

Ventricular arrhythmia in coronary artery disease: limits of a risk stratification strategy based on the ejection fraction alone and impact of infarct localization[†]

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Aims

Estimates of the left ventricular ejection fraction (LVEF) in patients with life-threatening ventricular arrhythmias related to coronary artery disease (CAD) have rarely been reported despite it has become the basis for determining patient's eligibility for prophylactic defibrillator. We aimed to determine the extent and distribution of reduced LVEF in patients with sustained ventricular tachycardia or ventricular fibrillation.

Methods and results

252 patients admitted for ventricular arrhythmia related to CAD were included: 149 had acute myocardial infarction (MI) (Group I, 59%), 54 had significant chronic obstructive CAD suggestive of an ischaemic arrhythmic trigger (Group II, 21%) and 49 patients had an old MI without residual ischaemia (Group III, 19%). 34% of the patients with scar-related arrhythmias had an LVEF $\geq 40\%$. Based on pre-event LVEF evaluation, it can be estimated that less than one quarter of the whole study population had a known chronic MI with severely reduced LVEF. In Group III, the proportion of inferior MI was significantly higher than anterior MI (81 vs. 19%; absolute difference, -62 ; 95% confidence interval, -45 to -79 ; $P \leq 0.0001$), though median LVEF was higher in inferior MI (0.37 ± 10 vs. 0.29 ± 10 ; $P = 0.0499$).

Conclusion

Patients included in defibrillator trials represent only a minority of the patients at risk of sudden cardiac death. By applying the current risk stratification strategy based on LVEF, more than one third of the patients with old MI would not have qualified for a prophylactic defibrillator. Our study also suggests that inferior scars may be more prone to ventricular arrhythmia compared to anterior scars.

Keywords

Ventricular arrhythmia • Myocardial infarction • Sudden death • Arrhythmic risk • Ejection fraction

Introduction

Ventricular tachyarrhythmias are responsible for most cases of sudden cardiac death (SCD). Two common patterns in the initiation of fatal arrhythmias have been recognized in coronary artery disease (CAD), ventricular arrhythmia triggered by acute ischaemia or infarction and ventricular arrhythmia related to an anatomical substrate, usually scarring from a previous myocardial

infarction (MI).¹ The relative incidence of these two mechanistic pathways is uncertain and they constitute two poles of a continuum of pathophysiological scenarios. In a large proportion of patients the interaction of ischaemia superimposed on a chronic scar is probably responsible for the genesis of lethal arrhythmias as demonstrated in numerous experimental studies.^{2–4} The epidemiological pattern of SCD is a major health care issue because of its implications in helping profiling risk based on individual subject

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characteristics and for the efficient designs of clinical trials. Most previous studies exploring the mechanistic pathways leading to SCD were necropsy studies. To our knowledge, no unselected large study integrated clinical characteristics and angiographic findings to distinguish the patterns of life-threatening ventricular arrhythmias in CAD. In particular, most studies defined SCD without documentation of ventricular tachyarrhythmia and information regarding myocardial areas of potential ischaemia was limited. Most importantly, estimates of the left ventricular ejection fraction (LVEF) could not be provided despite it is currently the most widely used clinical determinant of risk after infarction and has become the basis for determining a patient's eligibility for prophylactic implantable cardioverter defibrillator (ICD). The value of prophylactic ICD has been established in patients with severely reduced LVEF. It has however been suggested that these patients may represent a minority of the total SCD.^{5–7} The prospective prophylactic ICD trials enrolled patients in the highest-risk subgroups because they yield event rates high enough to design trials with a relatively limited number of patients. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) has shown that patients with remote MI and advanced LV dysfunction benefit from prophylactic ICD implantation.⁸ MADIT II was however a study of very high-risk patients and outcomes hence address highly specific segments of the population and represent relatively small numbers. It is of the utmost importance for everyone involved in developing and implementing strategies in primary prevention of SCD to know the actual impact of these trials on the general public health problem of sudden death.

The present study therefore aimed to determine the extent and distribution of reduced LVEF in patients with documented life-threatening ventricular arrhythmia related to CAD and the relative incidence of the mechanistic pathways leading to the arrhythmic event.

