

Left ventricular ejection fraction and presence of myocardial necrosis assessed by cardiac magnetic resonance imaging correctly risk stratify patients with stable coronary artery disease: a multi-center all-comers trial

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Received: 3 August 2016 / Accepted: 5 October 2016 / Published online: 13 October 2016
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Abstract

Background Cardiac magnetic resonance imaging (CMR) has become a diagnostic modality that allows for prognostic risk stratification in various cardiac diseases. CMR derived detection of myocardial necrosis by late gadolinium enhancement (LGE) and assessment of left ventricular functional parameters such as left-ventricular ejection fraction (LVEF) have been proven to be significantly associated with outcome and prognosis. Our study focusses on the validation of specific thresholds for these parameters in a multi-center daily all-comers cohort of stable coronary artery disease (CAD) patients.

Methods Multi-center data from tertiary high-volume CMR centers were pooled. Patients referred for viability testing for known or suspected CAD were enrolled. Functional parameters of both ventricles and myocardial necrosis were assessed. The primary endpoint was defined as cardiac death and non-fatal myocardial infarction. A multi-model approach was used for the evaluation of the predictive power of several LVEF thresholds and LGE.

Results The study cohort consisted of 2422 patients. Median age was 66 years; 25.9 % were female. Median follow-up was 2.86 years. During the follow-up period, 187 primary endpoints occurred. On multi-model testing, optimal thresholds for LVEF could be defined at ≤ 50 and

≤ 35 %. The addition of LGE as categorical variable further lead to a significant improvement of each risk prediction model, whilst quantification of LGE affection had no additional prognostic impact.

Conclusion LVEF thresholds at ≤ 50 and ≤ 35 % in combination with the assessment of LGE presence allows for excellent discrimination between low, mid and high prognostic risk in stable CAD.

Keywords Cardiac magnetic resonance imaging · Left-ventricular ejection fraction · Late gadolinium enhancement · Stable coronary artery disease · Prognosis · Risk stratification

Introduction

Cardiac magnetic resonance imaging (CMR) has become a diagnostic modality of choice for good risk stratification of patients with various cardiac diseases, including coronary artery disease (CAD) [1, 2]. Especially, CMR derived detection of myocardial necrosis by late gadolinium enhancement (LGE) has been proven to be significantly associated with major cardiovascular endpoints and poor prognosis [3, 4]. In patients suffering from ventricular tachycardia, LGE detection has substantial influence on the choice of the ablation strategy as well as on the probability of success [5]. Recently, the cost-effectiveness of CMR in the management of CAD patients could also be demonstrated [6]. There are recent meta-analyses trying to clarify the exact role of this parameter in terms of risk stratification and prognosis prediction, though there is a certain inhomogeneity throughout the studies that form the evidence base. Most of them are single-center studies with varying definitions of study populations and endpoints, which hinders comparison to a certain extent [7].

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Furthermore, CMR is considered the gold standard for evaluation and quantification of left ventricular function and ejection fraction (LVEF) [8]. LVEF is known to be one of the strongest parameters regarding outcome and prognosis. Several studies sought to determine age and gender specific normal values of LVEF [9]. They report a lower limit for normal LVEF from 49 to 55 %, which results in a relatively large “grey zone” [9]. Again, these values are mainly derived from single-center studies with less than 100 subjects per group and are not specifically validated in large all-comers CAD cohorts [10].

Aim of the present study was to validate prognostic thresholds for LVEF in a routine all-comers cohort of stable CAD patients. We ought to analyze the potential additional prognostic impact of LVEF and LGE when combined with traditional risk factors. Therefore, multi-center data of high volume tertiary CMR centers were pooled and analyzed.

Methods

Patients

The present study contains patient data from three tertiary high volume CMR centers (University Hospital Ulm, University Hospital of Heidelberg, German Heart Center Berlin). Data was collected from 2000 to 2007. The study is a retrospective analysis of patients consecutively referred for viability testing by CMR imaging for known or suspected CAD. All subjects were considered eligible for enrollment unless they exhibited predefined exclusion criteria such as cardiac or respiratory instability, concomitant limiting disease (e.g. cancer, high grade heart valve disease, pulmonary disease), pregnancy, inability to give informed consent, age <18 years, or myocardial infarction within the last 3 months. In- and exclusion criteria were the same at each site. All patients gave written informed consent. The institutional ethics committee of each CMR site approved the study, respectively.

