1989 [31]	Hawaii	7331	M	~54	ECG Q wave	6	0.6 at age 50—54, 1.3 at age 60—64, 0.5 at age 65—68
Bronx AS 1990 [17]	USA	349	M/F	79	ECG Q wave	≤ 8	24 (72 if history of MI)
Framingham 1990 [30]	USA	5070	M/F	35—94	ECG Q wave	34	M/F 2.7/1.3
Reykjavik 1995 [14]	Europe	9141	M	33—60 at entry	ECG	≤ 20	1.2 at age 50, 3.0 at age 60, 1.5 at age 75
Reykjavik 1998 [13]	Europe	9773	F	32—59 at entry	ECG	≤ 24	< 0.2 at age < 40, ~0.8 at age ~60, ~2.0 at age 75
ARIC 2002 [29]	USA	12 843	M/F	45—65	ECG Q wave[a]	9	0.9
Rochester 2005 [10]	USA	603	M/F	58	ECG	~17	1.5
Rotterdam 2006 [28]	Europe	5148[b]	M/F	68	ECG	6.4	3.8 (M/F 4.2/3.6)

ARIC: atherosclerosis risk in communities; AS: Aging Study; ECG: electrocardiogram; F: female; M: male; MI: myocardial infarction; MRFIT: multiple risk factor intervention trial.
[a] And ST-T abnormalities.
[b] 30% hypertensive.

Table 5 Incidence of silent MI in at-risk patients.

Cohort name and/or year	Region	*n*	Sex	Mean or range age (years)	Method of diagnosis	Follow-up duration (years)	Incidence (per 1000 patient-years)
Patients with arterial hypertension							
ASCOT-BPLA 2005 [33]	Europe	19 257[a]	M/F	63	ECG	5.5	0.6—0.8[b] M/F
HOT 1998 [34]	Europe, USA, Asia	18 790	M/F	61.5	ECG	3.8	1.8 (3.3 in diabetics)
MAPHY 1991 [35]	Europe, Canada	3234	M	40—64 at entry	ECG Q wave	4.2	4.9—7.2 M/F
MRC trial 1988 [18]	Europe	17 354	M/F	35—64	ECG Q wave	5.5	M/F 7.5/8.4[b]
Patients with a history of cardiovascular disease							
HERS 2001 [36]	USA	2763[c]	F	67	ECG Q wave	4.1	1.0[b]
4S 1998 [37]	Europe	4444[d]	M/F	59	Not specified	5.4	8.3

4S: Scandinavian Simvastatin Survival Study; ASCOT-BPLA: anglo-scandinavian cardiac outcomes trial-blood pressure lowering arm; CAD: coronary artery disease; ECG: electrocardiogram; F: female; HERS: Heart and Estrogen/progestin Replacement Study; HOT: Hypertension Optimal Treatment; M: male; MAPHY: metoprolol atherosclerosis prevention in hypertensives; MI: myocardial infarction; MRC: medical research council.
[a] 26.7% had diabetes.
[b] Calculated cumulative incidence per 1000 patients/year.
[c] Subjects with CAD (history of MI, revascularization, occlusion, etc.); 31.6% had diabetes.
[d] Patients with a history of MI and hypercholesterolaemia, 80% of men; 4.6% had diabetes.

Table 6 Incidence of silent MI in subjects with type 2 diabetes.

Cohort name and/or year	Region	*n*	Sex	Mean or range age (years)	Method of diagnosis	Follow-up duration (years)	Incidence (per 1000 patient-years)
Studies in diabetics mostly without a history of cardiovascular disease or with just risk factors							
CARDS 2004 [40]	Europe	2838[a]	M/F	62	ECG Q wave	3.9	0.9[b]
ASCOT DM2 2008 [39]	Europe	5127[c]	M/F	63	ECG	5.5	0.8[b]
FIELD 2010 [38]	Australia, Finland, New-Zealand	9795[d]	M/F	62	ECG Q wave	5	5.5[b]
Studies in diabetics with a history of cardiovascular disease							
PROactive 2005 [43]	Europe	5238[e]	M/F	62	ECG Q wave or R-wave reduction	2.9	2.9[b]
PROactive 2007 [42]	Europe	2445[f]	M/F	62	ECG Q wave or R-wave reduction	2.9	3.5[b]
BARI 2D 2009 [41]	North/South Americas, Europe	2368[g]	M/F	62	ECG Q wave	5.3	1.8[b]