Methods

Patients and study protocol

Between January 1998 and April 2006, consecutive patients admitted to our university-based hospital centre for sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) as first detected arrhythmia were registered. Patients with documented ventricular arrhythmias related to CAD occurring either out-of-hospital or upon admission in the emergency room were included. Arrhythmic events occurring in hospitalized patients or during coronary interventions were excluded. The clinical, angiographic and echocardiographic data were obtained during the index hospitalization. Eligibility was validated by specifically reviewing the clinical records. Patients were classified according to the presumptive mechanism by which CAD led to the clinical arrhythmias.

The study protocol was in accordance with the ethical standard of the Hospital Ethics Committee.

Angiography

The coronary arteries were divided into segments according to conventional terminology.⁹ Proximal narrowings of large diagonal or marginal branches were considered as stenoses of the left anterior descending or circumflex coronary arteries, respectively. Diseased coronary artery was graded according to its narrowest stenosis as

not significant (<70%), significant (≥ 70 –99%) or 100% obstruction. Left main stem disease was considered if there was a >50% stenosis. The number of significantly diseased coronary arteries was assigned from 1 to 3. Hypokinetic or normal areas supplied by an artery with a significant stenosis were considered to be areas of potential ischaemia. The LVEF was obtained from (in preferred order): a left ventriculogram, a radionuclide ventriculogram or an echocardiogram.

Myocardial infarction

The criteria for the diagnosis of acute MI was adapted from the report of the American College of Cardiology Task Force on Clinical Data Standards¹⁰ since patients may have died before blood samples for biomarkers could be obtained (or in the lag phase before they could be identified) and since episodes of VT or VF may be associated with a modest elevation of cardiac enzymes (principally cardiac troponins) due to metabolic demands exceeding supply, especially in patients with CAD.¹¹ For patients who survived the acute phase either of the two following criteria met the diagnosis of acute MI: (1) typical rise and fall of biochemical markers of myocardial necrosis (CK-MB $\geq 2 \times$ the upper limit of normal) with at least one of the following: ischaemic symptoms prior to the arrhythmic event, development of pathological Q waves on the ECG, ECG changes indicative of ischaemia (ST-segment elevation or depression) or coronary artery intervention; or (2) pathological findings of acute MI. For patients who died before blood samples could be obtained, each following criteria met the diagnosis acute MI: presumably new ST elevation, or new left-bundle branch-block and/or evidence of fresh thrombi by coronary angiography and/or at autopsy.

The diagnosis of previous MI was based either on the clinical records, the autopsy protocols, or the presence of a fixed defect on thallium scanning or a localized akinesis or dyskinesis as determined by left ventriculogram or echocardiogram with evidence of obstructive CAD.

Statistical analysis

Quantitative parameters are given as arithmetic mean \pm SD for continuous variables and percentages for categorical variables. 95% CIs for proportions and differences between categorical and continuous variables were calculated. The χ^2 test was used to test differences between proportions. The Student's *t*-test was used for comparison of continuous variables. Statistical significance was assumed for $P < 0.05$. Statistical analysis was performed using the software STATA, version 8 (Stat Corp, College Station, TX, USA).

Results

Patients and relative incidence of the mechanistic pathways leading to ventricular arrhythmia

382 consecutive patients were admitted for documented sustained VT or VF between January 1998 and April 2006. The study flow diagram is shown in *Figure 1*. In 41 patients the cause of the arrhythmia remained unknown either because of death without autopsy or limited investigations due to poor prognosis. In 74 patients (22%), the underlying cause of ventricular arrhythmia was not related to CAD.

