Telemedical cardiac risk assessment by implantable cardiac monitors in patients after myocardial infarction with autonomic dysfunction (SMART-MI-DZHK9): a prospective investigator-initiated, randomised, multicentre, open-label, diagnostic trial

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Summary

Background Cardiac autonomic dysfunction after myocardial infarction identifies patients at high risk despite only moderately reduced left ventricular ejection fraction. We aimed to show that telemedical monitoring with implantable cardiac monitors in these patients can improve early detection of subclinical but prognostically relevant arrhythmic events.

Methods We did a prospective investigator-initiated, randomised, multicentre, open-label, diagnostic trial at 33 centres in Germany and Austria. Survivors of acute myocardial infarction with left ventricular ejection fraction of 36–50% had biosignal analysis for assessment of cardiac autonomic function. Patients with abnormal periodic repolarisation dynamics (≥5·75 deg²) or abnormal deceleration capacity (≤2·5 ms) were randomly assigned (1:1) to telemedical monitoring with implantable cardiac monitors or conventional follow-up. Primary endpoint was time to detection of serious arrhythmic events defined by atrial fibrillation 6 min or longer, atrioventricular block class IIb or higher and fast non-sustained (>187 beats per min; ≥40 beats) or sustained ventricular tachycardia or fibrillation. This study is registered with ClinicalTrials.gov, NCT02594488.

Findings Between May 12, 2016, and July 20, 2020, 1305 individuals were screened and 400 patients at high risk were randomly assigned (median age 64 years [IQR 57–73]); left ventricular ejection fraction 45% [40–48]) to telemedical monitoring with implantable cardiac monitors (implantable cardiac monitor group; n=201) or conventional follow-up (control group; n=199). During median follow-up of 21 months, serious arrhythmic events were detected in 60 (30%) patients of the implantable cardiac monitor group and 12 (6%) patients of the control group (hazard ratio 6·33 [IQR 3·40–11·78]; p<0·001). An improved detection rate by implantable cardiac monitors was observed for all types of serious arrhythmic events: atrial fibrillation 6 min or longer (47 [23%] patients *vs* 11 [6%] patients; p<0·001), atrioventricular block class IIb or higher (14 [7%] *vs* 0; p<0·001) and ventricular tachycardia or ventricular fibrillation (nine [4%] patients *vs* two [1%] patients; p=0·054).

Interpretation In patients at high risk after myocardial infarction and cardiac autonomic dysfunction but only moderately reduced left ventricular ejection fraction, telemedical monitoring with implantable cardiac monitors was highly effective in early detection of subclinical, prognostically relevant serious arrhythmic events.

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Introduction

Survivors of acute myocardial infarction have a substantial risk for subsequent cardiovascular and cerebrovascular complications including arrhythmias, progression of heart failure, cardiac death, and stroke. Most fatal and non-fatal complications after myocardial infarction occur in patients with a left ventricular ejection fraction of 36% or higher for whom no preventive strategies exist.[1,2]

A significant proportion of patients after myocardial infarction exhibit disturbances of the cardiac autonomic nervous system, which are linked to arrhythmias and poor prognosis, independent of left ventricular function.[3–5] Cardiac autonomic function can be assessed non-invasively by analysing biosignals recorded from the body surface that contain patterns of autonomic regulatory processes.[6,7] Periodic repolarisation dynamics[8]

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Research in context

Evidence before this study

Most fatal and non-fatal complications after myocardial infarction, including sudden death, occur in patients with a left ventricular ejection fraction more than 35%, for whom no preventive measures are available. Cardiac autonomic dysfunction after myocardial infarction, assessed by advanced digital biomarkers such as periodic repolarisation dynamics and heart rate deceleration capacity, identifies a subgroup at high risk among patients with left ventricular ejection fraction more than 35% with prognosis as poor as that of patients with severely reduced left ventricular ejection fraction (≤35%). Cardiovascular complications might be preceded by subclinical serious arrhythmic events. Early detection of these events by telemedical monitoring using implantable cardiac monitors could enable continuous digital risk assessment and identify patients with imminent complications who require intensified management. We searched PubMed for articles published in any language, from database inception to July 11, 2021, using the search terms "myocardial infarction" and "implantable cardiac monitors" and found one ongoing randomised clinical trial (NCT02341534), evaluating implantable cardiac monitors in patients with previous infarction and a left ventricular ejection fraction more than 35% and a CHA_2DS_2-VASc score 4 or higher.

Added value of this study

To our knowledge, our study is the first randomised trial to test the use of telemedical monitoring with implantable cardiac monitors in patients with previous infarction and left ventricular ejection fraction 36% or higher. Between May 12, and July 20, 2020, 1305 individuals with previous acute myocardial infarction and left ventricular ejection fraction of 36–50% had biosignal analysis, to randomly assess the diagnostic use of implantable cardiac monitors in 400 patients at high risk with cardiac autonomic dysfunction. Telemedical monitoring with implantable cardiac monitors provided early detection of a high number of predefined serious arrhythmic events, including relevant bradyarrhythmic and tachyarrhythmic events, which escaped conventional follow-up because they were mostly asymptomatic. Detection of serious arrhythmic events using implantable cardiac monitors strongly predicted imminent cardiac and cerebrovascular complications in the intervention group. Similar positive predictive accuracy was observed between the intervention and control groups, but a three-times higher sensitivity was observed in the intervention group than in the conrol group.

Implications of all the available evidence

Our study provides the first evidence for the use of implantable cardiac monitors in patients at patients at high risk with previous infarction and left ventricular ejection fraction of 36% or higher and digital biomarkers of autonomic dysfunction. Telemedical monitoring using implantable cardiac monitors enables continuous digital risk assessment by early identification of patients at very high risk for impending complications. These patients require careful evaluation regarding diagnostic or therapeutic measures and close follow-up. Because our study was designed as a diagnostic study, it cannot provide information about the effect of such measures on clinical outcomes. The use of implantable cardiac monitors for continuous digital risk assessment in patients at high risk with previous infarction, therefore, might provide a new option for prevention, while the optimal treatment pathways have yet to be established.

and deceleration capacity of heart rate[9] are advanced digital biomarkers related to sympathetic and vagal dysregulations that predict poor outcomes after myocardial infarction, including sudden and non-sudden cardiac death independently of left ventricular ejection fraction.[9–13] In previous studies combined assessment of periodic repolarisation dynamics and deceleration capacity identified a high-risk group among patients with previous myocardial infarction and left ventricular ejection fraction of 36–50% that is similar in patient number and prognosis to the established high-risk group of patients with severely reduced left ventricular ejection fraction (≤35%).[11,12]

Clinical studies in patients with previous myocardial infarction and severely reduced left ventricular ejection fraction suggested that occurrence of arrhythmic events after myocardial infarction, even when asymptomatic, might precede cardiovascular and cerebrovascular complications.[14] Arrhythmic events might not directly cause complications, but serve as biomarkers for beginning cardiac deterioration. Therefore, early detection of severe arrhythmic events by implantable cardiac monitors could enable telemedical risk assessment and identify patients at very high risk for imminent complications.

We investigated whether telemedical monitoring using implantable cardiac monitors is effective for early detection of subclinical but prognostically relevant severe arrhythmias in patients with previous myocardial infarction, cardiac autonomic dysfunction, and only moderately reduced left ventricular ejection fraction.