CMR study

In all centers, CMR imaging was performed on a 1.5-T whole body clinical magnetic resonance scanner (Intera; Philips Medical Systems, Best, The Netherlands) using a cardiac five-element phased-array receiver coil.

For functional imaging, the heart was covered from apex to base in contiguous short-axis orientation using a steady-state free precession sequence. LGE images were acquired approximately 10–15 min after a bolus injection of gadolinium based contrast agent with an inversion-

recovery gradient-echo sequence. Sequence details have been published previously [2, 11, 12].

CMR analysis

A cine short-axis stack was acquired in each patient. Epi- and endocardial contours were drawn manually. Volumetric end-diastolic and end-systolic left and right ventricular volumes and ejection fractions were assessed in every patient using the standard software provided by the manufacturer (ViewForum[®], Philips Medical Systems, Best, The Netherlands) [13, 14]. Two experienced readers in consensus assessed myocardial necrosis visually at each site.

In a subgroup of patients, assessment of regional wall motion and number of LGE affected myocardial segments was performed. According to a recommended wall motion score, each myocardial segment was scored as normal or hyperkinetic = 1, hypokinetic = 2, akinetic = 3, dyskinetic = 4 or aneurysmal = 5 [15]. Wall motion score was expressed as sum as well as normalized to the number of segments. Analogously, the numbers of LGE affected segments were reported.

Follow-up

Follow-up information was acquired from patients' interviews by telephone or from outpatient clinics, hospital chart reviews or by contact with the patients' general practitioner or hospital. Primary endpoint was defined as cardiac death or non-fatal myocardial infarction. Cardiac death was defined as death from any cardiac cause (e.g. myocardial infarction, ventricular fibrillation or other lethal arrhythmia, heart failure) and sudden non-explainable death. Non-fatal myocardial infarction was defined according to the current universal definition [16]. An endpoint was considered early when it took place within 45 days after baseline examination. Patients were censored at the occurrence of the first primary event.

Statistical analysis

To test the relationship between two categorical classification factors, the Chi squared test was applied.

Continuous variables were tested for normal distribution by the D'Agostino–Pearson test. In case a normal distribution was given, variables were reported as mean \pm standard deviation and a two-tailed *t* test was applied for comparison. Variables without normal distribution were reported as median with percentiles and compared by the Mann–Whitney rank sum test.

Univariate regression analyses using Cox's proportional hazard models were performed to estimate the predictive

value of the variables. Hazard ratio (HR) and corresponding 95 % confidence interval (CI) are provided.

To test for incremental predictive power, following approach was applied: Multivariate models based on the results of univariate testing were defined and compared. Chi-square values were calculated with Cox's proportional hazard overall model fit. Integrated discrimination index and net reclassification index were assessed as well. In case of a significant increase in these variables, a particular model was judged superior [17]. Cumulative event curves were compared by the Kaplan–Meier method using a log-rank test.

Thresholds for the continuous parameter LVEF were defined to create categorical variables. To yield optimal thresholds with regard to risk prediction, we calculated statistical significance, hazard ratios and corresponding annual event rates.

Overall, a p value ≤ 0.05 was judged significant. Statistical analysis was performed using commercially available software (Stata13, College Station, USA, MedCalc, Mariakerke, Belgium).

Results

Patients

A total of 2501 patients were screened for enrollment, 56 had to be excluded due to insufficient image quality (2.2 %). Of the remaining 2444 patients, 20 cases were lost to follow-up. Thus, the study cohort consisted of 2422 subjects. The University Hospital of Ulm included 502 patients; the German Heart Center Berlin included 153 patients; the University Hospital of Heidelberg enrolled 1767 patients.

Median age was 66.0 (41.2; 82.1) years, 627 (25.9 %) of the patients were women. Median follow-up was 2.86 (0.85; 5.63) years. Clinical and demographic patients' characteristics, including cardiovascular risk factors and prior cardiac events, are provided in Table 1.

CMR results

There were no major complications in association with CMR examinations. Median left ventricular end-diastolic volume (LVEDV) was 156 ml (98; 263); median left ventricular ejection fraction (LVEF) was 61.0 % (32.0 %; 75.2 %), LGE was seen in 1182 (48.8 %) cases.