Of the 267 patients with ventricular arrhythmia related to CAD (78%), 15 patients with prior MI were excluded due to limited data, either because of death on admission without autopsy or of limited

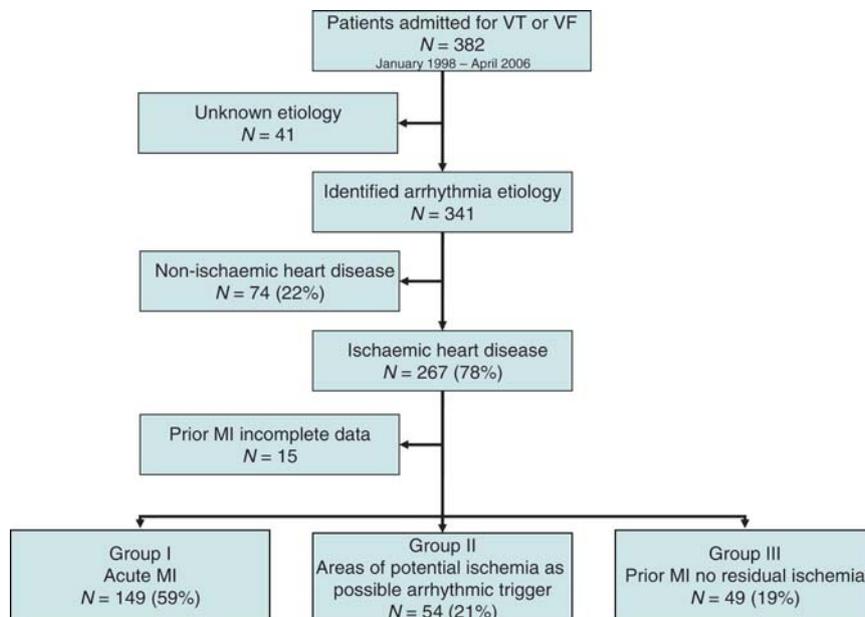


Figure 1 Study flow diagram of patients admitted for sustained ventricular tachycardia or ventricular fibrillation.

investigations due to poor prognosis. The remaining 252 patients were included in the study and classified in three groups according to the presumptive mechanism of the clinical arrhythmia: 149 patients fulfilled the criteria of acute MI (= Group I, 59%); in the 103 patients with no evidence of acute MI, 54 had significant coronary artery stenosis with areas of potential ischaemia as a possible arrhythmic trigger (superimposed or not on a chronic scar) (= Group II, 21%) and 49 patients had a prior MI but no areas of potential ischaemia according to angiography findings (= Group III, 19%).

Clinical characteristics according to the mechanism of arrhythmia

The clinical characteristics of patients according to the mechanistic pathways leading to ventricular arrhythmia are presented in Table 1. Mean age was 64 ± 12 years and 79% were male.

Ventricular fibrillation accounted for the majority of first recorded arrhythmias in Group I (VF and VT, 83 and 17%, respectively; $P < 0.0001$). This proportion was reversed in Group III (VF and VT, 35 and 65%, respectively; $P = 0.0006$) whereas the prevalence of both arrhythmias was similar in patients Group II (54 and 46%, respectively; $P = 0.44$). 52% of the patients presented with out-of-hospital cardiac arrest. The prevalence of haemodynamically stable and unstable VT did not significantly differ in Group II (19 and 28%, respectively; $P = 0.25$), while in Group III patients presented more frequently with stable VT (47 and 18%, respectively; $P = 0.003$). In Group I, 23% of patients had a previous MI whereas in Group II, transient ischaemia was superimposed on a chronic MI scar in most cases (74% of cases). The time interval between most recent MI and the arrhythmic event was known in 74% of the patients in Groups II and III and averaged 12.4 ± 9.4 years (median 10.5, range 0–34). Ventricular tachyarrhythmia

was the first clinical manifestation of CAD in more than half of the patients (54%) with the highest proportion in those with acute MI (75% in Group I vs. 37 and 8% in Groups II and III, respectively; $P < 0.0001$). Overall mean LVEF assessed after the arrhythmic event was $36 \pm 12\%$. The proportion of patients with an LVEF $\geq 40\%$ was 46% in Group I, 40% in Group II and 33% in Group III. As a whole, one third (34%) of the patients with chronic MI who had experienced a ventricular arrhythmia not related to acute MI had a LVEF $\geq 40\%$.

Data on LVEF evaluation performed within 5 years of the arrhythmic event were available for 54 and 65% of the patients in Groups II and III, respectively. The mean time interval between the last LVEF assessment and the arrhythmic event was 15 ± 17 months (median 6, range 0–57). Overall mean LVEF was $39 \pm 12\%$. About one half of the patients had an LVEF $\geq 40\%$ (52 and 50% in Groups II and III, respectively).