ASCOT DM2: Anglo-Scandinavian Cardiac Outcomes Trial Diabetes Mellitus type 2; BARI 2D: Bypass Angioplasty Revascularization Investigation 2 Diabetes; CAD: coronary artery disease; CARDS: Collaborative Atorvastatin Diabetes Study; ECG: electrocardiogram; F: female; FIELD: Fenofibrate Intervention and Event Lowering in Diabetes; M: male; MI: myocardial infarction; PROactive: PROspective pioglitAzone Clinical Trial In macroVascular Events.

[a] Greater or equal to 1 cardiovascular risk factor.

[b] Calculated cumulative incidence per 1000 patient-years.

[c] Either untreated (systolic/diastolic blood pressure $\geq$ 160/100 mmHg) or treated (systolic/diastolic blood pressure $\geq$ 140/90 mmHg) hypertension and $\geq$ 2 other risk factors.

[d] 21.8% with a history of MI, angina, or revascularization.

[e] History of a major cardiovascular event (MI, stroke, percutaneous coronary intervention, coronary artery bypass surgery), acute coronary syndrome, objective CAD, and/or peripheral artery disease.

[f] Previous MI.

[g] Angina at angiography, treated by revascularization or medical therapy.

two studies reported cumulative incidence rates varying from 1.0/1000 patient-years (detection by ECG) in the Heart and Estrogen/progestin Replacement Study (HERS) of women with CAD [36] to ~8/1000 patient-years (detection method not specified, more frequent clinic visits) in the Scandinavian Simvastatin Survival Study (4S) study mainly of hypercholesterolaemic men with a history of angina or MI [37].

Incidence of silent MI in diabetic patients

The incidence of silent MI in diabetic patients was assessed in six studies carried out during recent years for the evaluation of the clinical effects of antidiabetic agents in Europe, North and South America, and Australia and New Zealand (Table 6). Three studies were performed in patients mainly without a history of cardiovascular disease (primary preventive therapy) [38—40] and three studies in patients with a history of angina or macrovascular disease (secondary preventive therapy) [41—43]. In all of these studies, diabetic patients had associated risk factors (hypertension, hyperlipidaemia, proteinuria, retinopathy, smoking, family history, etc.). The duration of the follow-up was approximately 3—5.5 years, depending on the study. Silent MI was detected by ECG (or R-wave reduction in one study).

The incidence of silent MI was relatively low (0.8—0.9/1000 patient-years) in diabetic patients with risk factors but free of any major cardiac event (ASCOT type 2 diabetes mellitus [DM2] [39] and Collaborative Atorvastatin Diabetes Study [CARDS] [40] studies), intermediate (1.8/1000 patient-years) in diabetic patients with a history of angina treated by revascularization or medical therapy (BARI 2D study [41]), and highest (2.9—5.5/1000 patient-years) in studies that included only or partly (22%) diabetic patients with a history of MI (PROspective pioglitAzone Clinical Trial In macroVascular Events [PROactive] [42,43] and Fenofibrate Intervention and Event Lowering in Diabetes [FIELD] [38] studies, respectively). In the FIELD study [38], a silent MI occurred in 166 of the 7640 patients without a history of cardiovascular disease (mean estimated incidence of 4/1000 patient-years), and silent MI accounted for 38.3% of the first cases of MI (245 silent MIs of a total of 640 first MIs), whereas after a first MI (clinical or silent), 64.5% were silent [38].

Table 7 Risk factors for clinical MI and silent MI in diabetic patients in the FIELD study [38].