Methods

Study design and participants

The Implantable Cardiac Monitors in High-Risk Post-Infarction Patients with Cardiac Autonomic Dysfunction and Moderately Reduced Left Ventricular Ejection Fraction (SMART-MI-DZHK9) trial was a prospective, investigator-initiated, randomised, parallel group, open-label study done at 33 tertiary centres in Germany and Austria. The design and rationale of the trial have been published previously.[15] The study was done using the clinical-scientific infrastructure of the German Centre for Cardiovascular Research, Berlin, Germany. The trial

design was approved by the local ethics committee of the Munich university clinic (number 118–15), at all participating centres and by the legal authorities (Austrian Federal Office for Safety in Health Care). The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice principles. Safety assessment and monitoring was done by the Munich Study Center, Technical University Munich, Germany. The study is registered with ClinicalTrials.gov (NCT02594488). Study protocol is in the appendix.

Eligible patients were aged 18 to 80 years, had survived an acute myocardial infarction according to the definitions of the current European Society of Cardiology guidelines within the last 39 days that required percutaneous coronary intervention, had a left ventricular ejection fraction of 36–50% as assessed by local hospital standards (echocardiography, left ventricular angiography, or MRI) more than 48 h after index myocardial infarction or when creatine kinase muscle–brain was normalised, were in sinus rhythm and were under guideline-directed medical therapy. Patients were excluded if they had an indication for an implantable cardioverter defibrillator or pacemaker, had paroxysmal or permanent atrial fibrillation, had a life expectancy of 12 months or less, were unlikely to comply with follow-up, were pregnant, or participated in another trial that might interfere. All patients provided written informed consent. At baseline, medical history, comorbidities, symptoms, physiological parameters, laboratory values, results of physical examination, ECG-based variables, echocardiographic variables, and invasive data of each individual were obtained.

Randomisation and masking

Patients exhibiting signs of cardiac autonomic dysfunction (as described below) were randomly assigned in a 1:1 ratio to telemedical monitoring using implantable cardiac monitors (intervention group) or conventional follow-up (control group) using a web-based computer-generated sequence (Secutrial, interActive Systems, Berlin, Germany) with stratification according to study centre, age (younger than 70 years or 70 years and older) and left ventricular ejection fraction (<45% or ≥45%). The randomisation process was triggered by the study coordinating centre at the Ludwig Maximilian University (LMU), University Hospital Munich when the patient qualified as a patient at high risk. The randomisation was part of the electronic case report form (eCRF) module, which was independently hosted and managed by the Department of Medical Informatics at the University of Göttingen, Germany. Access to the result of randomisation for the local study centres was provided by the web-based eCRF. Treatment allocation was done according to a predefined block randomisation list with block size of four. There was no masking of patients or investigators to group allocation.

Procedures: biosignal analysis and risk stratification

After informed consent and at least 48 h after index myocardial infarction or when creatine kinase muscle–brain has normalised a 20-min high resolution (1 kHz) resting ECG was recorded in Frank leads configuration (Medilog AR4plus, Schiller, Baar, Switzerland). Recordings were done under standardised conditions in supine position. ECG raw data were transferred to the ECG core lab at the LMU University Hospital Munich, Germany, for blinded computation of digital biomarkers.

Cardiac autonomic function was characterised by two complementary digital biomarkers, periodic repolarisation dynamics[8] and deceleration capacity[9] of heart rate. Both markers were calculated according to previously established technologies using a customised, open-source software (SMARTlab 1.5). The technical details of both markers have been described previously.[8,9] Periodic repolarisation dynamics quantifies sympathetic activity-associated low frequency (<0·1 Hz) oscillations of cardiac repolarisation. Calculation of periodic repolarisation dynamics consists of four steps: (1) Frank-leads are converted to a set of polar coordinates defined by azimuth and elevation, and the amplitude; (2) T-wave vectors ($T°$) are constructed for all T waves, representing the spatiotemporal characteristics of each repolarisation; (3) instantaneous repolarisation instability is estimated by the angle $dT°$, defined by the scalar product of two successive repolarisation vectors $T°$; (4) periodic repolarisation dynamics is calculated as the average wavelet coefficient corresponding to frequencies of 0·1 Hz or lower after applying continuous wavelet transformation on the $dT°$-signal.[8] Periodic repolarisation dynamics was considered abnormal if 5·75 deg² or higher.[8]

Deceleration capacity is an integral measure of all deceleration-related, presumably vagally modulated oscillations of heart rate.[9] For assessment of deceleration capacity, the sequence of beat-to-beat intervals is transformed into a new time series by phase-rectified signal averaging preserving periodic components.[16] The procedure consists of three steps: (1) intervals between successive heartbeat intervals (RR intervals) are identified; (2) segments around anchors are averaged to obtain the so-called phase-rectified signal; (3) the central part of the phase-rectified signal averaging signal is quantified by wavelet-analysis. Deceleration capacity was considered abnormal if 2·5 ms or less.[17] Signs of cardiac autonomic dysfunction were considered present if one or both markers were abnormal.

Procedures: implantation and telemedical monitoring

In the implantable cardiac monitor group, a commercially available, Communauté Européenne-marked implantable cardiac monitors (Reveal LINQ, Medtronic Minneapolis, MN, USA) was implanted using local anaesthesia according to local standard operation procedures. Standard settings for the implantable cardiac monitors were used (appendix p 1). The device was