Patients that could have been identified to be at increased risk of ventricular arrhythmia, i.e. with known CAD and evidence of an old MI, represented 42% of the whole study population. Pre-event LVEF was known for 63% of these patients and was $\geq 40\%$ in half of them (47%). Of the remaining patients, one quarter (26%) had an LVEF $\geq 40\%$ after the arrhythmic event. It can therefore be estimated that no more than one quarter of the whole study population had a known chronic MI with advanced LV systolic dysfunction.

Angiographic data and infarct characteristics according to the mechanism of arrhythmia

The angiographic data and infarct characteristics according to the mechanistic pathways leading to ventricular arrhythmia are presented in Table 2 (Group I) and Table 3 (Groups II and III). In

Table 1 Clinical characteristics of patients with ischaemic heart disease according to the mechanistic pathways leading to ventricular arrhythmia

	Group I: acute MI (n = 149)	Group II: areas of potential ischaemia as ischaemic trigger (n = 54)	Group III: prior MI no residual ischaemia (n = 49)
Age (years) (mean ± SD)	61 ± 13	68 ± 11	68 ± 10
Male sex (%) (95% CI)	79 (72–85)	80 (69–91)	78 (65–90)
First recorded rhythm (%) (95% CI)			
Ventricular fibrillation	83 (77–89)	54 (40–67)	35 (21–49)
Unstable VT	11 (6–16)	28 (15–40)	18 (7–30)
Stable VT	6 (2–10)	19 (8–29)	47 (32–61)
Previous revascularization (CABG or PCI) (%) (95% CI)	11 (6–17)	31 (19–44)	61 (47–75)
Prior MI (%) (95% CI)	23 (16–31)	74 (62–86)	100
Time elapsed since last MI (years) (mean ± SD) ^a	6.7 ± 5.4	12.8 ± 10.9	12.3 ± 8.3
Arrhythmia as first clinical event of CAD (%) (95% CI)	75 (68–82)	37 (24–50)	8 (0–16)
LV ejection fraction evaluation before the arrhythmic event ^b			
Total (mean ± SD)	–	39 ± 14	38 ± 11
<0.30 (%) (95% CI)		24 (8–41)	16 (2–29)
0.30–0.39 (%) (95% CI)		24 (8–41)	34 (17–52)
≥0.40 (%) (95% CI)		52 (32–71)	50 (32–68)
LV ejection fraction assessed after the arrhythmic event ^c			
Total (mean ± SD)	38 ± 13	35 ± 13	34 ± 10
<0.30 (%) (95% CI)	26 (18–35)	34 (21–47)	29 (15–42)
0.30–0.39 (%) (95% CI)	27 (19–36)	26 (14–39)	39 (25–53)
≥0.40 (%) (95% CI)	46 (37–56)	40 (26–53)	33 (19–46)

^aData available for 50, 70 and 78% of the patients from Groups I, II, and III, respectively.

^bOnly evaluations performed within 5 years of the arrhythmic event considered. Data available for 54% of the patients in Group II and 65% in Group III. Mean time interval between the last LV ejection fraction evaluation and the arrhythmic event 15 ± 17 months (median 6, range 0–57).

^cData available for 75% of the patients in Group I and 100% in Groups II and III. CABG, coronary artery bypass graft; CAD, coronary artery disease; LV, left ventricular; MI, myocardial infarction; PCI, percutaneous coronary intervention; VT, ventricular tachycardia.

acute MI, there was ST-segment elevation (≥ 1 mm in two or more contiguous leads) in 80% of patients. The most frequent culprit artery was the left anterior descending (49%) followed by the right coronary artery (32%). There was a similar pattern of acute and chronic MI localization in Groups I and II with a non-significant

Table 2 Angiographic data and infarct characteristics in patients with ventricular arrhythmias related to acute MI (Group I)