	Clinical MI		Silent MI		Probability for heterogeneity
	OR (95% CI)	*P*	OR (95% CI)	*P*	
Male gender	1.38 (1.07—1.78)	0.01	1.15 (0.85—1.57)	0.37	0.37
Age	1.03 (1.02—1.05)	< 0.001	1.03 (1.01—1.05)	0.008	0.60
Diabetes duration	0.99 (0.98—1.01)	0.48	0.97 (0.95—0.99)	0.02	0.12
Prior cardiovascular disease	2.12 (1.71—2.64)	< 0.001	1.62 (1.22—2.17)	< 0.001	0.14
Diabetic neuropathy	1.34 (1.04—1.73)	0.02	1.07 (0.75—1.52)	0.72	0.30
HbA1c	1.14 (1.06—1.23)	< 0.001	1.04 (0.94—1.16)	0.41	0.17
Creatinine	1.01 (1.00—1.02)	0.009	1.00 (0.99—1.01)	0.55	0.25
Microalbuminuria	1.42 (1.12—1.80)	0.003	1.35 (1.00—1.83)	0.05	0.79
Macroalbuminuria	2.21 (1.53—3.20)	< 0.001	2.51 (1.56—4.03)	< 0.001	0.68
Insulin use	1.42 (1.08—1.88)	0.01	1.05 (0.70—1.59)	0.80	0.23

CI: confidence interval; FIELD: fenofibrate intervention and event lowering in diabetes; HbA1c: haemoglobin A1c; MI: myocardial infarction; OR: odds ratio.

Predictive factors of silent MI

Some studies assessed the risk factors for the occurrence of silent MI in subjects from the general population (six studies), in patients with a history of cardiovascular disease (three studies), or in diabetic patients (two studies). The most frequently reported risk factor for silent MI is hypertension, which was reported in all six studies in the general population and in one of the two studies in diabetic patients, but in none of the three studies in patients with a history of cardiovascular disease. Impaired glucose tolerance or diabetes was quoted as a risk factor in three of the six studies in the general population and in two of the three studies in patients with cardiovascular disease.

The recent FIELD study [38] evaluated the odds ratios (ORs) of different potential risk factors for clinical MI and silent MI in diabetic patients (Table 7). Among the nine factors that were found to be significantly predictive of clinical MI, three were also found to be significantly predictive of silent MI (age, prior cardiovascular disease, micro/macroalbuminuria), along with diabetes duration. Moreover, there was no significant difference between the ORs for clinical MI and silent MI for any potential risk factor tested, indicating similar risks for clinical MI and silent MI whatever the potential risk factor considered.

Silent MI and prognosis

Regarding the prognosis in silent MI, four studies in the general population found that the presence of silent MI increased the risk of all-cause mortality by a factor of 1.8—3.6, and the risk of cardiovascular mortality or a major ischaemic event by a factor of 1.9—3.2 [12,14,16,17]. Similarly, in three studies of patients with pre-existing cardiovascular disease, silent MI increased the risk of all-cause mortality by a factor of 1.9—3.4 and that of a major cardiac event by 2.2—8.3 [20,21,23]. As for diabetic patients, three studies reported increases in all-cause mortality by a factor of 1.1—5.0 and in cardiac mortality or a major cardiac event by 1.8—7.3 [24,25,38]. On the whole, in all studies (of patients with or without risk factors, a history of cardiovascular disease or diabetes), there was no major difference between silent MI and clinical MI as to the risk for mortality or a major cardiac event. Typically, the FIELD study reported very similar cumulative incidences of cardiovascular disease over 2 years of follow-up between diabetic patients with silent or clinical MI receiving placebo (hazard ratios of 4.55 and 4.51, respectively), while all-cause mortality rates were 13.8% and 15.2%, respectively, in the two patient groups [38].

Discussion

The present review of publications that reported data on silent MI detection indicates different prevalence rates depending on the patient population considered. In the cohorts that provided data from non-diabetic patients without known cardiovascular disease, the prevalence of silent MI was 0.3—5.4% (6.4% in very old subjects). Such large between-study variations are indicative of some heterogeneity between the studies in terms of the subjects'/patients' characteristics (e.g. sex, age, proportion of diabetic patients) and/or the method of silent MI detection. In diabetic patients without CAD, the prevalence of silent MI was about 4%, but it was found to rise to 10% in patients with peripheral neuropathy and up to about 30% in the presence of established coronary or peripheral artery disease.