In a subgroup of 655 patients, median wall motion score at rest was 18 (17; 38), median normalized wall motion score was 1.06 (1.0; 2.4). LGE was present in 351 (53.8 %) cases, median number of LGE affected segments were 1 (0;

8), median normalized LGE affection was 0.059 (0; 0.47). Table 1 shows CMR results in more detail.

Univariate prediction of primary endpoint

During the follow-up period, 187 primary endpoints occurred (over-all event rate 2.62 %). Only six endpoints (0.3 % of total events) happened within 45 days after baseline examination, and thus had to be considered early. Clinical features and CMR derived parameters were analyzed with regard to endpoint prediction. Results are depicted in Table 2. There were significant associations for age, sex, hypertension, hyperlipidemia, diabetes mellitus and previous revascularization. Concerning CMR derived parameters, LVEF and presence of LGE were variables with highly significant associations. Presence of LGE resulted in the highest hazard ratio of all evaluated variables (hazard ratio 3.29, $p < 0.0001$).

The subgroup analysis also revealed wall motion score and number of LGE affected segments to be significantly correlated with the occurrence of primary endpoints (hazard ratios of 3.20 and 12.76, respectively).

Multivariate analysis and evaluation of optimal LVEF categories

For further evaluation, multivariate models were defined (Table 3 for total cohort; Table 4 for subgroup). All models contained the clinical cardiovascular risk factors with significant results on univariate testing (age, sex, hypertension, hyperlipidemia, diabetes mellitus, and previous revascularization). In addition to that, Model 1 included the CMR derived parameter LVEF. This model yielded a χ^2 value of 62.805 ($p < 0.0001$). In model 2, the continuous variable LVEF was replaced by for LVEF categories (LVEF < 35 %, 35 % \leq LVEF < 45 %, 45 % \leq LVEF < 55 %, 55 % \leq LVEF), which resulted in an increase of χ^2 up to 69.093 ($p < 0.0001$). In model 3, LVEF categories were defined as LVEF < 30 %, 30 % \leq LVEF < 40 %, 40 % \leq LVEF < 50 % and 50 % \leq LVEF. A further increase of χ^2 value could be observed (79.029, $p < 0.0001$). Model 4 included only three LVEF categories (LVEF < 35 %, 35 % \leq LVEF < 50 % and 50 % \leq LVEF) which resulted in a χ^2 value of 76.045 ($p < 0.0001$). Of the clinical risk factors, only hypertension and diabetes mellitus maintained their statistical significance throughout the different models with hazard ratios between 1.4 and 1.6. The different LVEF categories exhibited higher hazard ratios between 2.5 and 4.3. Furthermore, the addition of LGE resulted in an improvement of each model with an increase of χ^2 values of 12–18 and significant results for integrated discrimination index and

Table 1 Patients' characteristics (total cohort) and subgroup

	Total (<i>n</i> = 2422)	Subgroup (<i>n</i> = 655)
Age (years)	66.0 (41.2; 82.1)	64.0 (42.0; 78.0)
Female sex, <i>n</i> (%)	627 (25.9)	200 (30.5)
Cardiovascular risk factors		
BMI, kg/m ²	26.26 (20.76; 33.3)	26.56 (21.36; 34.10)
Hypertension, <i>n</i> (%)	1736 (71.7)	481 (73.4)
Smoking, <i>n</i> (%)	540 (22.3)	210 (32.1)
Hyperlipidemia, <i>n</i> (%)	1373 (56.7)	437 (66.7)
Diabetes mellitus, <i>n</i> (%)	484 (20.0)	147 (22.4)
Family history, <i>n</i> (%)	589 (24.3)	195 (29.8)
Previous revascularization, <i>n</i> (%)	1017 (42.0)	310 (47.3)
Outcome		
Follow-up (days)	1043 (308.6; 2056.1)	1067 (211.0; 1514.5)
Primary endpoints, <i>n</i> (%)	187 (7.7)	70 (10.7)
CMR characteristics		
LVEDV, ml	156 (98; 263)	146.5 (91.1; 292.8)
LVEF, %	61 (32; 75.2)	60 (24.1; 75.2)
LGE, <i>n</i> (%)	1182 (48.8)	351 (53.8)
LGE, number of segments		1 (0; 8)
LGE, number of segments normalized		0.059 (0; 47)
Wall motion score		18.0 (17; 38)

BMI body mass index, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *LGE* late gadolinium enhancement