	Group I: acute MI (n = 149)
ST-segment elevation MI (%) (95% CI)	80 (73–86)
Infarct-related artery (%) (95% CI) ^a	
LAD	49 (40–58)
CX	13 (7–19)
RCA	32 (24–40)
Undetermined	6 (2–11)
Acute MI localization (%) (95% CI)	
Anterior	48 (40–56)
Inferior/posterior	44 (36–52)
Lateral	4 (1–7)
Undetermined	4 (1–7)
One-vessel disease (%) (95% CI) ^a	43 (34–52)
Chronic occlusion (bypass-vessel included) in a non-infarct-related artery (%) (95% CI) ^a	
no	82 (75–89)
LAD	2 (0–4)
LCX	6 (2–10)
RCA	10 (5–16)
Revascularization performed during hospitalization (PCI or CABG) (%) (95% CI)	71 (64–79)

^aAngiographic data available for 84% of the patients in Group I.

CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.

trend towards more frequent anterior MI compared to inferior/posterior MI (48 and 44% in Group I and 43 and 35% in Group II; $P = 0.54$ and 0.45 , respectively). In Group III, a reversed pattern was seen with statistically significantly more frequent inferior/posterior MI compared to anterior MI (69 and 16%, respectively; $P < 0.0001$). The infarct localizations are summarized in Figure 2. In Groups II and III, about half of the patients had chronic occluded coronary vessels with the right coronary artery more often involved.

Characteristics of patients with an old myocardial infarction and no residual ischaemia (Group III)

Clinical and angiographic data of patients with anterior vs. inferior/posterior scar and no residual ischaemia are presented in Table 4. In patients with old MI as only arrhythmic substrate, inferior MI was about four times more frequent compared to anterior MI. This association was found despite a significantly better LVEF in inferior MI compared to anterior MI (0.37 ± 0.1 vs. 0.29 ± 0.1 , respectively; $P = 0.0499$). The proportion of VF vs. VT was similar in both subgroups. There was a non-significant trend towards less diffuse CAD and lower prevalence of chronic occlusion of the infarct-related artery in patients with inferior MI. Unlike those

Table 3 Angiographic data and infarct characteristics according to the mechanistic pathways leading to ventricular arrhythmia in patients without evidence of acute MI

	Group II: areas of potential ischaemia as ischaemic trigger (n = 54)	Group III: prior MI no residual ischaemia (n = 49)
Prior MI localization (%) (95% CI)		
Anterior	43 (26–59)	16 (6–27)
Inferior/posterior	35 (20–50)	69 (56–83)
Anterior and inferior/posterior	23 (9–36)	14 (4–24)
One-vessel disease (%) (95% CI) ^a	30 (17–42)	63 (49–77)
Chronic occlusion (bypass-vessel included) (%) (95% CI) ^a		
no	46 (33–60)	45 (30–59)
LAD	19 (8–29)	12 (3–22)
LCX	9 (1–17)	18 (7–30)
RCA	35 (22–48)	39 (25–53)
Revascularization performed during hospitalization (PCI or CABG) (%) (95% CI)	56 (42–69)	0
Aneurysm post-MI (%) (95% CI)	10 (0–20)	22 (10–35)

^aAngiographic data available for all patients in Groups II and III. CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.

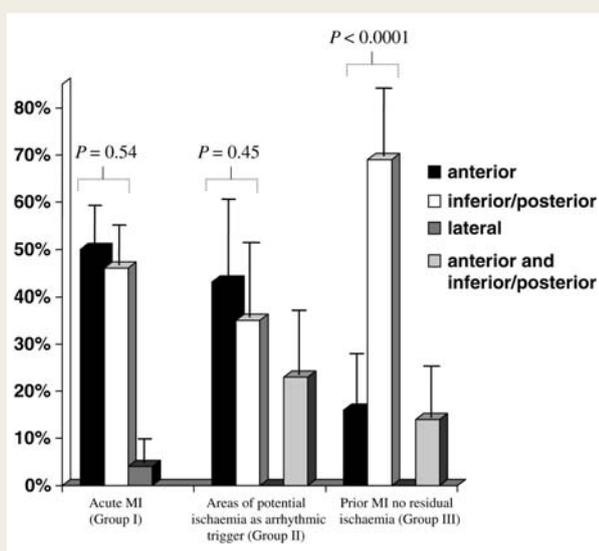


Figure 2 Acute and chronic myocardial infarction localization according to the mechanistic pathways leading to ventricular arrhythmia.

with prior inferior MI, most patients with anterior MI had an LV aneurysm (12 vs. 63%, respectively; $P = 0.0017$).