In the studies of non-diabetic subjects, the incidence of silent MI showed large variations: it was 1—1.5/1000 person-years in healthy subjects free from risk factors aged ~60 years, 1—5/1000 patient-years in patients with cardiovascular risk factors (e.g. hypertension, hyperlipidaemia) or elderly patients, up to ~8/1000 patient-years in the 4S study of mainly male patients with a history of CAD and hypercholesterolaemia, and much higher (24/1000 patient-years) in the Bronx AS cohort, which included very old subjects. In the studies of diabetic patients, the incidence of silent MI was about 1/1000 patient-years in two studies of patients without a history of cardiovascular disease,

2—3.5/1000 patient-years in three studies of patients with angina or a history of macrovascular disease and highest (4/1000 patient-years) in patients without a history of cardiovascular disease of the FIELD study.

The literature search for data on the prevalence and incidence of silent MI in patients with hypertension retrieved minimal information. Two cohorts of hypertensive patients without a history of cardiac disease suggested some relationship between diastolic blood pressure and the prevalence of silent MI (prevalence of ~1.4% in hypertensive patients with diastolic blood pressure 90—109 mmHg (MRC trial) versus 2.8% in patients with diastolic blood pressure 100—125 mmHg) (IPPPSH-Italy) [18,19]. Interestingly, regarding the incidence of silent MI, four large studies in hypertensive patients reported an inverse relationship between the incidence rate of silent MI and the date of study completion: 5—8/1000 patient-years in two studies (MRC trial [18], MAPHY study [35]) published in 1988 and 1991, and 1.8 and < 1/1000 patient-years in two studies (HOT [34] and ASCOT-BPLA studies [33]) published in 1998 and 2005, respectively. This observation might reflect gradual improvements over time in the medical management of patients at risk for cardiovascular disease.

Different factors should be considered when interpreting the findings reported herein, including the region where the studies were conducted, the method used for the detection of silent MI, and the date of completion of the studies. Patients are more aware nowadays about signs and symptoms of MI, and hence are more likely to seek prompt medical assistance. Also, enhanced diagnostic capabilities over the years may have resulted in lower proportions of unrecognized MIs in the more recent studies [29]. Caution is warranted when comparing data from studies that were conducted in different regions in the world, given the diversity of the populations and pathologies in which the prevalence and incidence of silent MI were assessed. However, the results do not reveal any major differences between Europe (essentially Northern countries) and other regions of the world, and there is relative between-region homogeneity of data for patient populations and pathologies with comparable characteristics (age, presence or absence of diabetes, and/or history of cardiovascular diseases).

The intrinsic value of the reported data on the prevalence and incidence of silent MI should be examined in relation to the detection method that was used in the studies. The apparent large increase in the prevalence of silent MI among patients with a history of cardiovascular disease may have been influenced notably by the detection method used. In most studies of patients with a history of cardiovascular disease (two of three studies of diabetic patients and all four studies of non-diabetic patients), it is notable that silent MI was detected by stress scintigraphy or echography or by DGE-MRI, unlike all of the studies of patients free of known cardiovascular disease, in which silent MI was detected by routine ECG. However, ECG may have low sensitivity, as silent MI ECG findings may not persist in the long term due to regression of Q waves with time [31]. Also, infarction size greatly influences its detectability by ECG [44], so that a relatively large proportion of small silent MIs are not associated with characteristic Q waves (''non-Q-wave'' silent MIs), while they can be revealed by cardiac MRI [20]. Finally, stress echocardiography may detect silent myocardial ischaemia that may be reversible at rest, and in this case not reflective of silent MI.

In common clinical practice, it is clear that only ECG, despite its imperfections, can be used routinely for the examination of patients at high risk of MI, but who are free from symptoms. Biological markers such as troponin are unhelpful here, and MI should thus be confirmed, for instance by echocardiography, which is considered the most useful non-invasive test in the assessment of Q waves despite its rather low sensitivity, especially for small MIs.

Conclusions

Similarly to silent myocardial ischaemia, silent MI involves a high proportion of patients with risk factors such as hypertension, a history of cardiovascular disorders, and diabetes. The fact that the prevalence of silent MI increases markedly with increasing age and with a history of cardiovascular disease (coronary or peripheral artery disease), and that its prognosis is considered close to that of clinical MI [9,14,16,17], amply justify its systematic early detection and active management in at-risk patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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