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See **Online** for appendix

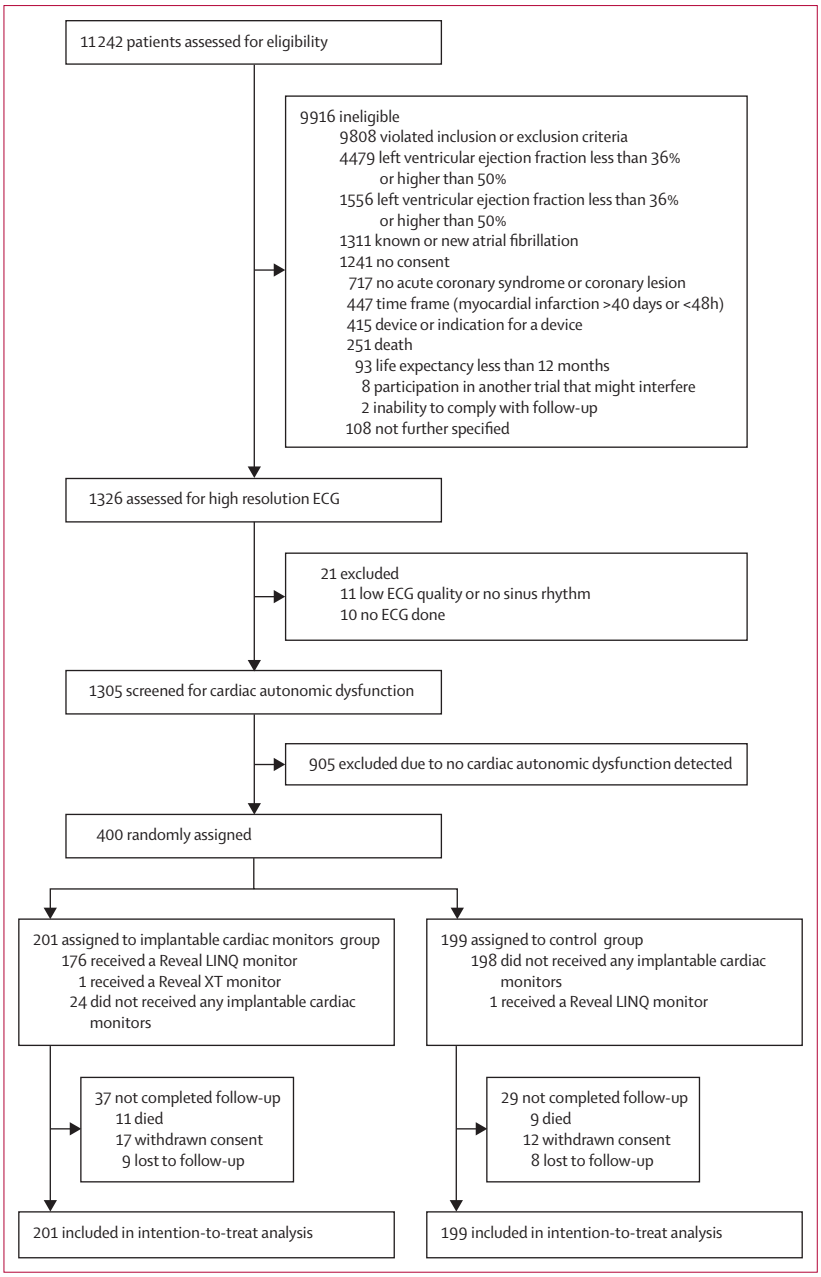

Figure 1: **Trial profile**
The primary endpoint was assessed in all patients according to the randomly assigned trial group, irrespective of the actual monitoring strategy used (the intention-to-treat population). Patients were evaluated from randomisation (time zero) until death, withdrawal of consent, or the last contact date. Patients might have violated several inclusion or exclusion criteria.

connected to the Medtronic CareLink Network. Device data were transmitted daily to the implantable cardiac monitor core lab at the LMU University Hospital where transmissions were checked daily by a study physician. In case of predefined serious arrhythmic events feedback to the local study team was provided within 48 h. At the local study centres, treatment decisions were made at the discretion of the treating physicians in accordance with current guidelines. All diagnostic and therapeutic procedures guided by implantable cardiac monitors were prospectively documented in the eCRF (Secutrial).

Procedures: follow-up

In both groups, follow-up visits were done on an outpatient basis according to a predefined protocol every 6 months (timeframe range 14 days) until study closure. Study-related follow-up visits were done on top of clinical follow-ups. Patients were evaluated for presence of symptoms or previous events (arrhythmias, myocardial infarction, stroke, systemic thromboembolism, unplanned hospitalisation, bleeding, and infection). A 12-lead ECG was recorded. In patients with implantable cardiac monitors the device was interrogated. Further diagnostic evaluation and therapies were done at the discretion of the local investigator. Information of diagnostic and therapeutic measures including device implantations, invasive procedures, and pharmacological treatments were also retrieved from hospital records via telephone or mail from patients, relatives, general practitioners, or local authorities and documented in the eCRF. In case of potential endpoint-relevant serious adverse events, source data were solicited. All serious adverse events and clinical endpoints in this trial were monitored onsite. Risk based onsite monitoring was done for the source data of all study patients. During the COVID-19 pandemic online monitoring was allowed. Patients without signs of cardiac autonomic dysfunction were enrolled into a registry.

Outcomes

The primary endpoint of the study was time to detection of serious arrhythmic events, which included atrial fibrillation 6 min or longer, atrioventricular block class IIb or higher, fast non-sustained ventricular tachycardia (non-sustained ventricular tachycardia with a cycle length of ≤320 ms or frequency of >187 beats per min lasting for ≥12 s corresponding to ≥40 beats), and sustained ventricular tachycardia or ventricular fibrillation. The thresholds and criteria of the individual arrhythmic components were based on the results of clinical studies or represent established criteria for diagnostic or therapeutic interventions. Atrial fibrillation with duration of 6 min or longer was used as in the ASSERT study[18] and indicated an increased stroke risk. Atrioventricular block class IIb or higher after myocardial infarction detected by an implantable cardiac monitor was associated with mortality in the CARISMA study.[14] The non-sustained ventricular tachycardia criteria followed the conservative implantable cardioverter defibrillators device programming in the long detection patient group of the ADVANCE III study.[19]

Secondary endpoints included the single components of serious arrhythmic events, sinus arrest longer than 6 s, death, cardiovascular death, and major adverse cardiac and cerebrovascular events defined by cardiovascular

death, stroke, systemic arterial thromboembolism, and unplanned hospitalisation for decompensated heart failure. Additionally, the composite of death and major adverse cardiac and cerebrovascular events, the composite of sinus arrest longer than 6 s and atrioventricular class block IIb or higher and the composite of atrioventricular class block IIb or higher, fast non-sustained ventricular tachycardia, and sustained ventricular tachycardia or ventricular fibrillation were considered. Safety endpoints included complications related to implantable cardiac monitors and thrombolysis in myocardial infarction major bleeding (Bleeding Academic Research Consortium score of ≥2). All primary and secondary endpoints were adjudicated by an independent endpoint committee masked to patient information.

Statistical analysis

The study was designed to detect an at least 2·7-times annual difference in the event rates of the primary endpoint on a two-sided 5% significance level with a power of 90%. The annual detection rate of serious arrhythmic events was estimated to be 13% in the with implantable cardiac monitors group[14] and 5% in the control group. It was estimated that at least 46 accumulated (pooled) events would be required. Assuming an accrual time of 24 months and a minimum follow-up time of 6 months, a total of 352 patients was expected to yield the necessary number of events if the accrual rate is uniform. Considering a dropout rate of 15%, including deaths as well as patients refusing to continue follow-up, 400 patients had to be randomised. Because the recruitment rate was lower than initially assumed, the steering committee decided in March 15, 2018, to expand the recruitment period by 24 months. Recruitment ended on July 20, 2020, after the target sample size was reached. The longer mean follow-up of the patients positively affected the power of the study, which increased to 94·4%.

Continuous data are presented as medians with IQRs and were compared using Wilcoxon test. Categorical data are summarised with the use of frequencies and proportions and were compared using χ^2 test. Outcomes were analysed using time-to-event methods. The intervention effect on the primary and secondary endpoints was tested using semi-parametric multistate Cox-regression analysis,[20] with inclusion of death as competing risk in the multistate model. For some secondary endpoints, zero events occurred in the control group. For these analyses, exact log-rank test was used post hoc. All analyses were stratified for age (<70 or ≥70 years) and left ventricular ejection fraction (<45 or ≥45%) and were adjusted for recruiting centres as random effect (frailty). Subgroup analyses were done based on tests for interaction using multistate Cox regression analysis, where death was included as competing risk. Subgroup analyses were explorative and were not adjusted for other covariables. A test of