Discussion

To the best of our knowledge, this is the single largest study to date that has integrated clinical and angiographic characteristics to evaluate the epidemiological pattern of ventricular arrhythmia in CAD and bring into question the actual impact of recent prophylactic ICD trials on the general health problem of SCD.

Relative incidence of the mechanistic pathways leading to ventricular arrhythmia

Acute MI was the most frequent mechanism leading to ventricular arrhythmia representing ~60% of cases, consistent with previous necropsy series of sudden coronary death.^{12,13} About half of the remaining cases had a chronic MI scar without residual ischaemia and half had areas of potential transient ischaemia as possible arrhythmic trigger. In the latter subgroup, a MI scar was found in 74% and the interaction of transient ischaemia superimposed on chronic MI may have been responsible for the genesis of the arrhythmic event as demonstrated in numerous experimental studies.^{2–4} Nevertheless, the proportion of patients in which transient ischaemia indeed led to the arrhythmic event cannot be assessed.

Arrhythmia related to significant obstructive CAD potentially leading to ischaemic episodes without acute or old MI, i.e. 'purely' ischaemic arrhythmia, represented only 6% of the whole study group. Our findings hence tend to confirm that the response to acute transient ischaemia on normal myocardium relatively seldom leads to life-threatening arrhythmia compared with acute ischaemia superimposed on acute, subacute or healed MI.^{2–4}

In patients with a myocardial scar as only arrhythmic substrate, significant superimposed ischaemia was deemed extremely unlikely based on the workup performed including angiography findings. Whereas the proportion of healed MI in SCD has been extensively studied, the proportion of patients with a myocardial scar as only arrhythmic substrate, i.e. without associated areas of potential ischaemia, has been only rarely evaluated. To our knowledge, only two studies with a comparable methodology evaluated this issue: in the chronic phase of MI, the proportions of patients with no residual ischaemia were 44 and 67% compared to 55% in the present study.^{14,15} Similarly, two stress-rest perfusion scintigraphic studies of survivors of SCD not related to acute MI reported a proportion of patients with scar tissue alone of slightly more than one half (55 and 58%, respectively) and scar tissue in combination with ischaemic segments in the remaining cases.^{16,17}

Left ventricular ejection fraction and ventricular arrhythmia in the chronic phase of MI

Despite the fact that LVEF is currently the most widely used clinical determinant of risk after infarction and has become one of the basis for determining a patient's eligibility for prophylactic ICD, we found that more than one third of the patients with

Table 4 Characteristics of patients with ventricular arrhythmia arising from chronic scar without superimposed ischaemia (Group III) according to the localization of prior MI (n = 42)

	Prior anterior MI	Prior inferior/posterior MI	Absolute difference	P
Prior MI localization (%) (95% CI)	19 (7–31)	81 (69–93)	–62 (–45 to –79)	<0.0001
Ventricular fibrillation as first recorded rhythm (%) (95% CI)	25 (0–55)	35 (19–51)	–10 (+24 to –44)	0.58
LVEF (mean ± SD) (95% CI)	0.29 ± 0.1	0.37 ± 0.1	–0.08 (–0.16 to 0)	0.0499
Chronic occlusion of the infarct-related artery (bypass-vessel included) (%) (95% CI)	75 (45–100)	50 (33–67)	+25 (–9 to +59)	0.20
No or one vessel disease (%) (95% CI)	88 (65–100)	65 (49–81)	+23 (–5 to +51)	0.21
Left ventricular aneurysm post-MI (%) (95% CI)	63 (29–96)	12 (1–23)	+51 (+15 to +86)	0.0017

LVEF, left ventricular ejection fraction; MI, myocardial infarction.