Table 2 Univariate analysis of primary endpoint prediction

	Hazard ratio	Confidence interval	<i>p</i>
Age	1.01	1.00, 1.03	0.030
Female sex	0.59	0.41, 0.86	0.006
Cardiovascular risk factors			
BMI	0.98	0.94, 1.02	0.262
Hypertension	1.88	1.28, 2.76	0.001
Smoking	1.38	0.99, 1.92	0.056
Hyperlipidemia	1.59	1.16, 2.18	0.004
Diabetes mellitus	1.78	1.29, 2.47	<0.001
Family history	1.01	0.72, 1.41	0.967
Previous revascularization	1.48	1.10, 1.98	0.009
CMR characteristics			
LVEDV	1.00	1.00, 1.00	0.028
LVEF	0.97	0.96, 0.98	<0.0001
LGE	3.29	2.35, 4.60	<0.0001
Subgroup (<i>n</i> = 655)			
LGE number of segments normalized	12.76	2.75, 43.37	<0.0001
Wall motion score normalized	3.20	2.08, 4.91	<0.0001

BMI body mass index, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *LGE* late gadolinium enhancement

net reclassification index. Presence of LGE yielded hazard ratios between 2.3 and 2.5 ($p < 0.0001$). Table 3 depicts the results in more detail.

Analogously, multivariate testing was performed in the subgroup of 655 patients (Table 4). In principle, comparable results could be observed with models 2 and 3

Table 3 Multivariate analysis of primary endpoint prediction (total cohort)

	Model 1	Model 2	Model 3	Model 4
Age	HR: 1.01 CI: 0.99; 1.02 <i>p</i> : 0.62	HR: 1.00 CI: 0.99; 1.02 <i>p</i> : 0.50	HR: 0.100 CI: 0.99; 1.02 <i>p</i> : 0.55	HR: 1.00 CI: 0.99; 1.02 <i>p</i> : 0.57
Male sex	HR: 1.45 CI: 0.99; 2.13 <i>p</i> : 0.06	HR: 1.32 CI: 0.90; 1.94 <i>p</i> : 0.17	HR: 1.32 CI: 0.89; 1.95 <i>p</i> : 0.16	HR: 1.30 CI: 0.88; 1.92 <i>p</i> : 0.19
Cardiovascular risk factors				
Hypertension	HR: 1.54 CI: 1.01; 2.34 <i>p</i> : 0.04	HR: 1.64 CI: 1.08; 2.49 <i>p</i> : 0.02	HR: 1.56 CI: 1.02; 2.37 <i>p</i> : 0.04	HR: 1.60 CI: 1.06; 2.43 <i>p</i> : 0.03
Hyperlipidemia	HR: 1.18 CI: 0.84; 1.67 <i>p</i> : 0.34	HR: 1.15 CI: 0.81; 1.63 <i>p</i> : 0.43	HR: 1.14 CI: 0.80; 1.61 <i>p</i> : 0.46	HR: 1.15 CI: 0.81; 1.62 <i>p</i> : 0.44
Diabetes mellitus	HR: 1.52 CI: 1.08; 2.13 <i>p</i> : 0.015	HR: 1.40 CI: 1.00; 1.98 <i>p</i> : 0.05	HR: 1.43 CI: 1.01; 2.01 <i>p</i> : 0.04	HR: 1.41 CI: 1.00; 1.98 <i>p</i> : 0.05
Previous revascularization	HR: 1.18 CI: 1.08; 2.13 <i>p</i> : 0.29	HR: 1.06 CI: 0.77; 1.45 <i>p</i> : 0.72	HR: 1.02 CI: 0.75; 1.40 <i>p</i> : 0.90	HR: 1.03 CI: 0.75; 1.41 <i>p</i> : 0.87
CMR characteristics				
LVEF (continuous)	HR: 0.97 CI: 0.96; 0.98 <i>p</i> : <0.0001	n/i	n/i	n/i
LVEF <35 %	n/i	HR: 3.55 CI: 2.24; 5.65 <i>p</i> : <0.0001	n/i	n/i
35 % ≤ LVEF <45 %	n/i	HR: 3.12 CI: 2.06; 4.72 <i>p</i> : <0.0001	n/i	n/i
45 % ≤ LVEF <55 %	n/i	HR: 1.33 CI: 0.88; 2.01 <i>p</i> : 0.17	n/i	n/i
LVEF <30 %	n/i	n/i	HR: 2.99 CI: 1.63; 5.50 <i>p</i> : 0.0004	n/i
30 % ≤ LVEF <40 %	n/i	n/i	HR: 4.34 CI: 2.80; 6.72 <i>p</i> : <0.0001	n/i
40 % ≤ LVEF <50 %	n/i	n/i	HR: 2.58 CI: 1.75; 3.81 <i>p</i> : <0.0001	n/i
LVEF <35 %	n/i	n/i	n/i	HR: 3.72 CI: 2.36; 5.89 <i>p</i> : <0.0001
35 % ≤ LVEF <50 %	n/i	n/i	n/i	HR: 2.87 CI: 2.02; 4.06 <i>p</i> : <0.0001
<i>X</i> ²	62.805	69.093	79.029	76.045