	Implantable cardiac monitor group (n=201)	Control group (n=199)
Age, years	64 (57–73)	65 (57–73)
Sex		
Male	152/201 (76%)	170/199 (85%)
Female	49/201 (24%)	29/199 (15%)
Caucasian	201/201 (100%)	199/199 (100%)
Cardiovascular risk factors		
Diabetes	60/200 (30%)	59/198 (30%)
Use of insulin for diabetes	25/199 (13%)	22/199 (11%)
Current smoker	64/198 (32%)	62/195 (32%)
Arterial hypertension	139/199 (70%)	147/198 (74%)
Hypercholesterinaemia	103/196 (53%)	95/195 (49%)
CHA_2DS_2-VASc score	3 (2–4)	3 (2–4)
CHA_2DS_2-VASc score 3 or higher	131/201 (65%)	120/199 (60%)
Medical history		
History of previous myocardial infarction	27/199 (14%)	35/199 (18%)
Renal dysfunction	21/200 (10%)	22/199 (11%)
Peripheral artery disease	9/201 (4%)	12/197 (6%)
History of stroke	8/201 (4%)	12/198 (6%)
Chronic obstructive pulmonary disease	16/199 (8%)	13/199 (7%)
Heart rate, beats per min	74 (68–81)	73 (64–84)
Body-mass index, kg/m²	28·4 (25·5–31·0)	27·2 (24·4–29·9)
Creatinine, mg/dL	1·00 (0·87–1·20)	1·00 (0·87–1·19)
Index myocardial infarction		
Non-ST segment elevation myocardial infarction	79/201 (39%)	85/199 (43%)
ST segment elevation myocardial infarction	122/201 (61%)	114/199 (57%)
Killip class ≥II	21/181 (12%)	17/171 (10%)
Culprit lesion		
Left anterior descending coronary artery	115/201 (57%)	111/199 (56%)
Right coronary artery	50/201 (25%)	65/199 (33%)
Other	36/201 (18%)	23/199 (12%)
Left ventricular ejection fraction*	45% (40–48)	45% (40–48)
Treatment		
Percutaneous coronary intervention	200/201 (100%)	197/199 (99%)
Aspirin	196/199 (98%)	194/199 (97%)
Clopidogrel	35/197 (18%)	32/197 (16%)
Prasugrel	95/197 (48%)	94/197 (48%)
Ticagrelor	67/197 (34%)	71/197 (36%)
Betablocker	190/199 (95%)	178/199 (89%)
Renin-angiotensin system inhibition	193/199 (97%)	185/199 (93%)
Mineralocorticoid receptor antagonist	70/199 (35 %)	78/199 (39%)
Loop diuretics	56/199 (28%)	51/199 (26%)
Thiazide diuretics	21/199 (11%)	20/199 (10%)
Statins	190/199 (95%)	195/199 (98%)
Cardiac autonomic function		
Periodic repolarisation dynamics, deg²	5·99 (3·43–9·52)	6·80 (3·42–9·10)
Deceleration capacity, ms	1·77 (0·78–2·43)	1·96 (0·16–3·66)
Atypical periodic repolarisation dynamics (≥5·75 deg²)	109/201 (54%)	123/199 (62%)
Atypical deceleration capacity (≤2·5 ms)	154/200 (77%)	138/198 (70%)
Atypical periodic repolarisation dynamics (≥5·75 deg²) and deceleration capacity (≤2·5 ms)	62/200 (31%)	62/199 (31%)

Data are median (IQR) or n/N (%). Information on enrolment by centre provided in the appendix (p 4). *Assessed by echocardiography in all patients.

Table 1: **Baseline characteristics of the intention-to-treat study population**

	Implantable cardiac monitor group (n=201)	Control group (n=199)	Hazard ratio (95% CI)	p value
Primary endpoint: serious arrhythmic events	60 (30%)	12 (6%)	6·33 (3·40–11·78)	<0·0001
Secondary endpoints				
Single components of serious arrhythmic events				
Atrial fibrillation ≥6 min	47 (23%)	11 (6%)	5·24 (2·71–10·14)	<0·0001
Atrioventricular block ≥IIb	14 (7%)	0	..	<0·0001*
Fast non-sustained ventricular tachycardia	6 (3%)	0	..	0·013*
Sustained ventricular tachycardia or ventricular fibrillation	6 (3%)	2 (1%)	2·94 (0·59–14·55)	0·19
Composite of fast non-sustained ventricular tachycardia and sustained ventricular tachycardia or ventricular fibrillation	9 (4%)	2 (1%)	4·51 (0·97–20·93)	0·054
Clinical endpoints				
Death	11 (5%)	9 (5%)	1·29 (0·53–3·11)	0·58
Cardiovascular death	8 (4%)	3 (2%)	2·76 (0·73–10·42)	0·13
Composite of death and major adverse cardiac and cerebrovascular events	25 (12%)	26 (13%)	1·03 (0·60–1·79)	0·91
Hospitalisation due to acute decompensated heart failure	13 (6%)	15 (8%)	0·96 (0·46–2·02)	0·91
Other arrhythmic secondary endpoints				
Sinus arrest >6 s	6 (3%)	0	..	0·012*
Composite of atrioventricular block ≥IIb, fast non-sustained ventricular tachycardia and sustained ventricular tachycardia or ventricular fibrillation	23 (11%)	2 (1%)	12·19 (2·87–51·73)	0·0007
Composite of sinus arrest >6 s and AV block ≥IIb	18 (9%)	0	..	<0·0001*
Safety				
Thrombolysis in myocardial infarction major bleeding (Bleeding Academic Research Consortium ≥2)	14 (7%)	13 (7%)	1·12 (0·53–2·39)	0·77
Device related complications	2 (1%)	..	..	NA

Data are n (%), unless otherwise stated. NA=not applicable. *Tested with exact log-rank test.

Table 2: **Clinical endpoints in the intention-to-treat study population**

interaction between the randomised treatment group and the subgroup variable was done by including the relevant subgroup variable and the interaction between treatment and the subgroup variable in each Cox model. The effect of serious arrhythmic events on clinical outcomes was tested by introducing the occurrence of serious arrhythmic events as time-dependent covariate in Cox regression models stratified for age (aged <70 years and aged ≥70 years) and left ventricular ejection fraction (<45% and ≥45%).[21] Survival curves and cumulative proportions were estimated using the Kaplan-Meier method with 95% CI calculated based on Greenwood's method and were compared using log-rank statistics. Sensitivities and positive predictive values were extrapolated post hoc from the survival curves at the end of the follow-up time. Comparison between sensitivities and positive predictive values were done using bootstrapping based on 10 000 random resamples. For comparison against survival curves without events maximally selected rank-statistics was used.[22] Hazard ratios and p values were calculated for the entire follow-up period until the end of the study. Primary and secondary analyses followed the intention-to-treat principle. An as-treated analysis was also done for efficacy and safety endpoints. Sensitivity analyses assessed the primary endpoint with a proportional hazard model, including death as censoring event. A sensitivity analysis was done introducing implantable cardiac monitors explantation as censoring event. For all analyses, differences were considered statistically significant when the two-sided p value was less than 0·05. All statistical analyses were done using CRAN R (version 3.6.3). Multistate analyses were done using the mstate (version 0.3.1), survival (version 3.2.10), and coxme (version 2.2-16) packages. This study is registered with ClinicalTrials.gov, NCT02594488.

Role of the funding source

The sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 12, 2016, and July 20, 2020, of the 1305 patients who underwent risk-stratification (figure 1), 400 were classified as high-risk patients and were randomly assigned to implantation of a cardiac monitor (implantable cardiac monitor group; n=201) or conventional follow-up (control group; n=199). Time from index myocardial infarction to randomisation was 5 days (IQR 3–8).