life-threatening ventricular arrhythmias in the chronic phase of MI have an LVEF $\geq 40\%$. These patients would hence not have qualified for primary prevention ICD implantation according to current guidelines. These data are even more compelling when one realizes that the LVEF measurements were made early after resuscitation, therefore likely underestimated because of the post-resuscitation myocardial stunning. The available data on pre-event LVEF evaluation suggested that almost half of the patients with prior MI had an LVEF $\geq 40\%$. However, this data must be interpreted with caution because of the time interval between LVEF assessment and the arrhythmic event. Moreover, these data may not be representative of the population at risk since patients whose arrhythmia was the first clinical manifestation of CAD are probably under-represented and, on the other hand, symptomatic patients with greater severity of pre-existing CAD are more likely to have LVEF evaluated. There is no doubt that patients with CAD and depressed LVEF have a higher rate of SCD. However, LVEF is poor at distinguishing patients who will die from arrhythmia from those who will die of other cardiovascular causes.^{18,19} This is illustrated in the Multicenter Unsustained Tachycardia Trial (MUSTT) where no significant differences in the per cent of deaths attributed to arrhythmia were found in patients with LVEF $< 30\%$ vs. those with LVEF 30–40%.²⁰ Since the number of patients surviving the acute phase of MI with less severely reduced LVEF is much greater, they represent a significant proportion of the total number of patients with SCD. In the Cardiac Arrhythmia Suppression Trial (CAST)²¹ ~60% of deaths were due to arrhythmias in patients with LVEF 20–29% as well as in those with 30–39%. However, 1.7 times as many patients had an LVEF of 30–39% as had an LVEF 20–29%. Therefore, although the rate of death or cardiac arrest was higher for patients with more depressed LVEF, the greater number of patients with higher LVEF resulted in virtually equal absolute numbers of cardiac arrests in both groups. Accordingly, the highest-risk subgroups such as those studied in the prospective prophylactic ICD trials may not account for the majority of events in patients with CAD. Two studies previously reported LVEF in SCD. The Oregon Sudden Unexpected Death Study²² evaluated 80 subjects with CAD. The LVEF before SCD was severely reduced in 34% of the patients, mildly to moderately reduced in 30%, and normal in 36%. In a community-based study of

SCD in Maastricht, the Netherlands,²³ among 200 cases of SCD with previous assessment of LVEF, 51% had a normal LV function and only 19% had an LVEF $\leq 30\%$. This study was however limited to cases 20–75 years old and included all causes of SCD, yet more than 70% of SCD were related to CAD.

Primary prevention of SCD requires the ability to identify individual patients at risk from among population pools. However, our study shows that ventricular arrhythmia is the first clinical manifestation of CAD in about half of the patients consistent with previous studies on SCD.^{13,24,25} Patients with known CAD and evidence of a prior MI represented 42% of the whole study group. Based on the available data on pre-event LVEF and the proportion of patients with LVEF $\geq 40\%$ after the arrhythmic event, it can be estimated that no more than one quarter of the whole study population would have been covered by the current guidelines for prophylactic ICD implantation.

Most previous studies on risk stratification and primary prevention of SCD used relatively brief follow-up period, usually ~2 years. Our study shows that the median interval between most recent MI and the arrhythmic event was many years (10.5) with a very wide variation. The later occurrence of ventricular arrhythmia years after MI had also been observed in the community-based study of SCD in Maastricht²³ and was indirectly suggested by the survival benefit of ICD in MADIT II that appeared to be greater for remote MI and remained substantial for up to ≥ 15 years after MI.²⁶ These findings raise the issue of how long studies on risk stratification and primary prevention of SCD should report follow-up to fully appraise the predictive value of a risk factor or the survival benefit of ICD.

Importance of the infarct localization

While previous studies focused on the 'quantitative' issue of prior MI characterization, the question whether a specific localization of prior MI could be at higher risk of substrate-related arrhythmia has to our knowledge not been addressed. We demonstrated an unexpected highly significant relation between inferior MI and substrate-related arrhythmias that is even more compelling considering that LVEF was significantly higher after old inferior MI. However, this relation applies only to patients with MI scars without areas of potential ischaemia since in the setting of

superimposed ischaemia a similar proportion of prior anterior and inferior MI was found. It is unlikely that this association was related to a higher probability of return of spontaneous circulation in patients with prior inferior compared to anterior MI. If this selection bias was relevant we would have expected similar findings in patients with residual ischaemia and especially those with acute MI and there was indeed a trend towards more frequent anterior MI in these subgroups.