Table 3 continued

	Model 1	Model 2	Model 3	Model 4
<i>p</i>	<0.0001	<0.0001	<0.0001	<0.0001
Addition of LGE	HR: 2.50 CI: 1.68; 3.74 <i>p</i> : <0.0001	HR: 2.59 CI: 1.72; 3.88 <i>p</i> : <0.0001	HR: 2.35 CI: 1.57; 3.53 <i>p</i> : <0.0001	HR: 2.36 CI: 1.58; 3.54 <i>p</i> : <0.0001
χ^2	84.231	91.221	97.126	94.426
<i>p</i>	<0.0001	<0.0001	<0.0001	<0.0001
IDI-estimate	0.00966	0.01148	0.01285	0.01188
Standard error	0.00225	0.00236	0.00247	0.00236
<i>P</i>	<0.0001	<0.0001	<0.0001	<0.0001
NRI-estimate	0.13790	0.13597	0.15753	0.13118
Standard error	0.04913	0.05045	0.05275	0.05076
<i>p</i>	0.00500	0.00704	0.00282	0.00975

BMI body mass index, *CI* confidence interval, *HR* hazard ratio, *IDI* integrated discrimination index, *n/i* not included, *n/s* not significant, *NRI* net reclassification index, *LVEF* left ventricular ejection fraction, *LGE* late gadolinium enhancement

exhibiting highest overall χ^2 values. Addition of LGE as categorical variable also lead to a significant improvement of each model, whilst the addition of the normalized LGE affection did not (Table 4).

Risk stratification and event rates

Table 5 shows number of events and event rates in dependency of LVEF category. Event rates were similar for patients with LVEF ≥ 55 vs. LVEF ≥ 50 % (1.92 vs. 1.82 %, respectively). A significant increase in event rates could be observed in subjects with LVEF < 35 vs. LVEF < 30 % (7.06 vs. 5.95 %), most probably because of the significant greater number of patients with LVEF < 35 % ($n = 143$) than with LVEF < 30 % ($n = 89$).

Event-free survival

Event-free survival in dependency of LVEF is depicted in Fig. 1. Panel A shows LVEF categories according to model 2 (LVEF < 35 %, 35 % \leq LVEF < 45 %, 45 % \leq LVEF < 55 %, 55 % \leq LVEF), panel B illustrates model 3 (LVEF < 30 %, 30 % \leq LVEF < 40 %, 40 % \leq LVEF < 50 %, 50 % \leq LVEF) and panel C model 4 (LVEF < 35 %, 35 % \leq LVEF < 50 %, 50 % \leq LVEF).

In Panel A, a good separation could be observed between the survival curves of the groups with mildly impaired LVEF (45 % \leq LVEF < 55 %) and moderately impaired LVEF (35 % \leq LVEF < 45 %). In contrast, the curves depicting patients with normal LVEF (LVEF ≥ 55 %) and mildly impaired LVEF were basically identical. The same is true when looking at the curves of subjects with moderately and severely impaired LVEF (LVEF < 35 %).

In panel B, an early separation could be observed between patients with normal LVEF (LVEF ≥ 50 %) and mildly impaired LVEF (40 % \leq LVEF < 50 %). There was also a good distinction between patients with mild and moderate impairment of LVEF (30 % \leq LVEF < 40 %). In contrast, there was no further separation of patients with severely impaired LVEF (LVEF < 35 %),

In panel C, the model with only two categories of LVEF impairment is depicted. A good separation of the different groups could be observed.