The baseline characteristics and treatments of the study population are shown in table 1. In the implantable cardiac monitor group, a monitoring device was implanted in 177 patients (88%; Reveal LINQ in

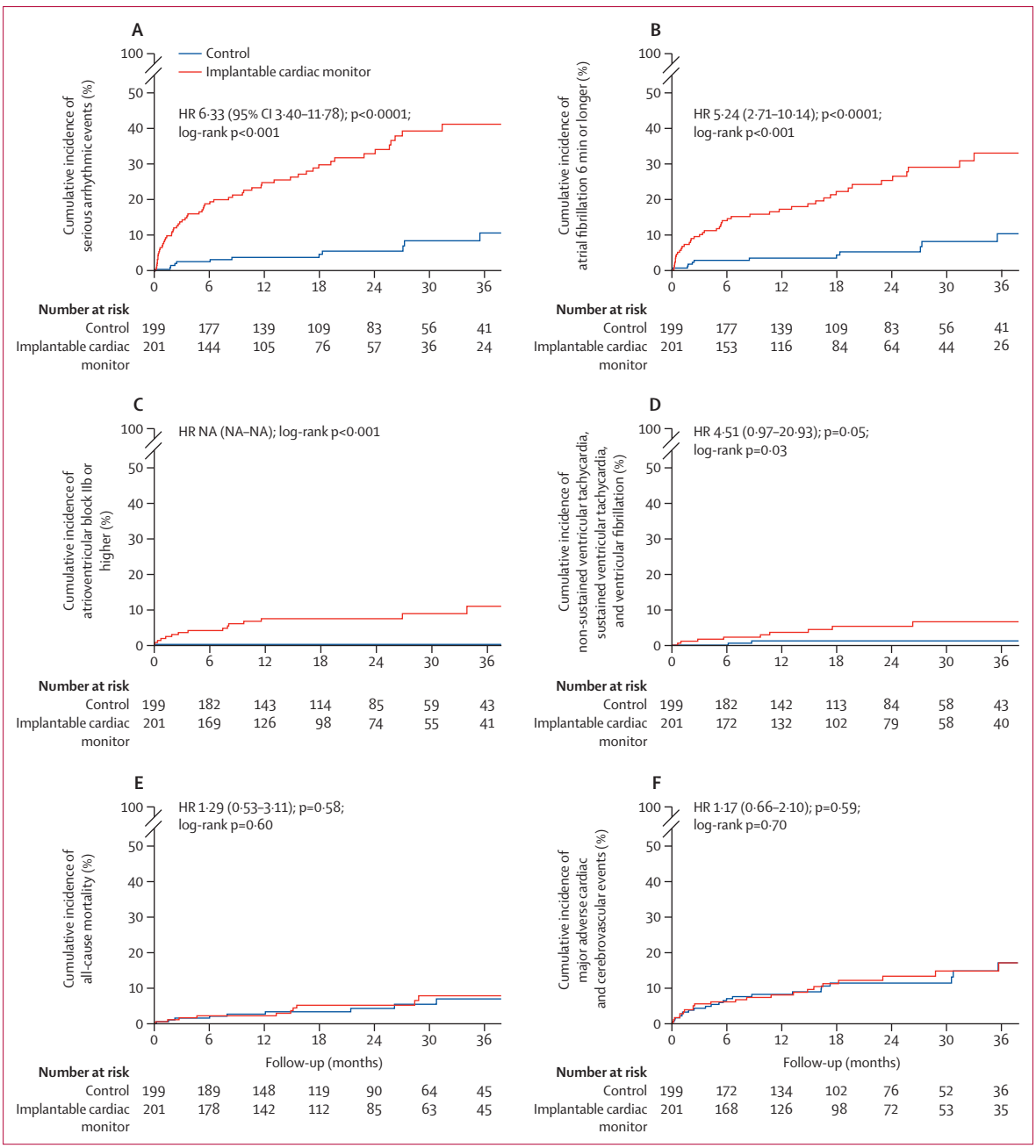

Figure 2: **Cumulative event rates for arrhythmic and clinical endpoints**
(A) Serious arrhythmic events (primary endpoint). (B) Serious arrhythmic events. (C) Atrioventricular block IIb or higher. (D) Ventricular arrhythmias (fast non-sustained ventricular tachycardia with a cycle length of ≤320 ms for ≥40 beats or sustained ventricular tachycardia or ventricular fibrillation. (E) Death. (F) Major adverse cardiac and cerebrovascular events. HR=hazard ratio. NA=not applicable. HRs and p values refer to the entire follow-up period. Because of low number of patients with follow-up time greater than 36 months, Kaplan-Meier curves were truncated at month 36.

176 patients; Reveal XT in one patient) two days (1–5) after randomisation. In 24 (12%) patients of the implantable cardiac monitor group no device was implanted because of patient's refusal (n=21), death before implantation (n=2) or pacemaker implantation (n=1). In the control group, an implantable cardiac monitor (Reveal LINQ) was implanted in one patient at the discretion of the treating physician. Median follow-up was 21 (IQR 11–34) months. 17 (4%) patients were lost to follow-up during the study.

Serious arrhythmic events were detected in 60 (30%) patients in the implantable cardiac monitor group and in 12 (6%) patients in the control group (hazard ratio [HR] 6·33 [95% CI 3·40–11·78]; p<0·0001; table 2). Cumulative detection rates in the intervention group

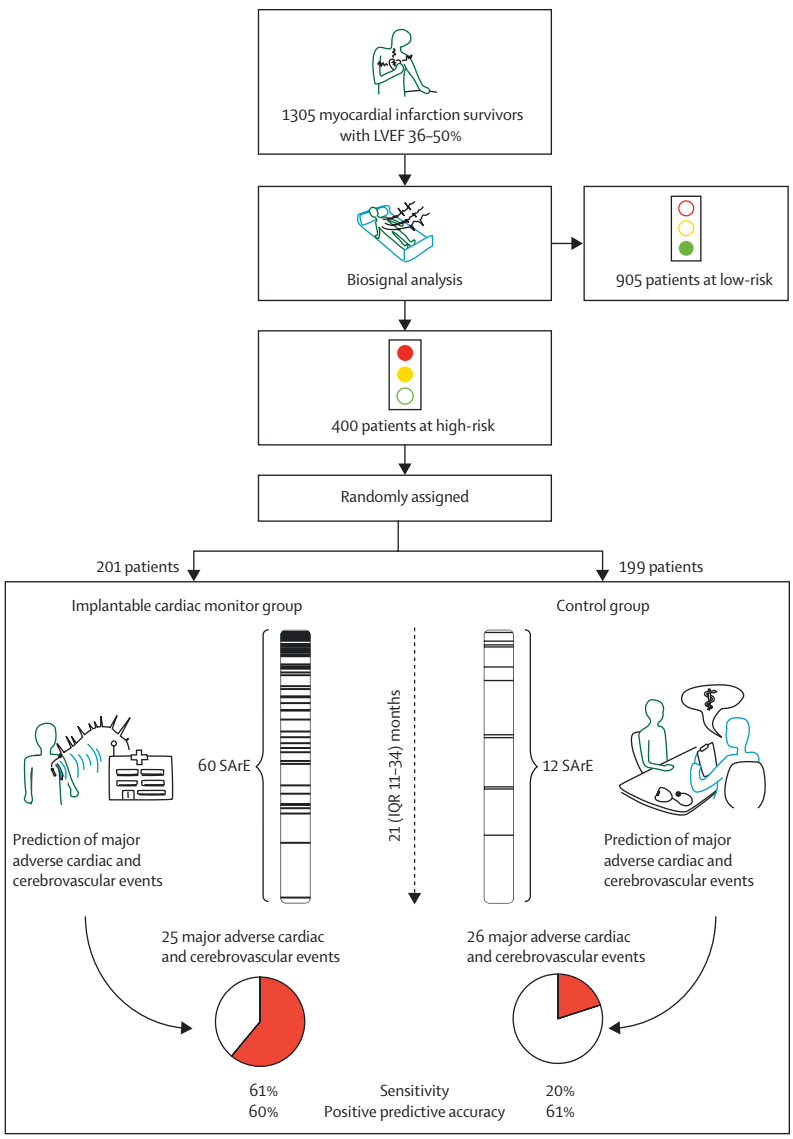

Figure 3: **Continuous telemedical risk assessment by implantable cardiac monitors**
1305 survivors of acute myocardial infarction with left ventricular ejection fraction between 36% and 50% underwent biosignal analysis. 400 patients at high risk with signs of cardiac autonomic dysfunction (abnormal periodic repolarisation dynamics or abnormal deceleration capacity) were randomly assigned to telemedical monitoring with implantable cardiac monitors (implantable cardiac monitor group) or conventional follow-up (control group). Telemedical monitoring was superior to conventional follow-up in detection of subclinical SArEs (black lines in bars indicate time of first events). Please note that only the first SArE is considered in each patient. Compared with conventional follow-up, detection of SArEs by telemonitoring provided three-times higher sensitivity in predicting subsequent serious adverse cardiac and cerebrovascular events, while maintaining positive predictive accuracy. SArE=serious arrhythmic events.