The mechanism underlying this apparent propensity of inferior MI to suffer from substrate-related arrhythmia is unclear. Right ventricular (RV) involvement may have contributed since it accompanies 30 to 50% of inferior wall MI. As the prevalence of ventricular arrhythmias is related to infarct size, it could be an unappreciated source of ventricular arrhythmias despite relatively unaffected LVEF. There have been reports demonstrating that RV involvement in inferior MI was associated with a higher risk of sustained VT and VF despite similar LV infarct size and function.²⁷ Similarly, patients with residual RV dysfunction after inferior MI showed an increased risk of sudden death independent of LVEF.²⁸ An alternative explanation may pertain to the differences in cardiac autonomic innervation. Experimental and clinical studies have demonstrated that the electrical stability of the myocardium depends in part on the balance between the two limbs of the autonomic nervous system.^{29,30} Specifically, sympathetic hyperactivity favours the onset of ventricular arrhythmia, whereas vagal activation exerts a protective effect after healed MI. A greater density of receptors with vagal afferents has been demonstrated in the infero-posterior wall of the left ventricle as exemplified by the enhanced vasodepressor and cardio-inhibitory reflexes noted in response to inferior wall MI.^{31,32} Inferior wall MI may hence damage the afferent traffic on vagal sensory endings given their preferential distribution. This would displace the entire range of protective vagal responses towards lower values, thus increasing the risk of malignant arrhythmia. Some observations consistent with this hypothesis suggested that the ability to augment vagal activity was lower in patients with inferior MI compared to anterior MI.^{33,34}

Study limitations

Our study has several potential limitations. First, we included patients admitted to the hospital, hence with initial return of spontaneous circulation, which may constitute a bias inherent to the purpose of the study. Our findings may not reflect the characteristics of the overall population with out-of-hospital ventricular arrhythmias since patients who died before admission (or if resuscitation was not attempted) had to be excluded. However, since the single most important factor that determines the chances of initial return of spontaneous circulation is access to prompt defibrillation rather than the patient's characteristics,³⁵ this selection bias should not have a major influence on how representative the study population is. This is illustrated by the absence of important differences compared to previous studies that included unselected patients with out-of-hospital SCD. Second, the diagnosis of acute MI was mostly based on clinical criteria and on coronary angiography performed in the majority of cases. The criteria used took account of the fact that episodes of VT or VF may be associated by a modest elevation of cardiac enzymes due to

metabolic demands exceeding supply. Nevertheless, it may be possible that, in few cases, the arrhythmia was indeed related to an acute MI with only transient active coronary lesions and/or minimal consecutive myocardial damage. Similarly, the diagnosis of prior MI was based on clinical records and imaging techniques in the majority of cases. Necropsy was performed in a minority of cases and imaging techniques with high resolution as cardiac MRI was not performed. Accordingly, some previous silent MI may not have been recognised. It must however be underlined that the criteria used in the study were similar to those used in general clinical practice for the identification of candidates for prophylactic ICD.

Clinical implications

We demonstrated that patients included in recent prophylactic ICD trials represent only a minority of those at risk of SCD. Since current recommendations are largely based on these trials, our findings challenge the adequacy of the actual primary prevention strategy. Our study hence supports the conclusion that a risk stratification strategy based only on the predictive power of depressed LVEF applies to small subgroups and misses numerous candidates for prophylactic ICD from general population pools. Accordingly, future research efforts should not be restricted to patients with depressed LVEF and new methods are warranted to allow the identification of high-risk clusters within larger subgroups that have lesser degrees of increased risk.

According to current guidelines, aggressive attempts should be made to treat myocardial ischaemia and evaluation of the need for an ICD should be deferred after revascularization of accessible coronary artery stenosis. We could demonstrate in this subset of patients, i.e. with prior MI and no areas of potential ischaemia, a highly significant relation between inferior MI and ventricular arrhythmias. The hypothesis that inferior MI scars may be more prone to electrical instability compared to anterior scars warrants further investigations.

Conflict of interest: none declared.

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