versus control group were 18·9% (13·0–24·4) versus 2·7% (0·3–5·0) after 6 months (p<0·0001), 25% (18·0–31·0) versus 4% (1·0–6·7) after 12 months (p<0·0001), and 49% (33·8–60·8) versus 11% (3·8–17·2; p<0·0001) at the end of the study (57 months; figure 2A, figure 3). In the intervention group, index arrhythmias first detected were atrial fibrillation 6 min or longer in 43 patients, atrioventricular block IIb or higher in ten patients, fast non-sustained ventricular tachycardia in three patients and sustained ventricular tachycardia or ventricular fibrillation in four patients. In the control group, index arrhythmias first detected were atrial fibrillation 6 min or longer in 11 patients and sustained ventricular tachycardia or ventricular fibrillation in one patient. In the implantable cardiac monitor group, 41 (68%) of the 60 serious arrhythmic events were classified as asymptomatic compared to seven (58%) of the 12 in the control group.

An improved detection was observed for all types of serious arrhythmic events (table 2, figure 2, appendix p 5). Of the 47 patients with detection of atrial fibrillation 6 min or longer in the implantable cardiac monitor group, 32 (68%) had atrial fibrillation episodes 1 h or longer, 20 (43%) patients had atrial fibrillation episodes 5·5 h or longer, and 8 (17%) patients had atrial fibrillation episodes 24 h or longer. Table 2 also lists the clinical endpoints. During the study, 11 patients of the implantable cardiac monitor group and nine patients of control group died (HR 1·29 [95% CI 0·53–3·11]; p=0·580). Details of deaths are provided in the appendix (p 1). There were no statistically significant differences in the other clinical endpoints between both groups. There were also no differences of recurrent myocardial infarction between both groups (ten patients in the implantable cardiac monitor *vs* 12 and in the control group; p=0·87).

During the study, the implantable cardiac monitors was explanted in one patient due to device infection. In another patient, the device had to be repositioned due to low sensing. There were no statistically significant differences with respect to thrombolysis in myocardial infarction major bleeding (Bleeding Academic Research Consortium score of ≥2; table 2).

The efficacy of detection of serious arrhythmic events with implantable cardiac monitors was consistent among all subgroups (figure 4).

Throughout the study, more diagnostic and therapeutic interventions were initiated in the implantable cardiac monitor group than in the control group, including implantations of cardioverter–defibrillators (13 patients *vs* five patients; p=0·056), pacemaker implantations (six *vs* none; p=0·041), electrophysiological studies (12 *vs* three; p=0·019), catheter ablations (10 *vs* three; p=0·051) and initiations of oral anticoagulation due to atrial fibrillation (37 *vs* 11; p<0·0001). There were no significant differences in revascularisation procedures (40 *vs* 48; p=0·37) and heart failure medications (appendix p 2).

In an explorative analysis, the time-dependent association between detection of serious arrhythmic events and clinical endpoint was analysed (table 3). In both the intervention group and the control group, detection of serious arrhythmic events significantly predicted subsequent major adverse cardiac and cerebrovascular events (HR 6·82 [95% CI 2·86–16·22], p<0·0001, and HR 7·30 [2·37–22·82]; p=0·0006 for both). In the intervention group and the control group, the positive predictive accuracy of serious arrhythmic events for

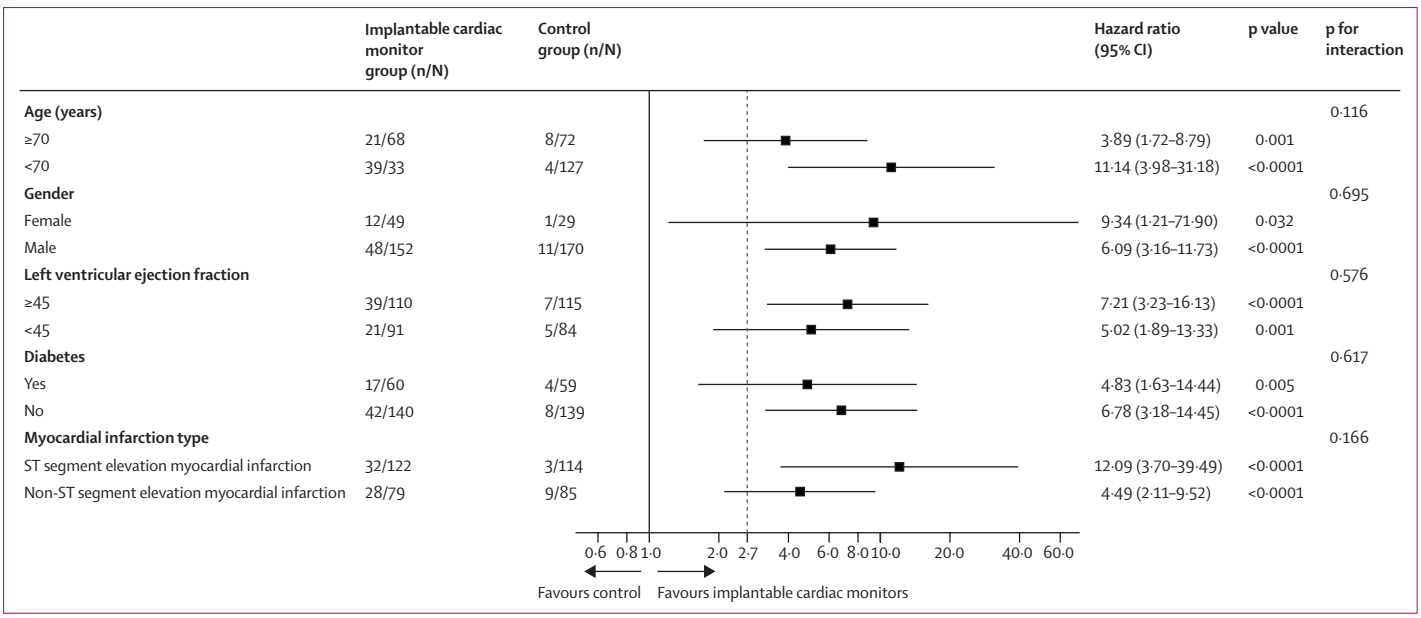

Figure 4: **Subgroup analysis of time to detection of serious arrhythmic events**
Death was introduced as competing risk for all analyses. Vertical line depicts hypothesised hazard ratio of 2·7.

prediction of subsequent major adverse cardiac and cerebrovascular events was similar (60% [95% CI 35–85] *vs* 61% [12–92]; p=0·990), but sensitivity was three-times higher in the intervention group (61% [39–83] *vs* 20% [4–40]; p=0·007). The effect of the different types of events detected by implantable cardiac monitors on serious arrhythmic events on MACCE is shown in the appendix (p 5). Implantable cardiac monitor-based detection of atrial fibrillation 6 min or longer and implantable cardiac monitor-based detection of non-sustained or sustained ventricular tachcardias or fibrillation indicated HRs of 7·93 (95% CI 3·50–17·95) and 5·48 (95% CI 1·73–17·37) for subsequent major adverse cardiac and cerebrovascular events. However, detection of atrioventricular block IIb or higher was not significantly associated with subsequent major adverse cardiac and cerebrovascular events (HR 1·05 [0·13–8·58]).

Prespecified sensitivity and as-treated analyses confirmed the main findings of the study (appendix p 3).

Discussion

Our findings demonstrate that telemedical monitoring with implantable cardiac monitors in patients with previous myocardial infarction and cardiac autonomic dysfunction was highly effective in early detection of subclinical serious arrhythmic events. The detection rate was increased for all types of bradyarrhythmic and tachyarrhythmic serious arrhythmic events. Detection of serious arrhythmic events by implantable cardiac monitors strongly predicted imminent cardiac and cerebrovascular complications with a similar positive predictive accuracy, but with a three-times higher sensitivity compared to conventional follow-up.

A myocardial infarction can inflict profound damage on the cardiac autonomic nervous system. At the myocardial level, destruction of neuronal tissue in the infarcted heart with subsequent hyperinnervation in the border zone results in the formation of a heterogeneous arrhythmogenic substrate.[3] Remodelling and maladaptive processes at the cardiac neuroaxis lead to sustained autonomic dysregulation and sympathetic hyperactivity. Jointly, these processes establish a vicious cycle that culminates not only in the development of malignant arrhythmias,[23] but also in progressive myocardial and vascular dysfunction. These interrelated, self-reinforcing processes at the various levels of the autonomic nervous system provide the mechanistic fundament for the overall poor prognosis of patients with previous infarction and cardiac autonomic dysfunction.[3]

Autonomic changes leave traces in biological signals that can be captured by advanced methods of biosignal analysis. Periodic repolarisation dynamics quantifies low-frequency modulations of repolarisation presumably caused by phasic efferent sympathetic activation of heterogeneously innervated myocardium.[8,24,25] Therefore, periodic repolarisation dynamics should be closely linked to the susceptibility to malignant arrhythmias. In two primary prophylactic implantable cardioverter defibrillator studies[10,13] in patients with reduced left ventricular ejection fraction—a post-hoc analysis of the MADIT-2 study and in the prospective EU-CERT study—increased periodic repolarisation dynamics was statistically significantly associated with malignant ventricular arrhythmias, adequate implantable cardioverter defibrillator shocks, and sudden cardiac death. In addition to its prognostic value, periodic repolarisation dynamics also predicted the

	Implantable cardiac monitor group (n=201)		Control group (n=199)	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Death	3·28 (1·02–10·61)	0·047	..*	..*
Cardiovascular death	3·89 (0·86–17·63)	0·078	..*	..*
Death, stroke, thromboembolic complications, or hospitalisation due to acute decompensated heart failure	6·12 (2·64–14·21)	<0·0001	6·99 (2·24–21·79)	0·0008
Cardiovascular death, stroke, thromboembolic complications, hospitalisation due to acute decompensated heart failure (major adverse cardiac and cardiovascular events)	6·82 (2·86–16·22)	<0·0001	7·30 (2·37–22·82)	0·0006

*No deaths occurred in patients experiencing serious arrhythmic events in the control group.

Table 3: **Time-dependent association of serious arrhythmic events with subsequent clinical outcomes (explorative analysis)**

implantable cardioverter defibrillator treatment effect on mortality reduction.[10] Deceleration capacity quantifies all deceleration-related periodic modulations of heart rate, regardless of their frequency and origin. Deceleration capacity is a robust, integral measure of autonomic nervous system integrity that strongly correlates with a patient's overall prognosis without being restricted to a specific disease mechanism. Both markers capture different facets of autonomic function, allowing these parameters to complement each other.[11]

The type and incidence of bradyarrhythmia and tachyarrhythmia detected in our patients were similar to those that can be detected by continuous monitoring in patients with previous myocardial infarction and severely reduced left ventricular function as illustrated by a comparison with the CARISMA study (estimated 2-year event rates in our study compared with CARISMA:[14] atrial fibrillation 25% *vs* 28%, AV block ≥IIb 7% *vs* 10%, sustained ventricular tachycardia or non-sustained ventricular fibrillation 4% *vs* 3%). The incidence of ventricular tachycardia was numerically lower in our study than in CARISMA[14] (3% *vs* 13%) as we followed more stringent non-sustained ventricular tachycardia criteria adopted from modern implantable cardioverter–defibrillator programming (cycle length >187 beats per min for ≥40 beats[19] *vs* ≥125 beats per min for ≥16 beats). The overall incidence of severe ventricular arrhythmias in our study was similar to that observed in contemporary treated high-risk populations with established criteria for primary prophylactic implantable cardioverter defibrillator implantation.[26] It should also be noted, that the incidence of ventricular fibrillation might be underestimated in our study as in case of death, the implantable cardiac monitors could not be interrogated. The primary composite endpoint of our study was driven by atrial fibrillation as index arrhythmia. However, excluding atrial fibrillation from the composite primary endpoint still resulted in a highly statistically significant difference between the implantable cardiac monitor group and control group with cumulative 3-year detection rates of AV block IIb or higher and non-sustained ventricular tachycardia or sustained ventricular tachycardia or ventricular fibrillation of 17% (95% CI 9·7–24·4) versus 1% (0·0–2·8; p<0·001).

Time-dependent detection of serious arrhythmic events was strongly predictive for subsequent major adverse cardiac and cerebrovascular events in our patients. In both groups, detection of a serious arrhythmic event indicated an approximately seven-times hazard rate for subsequent major adverse cardiac and cerebrovascular events with a high positive predictive value of approximately 60%. Although the prognostic impact of serious arrhythmic events on major adverse cardiac and cerebrovascular events was not related to the mode of detection, telemonitoring with implantable cardiac monitors provided a three-times higher sensitivity of 61% (95% CI 39–83) compared with conventional follow-up, which had a sensitivity of only 20% (4–40). Thus, monitoring with implantable cardiac monitors is superior to conventional follow-up enabling continuous cardiac risk assessment integrating the dynamic progression of an individual patient's risk over time. The strong predictive value was evident for all types of serious arrhythmic events including sinus arrest more than 6 s with exception of AV block IIb or higher. The latter finding, however, is in striking contrast to findings of the CARISMA study[14] and probably explained by preventive device implantation in eight out of the 14 patients with AV block IIb or higher.

Our study has important clinical implications. Early detection of subclinical but prognostically relevant serious arrhythmic events by implantable cardiac monitors warrants close follow-up and careful evaluation for diagnostic and therapeutic measures, including optimisation of medical therapy. As unplanned hospitalisations due to heart failure were a substantial component of predicted major adverse cardiac and cerebrovascular events, careful assessment of myocardial function by advanced imaging techniques seems warranted. Personalised treatment decisions are needed that consider the severity of the underlying disease, the clinical condition, and the type of arrhythmia. In general, arrhythmic events including atrial fibrillation can be considered as early warning signals indicating ongoing cardiac deterioration that require a holistic approach. However, some arrhythmias (eg, intrinsic AV block ≥IIb) also require specific therapeutic measures or trigger diagnostic procedures that may lead to adjustment of

specific therapeutic management (eg, inducible fast monomorphic ventricular tachycardia by programmed ventricular stimulation leading to implantable cardioverter defibrillator implantation). Detection of subclinical atrial fibrillation is particularly challenging in this regard because the question of oral anticoagulation is currently unanswered. This question should be individually addressed by a shared decision considering the function between a patients' stroke risk and atrial fibrillation duration.[27] In our study, the median atrial fibrillation duration leading to anticoagulation was 4·5 h (IQR 1·0–12·0). In our study, we observed an increased number of diagnostic and therapeutic measures by the treating physician, which were done in accordance with current guidelines. Such measures always carry the risk of overtreatment, which can also cause harm. In this context, we find it reassuring that there was no increase in major bleeding.

Our study was designed as a diagnostic trial. Due to the sample size of our study no conclusion can be drawn with regard the effect of implantable cardiac monitor-guided therapies on clinical outcomes. We estimated that more than 2600 patients would be needed to be randomly assigned to detect an overall 25% reduction in major adverse cardiac and cerebrovascular events over a period of 3 years with a power of 80% on one-sided α of 2·5%. It should be taken into account that a net clinical benefit of an invasive preventive measure often becomes apparent years after the procedure, when possible procedure-related side-effects are compensated.[28,29] It should also be considered that not all preventive measures taken have the same level of evidence and effectiveness. For example, although subclinical atrial fibrillation is associated with stroke,[30] the benefit of oral anticoagulation is the subject of ongoing trials (NCT01938248, NCT02618577).

The limitations of our study should be recognised. Risk stratification in our study focused on cardiac autonomic function. Implementation of clinical, imaging-based and other markers probably improves risk stratification. The autonomic markers used in this study are representative of specific autonomic abnormalities associated with poor prognosis after myocardial infarction. However, strong risk prediction can also be achieved by combining other autonomic markers. Cardiac autonomic function was assessed early after myocardial infarction but might recover. The optimum time for assessment of autonomic function is currently unknown. The primary endpoint was composed of different types of atrial and ventricular arrhythmias that have different prognostic meanings and implicate different clinical consequences. The multicentre setting of our study did not allow comprehensive assessment of advanced echocardiographic parameters of left ventricular function or myocardial performance. As in cases of death the implantable cardiac monitors were not interrogated, ventricular fibrillation leading to death might be underestimated. The criteria for serious arrhythmic events were defined prospectively. It is possible that other criteria could lead to a better risk prediction. Our study was an open-label trial with all the limitations that such an approach implies. As in most myocardial infarction studies, women were underrepresented in our trial, which might limit generalisability of the results. The independent endpoint committee was masked to patient information but not to treatment groups. Responses to arrhythmic events by treating physicians were not standardised. Finally, as a diagnostic trial, our study was not powered to test the effects of interventions guided by implantable cardiac monitors on clinical endpoints. It should also be considered that the optimal management of subclinical arrhythmias is the subject of ongoing studies and is largely undefined at this time.

In conclusion, telemedical monitoring with implantable cardiac monitors was highly effective in the early detection of severe arrhythmic events in patients with cardiac autonomic dysfunction and only moderately reduced left ventricular ejection fraction. Telemedical monitoring with implantable cardiac monitors allows continuous cardiac risk assessment in a large group of patients at high risk with myocardial infarction and left ventricular ejection fraction higher than 35% and provides a new opportunity for personalised treatment decisions.

Contributors

AB, SK, SM, and KDR contributed to the conceptualisation of the study. EE, NS, and LvS contributed to the data curation (in general). NS, MK, FW, JS, and LvS contributed to the data curation (ECG and implantable cardiac monitor core laboratory). UM and AAT contributed to the formal analysis. AB, SM, and SK contributed to the funding acquisition. NS, MK, MSc, FW, JS, AK, CB, MSt, MHu, TG, RW, RSa, RSc, MLu, ALu, NG, PC, ALi, LSM, MSc,, MCB, FB, SS, CL, MLi, MHi, RRT, CU, JRE, MZ, GS, SK, and KDR contributed to the investigation. LvS was responsible for the project administration. UM amd AAT contributed to the statistical analysis. AB, SK, SM, and KDR supervised the entire trial. AB, SM, and KDR contributed to the writing of the original draft. AB, LvS, MK, MSc, FW, JS, AAT, TD, AK, EE, UM, SK, KDR, and SM had access to all raw data (including ECG and implantable cardiac monitor data). AB, KDR, UM, AAT, and SM verified the data. All authors contributed to the writing, review, and editing of the manuscript. The co-corresponding authors, AB and KDR, had full access to all the data in the study and had final responsibility for the decision to submit for publication. AB, KDR, UM, AAT, and SM verified the data. Upon request, investigators can be given access to the raw data for further scientific projects provided the positive evaluation of a scientific application by the use and access committee of the German Centre for Cardiovascular Research.

Declaration of interests

AB received funding from Medtronic Bakken Research Center as co-funding for the SMART-MI trial (providing implantable cardiac monitors and staff cost for implantable cardiac monitors core lab); and speaker honoraria from Bayer, Boerhinger Ingelheim, Edwards, Medtronic, and Novartis. MSt received consulting fees, speaker honoraria, and travel expenses from Medtronic. RW received grants from German Centre for Cardiovascular Research, Bristol Myers Squibb–Pfizer, and Grant Boston Scientific; speaker honoraria from Biotronik, Boston Scientific, Medtronic, Abiomed, Bristol Myers Squibb–Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Bayer, and Novartis; and travel expenses from Boston Scientific, Bristol Myers Squibb–Pfizer, Boehringer Ingelheim, Daiichi Sankyo, and Bayer. RW participated on advisory boards for Biotronik, Philips, Boehringer Ingelheim, and Daiichi Sankyo. ALu received grants and consulting fees from Boston Scientific and Biosense Webster; speaker honoraria from Boston Scientific, Biosense Webster ,and Medtronic; travel expenses from

Boston Scientific; and participated on data safety monitoring boards and societies for Boston Scientific. NG received grants from Boston Scientific and Medtronic and travel expenses from Bayer Vital. PC received research grants from Philips. LSM received grants from the German Research Foundation and the EU; speaker honoraria from Bayer, Astra Zeneca, Pfizer, Bristol Myers Squibb, Daiichi Sankyo, and Boehringer Ingelheim; travel expenses from Servier, Boehringer Ingelheim, and Vifor; and participated on data safety monitoring boards for Else Kröner-Fresenius-Stiftung. LSM is stock holder of Bayer and Fresenius Medical Care. MCB received consulting fees from Medtronic and Boston Scientific; speaker honoraria from Medtronic, Boston Scientific, and St Jude Medical; travel expenses from Medtronic, Jonhson & Johnson, Boston Scientific, and St Jude Medical; and participated on advisory boards for Medtronic. CL is member of the Expert Panel for medical devices for the European Commission. CU received consulting fees and speaker honoraria from Medtronic. JRE received consulting fees and speaker honoraria from Medtronic, Abbott, and Boston Scientific. UM received grants from German Centre for Cardiovascular Research (DZHK). All other authors declare no competing interests.

Data sharing

Deidentified individual participant data will be made available after the main analyses of the SMART-MI-DZHK9 trial are finished. Study proposals will need to be approved by the German Centre for Cardiovascular Research (DZHK).

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