Discussion

The most important finding of this multi-center trial is the fact that reduced LVEF and presence of LGE are parameters with high prognostic potential predictability. Addition of either of these parameters to a multivariate risk prediction model resulted in significant improvement of the respective model over conventional risk factors (increase in χ^2 values, significant NRI- and IDI-estimates). Hence, proving the incremental prognostic prediction.

Several studies have shown significant association of CMR derived parameters with major cardiovascular endpoints such as myocardial death, myocardial infarction and ventricular arrhythmias [4, 7]. Especially, presence of reversible ischemia, reduced LVEF, and myocardial scar assessed by LGE were prognostic parameters of paramount importance [18]. Attempts to quantify these parameters to improve predictive power lead to varying results. Most of the studies forming the current evidence base are single-center studies with diverging numbers of patients being included. A study containing 376 patients with stable CAD who underwent LVEF and LGE assessment by CMR

Table 4 Multivariate analysis of primary endpoint prediction (subgroup)

	Model 1	Model 2	Model 3	Model 4
Age	HR: 1.04 CI: 1.01; 1.08 <i>p</i> : 0.007	HR: 1.04 CI: 1.01; 1.07 <i>p</i> : 0.007	HR: 0.1.04 CI: 1.01; 1.07 <i>p</i> : 0.01	HR: 1.04 CI: 1.01; 1.07 <i>p</i> : 0.01
Male sex	HR: 1.27 CI: 0.63; 2.58 <i>p</i> : 0.50	HR: 1.39 CI: 0.68; 2.83 <i>p</i> : 0.36	HR: 1.46 CI: 0.72; 2.97 <i>p</i> : 0.29	HR: 1.35 CI: 0.66; 2.73 <i>p</i> : 0.41
Cardiovascular risk factors				
Hypertension	HR: 1.42 CI: 0.70; 2.86 <i>p</i> : 0.33	HR: 1.59 CI: 0.78; 3.22 <i>p</i> : 0.20	HR: 1.41 CI: 0.70; 2.85 <i>p</i> : 0.34	HR: 1.43 CI: 0.71; 2.88 <i>p</i> : 0.31
Hyperlipidemia	HR: 0.96 CI: 0.52; 1.78 <i>p</i> : 0.90	HR: 1.06 CI: 0.57; 1.98 <i>p</i> : 0.85	HR: 1.01 CI: 0.55; 1.86 <i>p</i> : 0.97	HR: 1.00 CI: 0.54; 1.86 <i>p</i> : 0.99
Diabetes mellitus	HR: 1.43 CI: 0.83; 2.51 <i>p</i> : 0.015	HR: 1.39 CI: 0.79; 2.43 <i>p</i> : 0.25	HR: 1.53 CI: 0.87; 2.67 <i>p</i> : 0.14	HR: 1.48 CI: 0.85; 2.59 <i>p</i> : 0.17
Previous revascularization	HR: 0.85 CI: 0.48; 1.51 <i>p</i> : 0.58	HR: 78 CI: 0.44; 1.39 <i>p</i> : 0.40	HR: 0.84 CI: 0.47; 1.49 <i>p</i> : 0.55	HR: 0.83 CI: 0.47; 1.47 <i>p</i> : 0.52
CMR characteristics				
LVEF (continuous)	HR: 0.97 CI: 0.95; 0.98 <i>p</i> : <0.0001	n/i	n/i	n/i
LVEF <35 %	n/i	HR: 3.69 CI: 1.91; 7.13 <i>p</i> : <0.0001	n/i	n/i
35 % ≤ LVEF <45 %	n/i	HR: 4.29 CI: 2.11; 8.70 <i>p</i> : <0.0001	n/i	n/i
45 % ≤ LVEF <55 %	n/i	HR: 0.91 CI: 0.36; 2.28 <i>p</i> : 0.83	n/i	n/i
LVEF <30 %	n/i	n/i	HR: 3.51 CI: 1.69; 7.28 <i>p</i> : 0.0007	n/i
30 % ≤ LVEF <40 %	n/i	n/i	HR: 5.54 CI: 2.81; 10.93 <i>p</i> : <0.0001	n/i
40 % ≤ LVEF <50 %	n/i	n/i	HR: 2.10 CI: 1.00; 4.39 <i>p</i> : 0.049	n/i
LVEF <35 %	n/i	n/i	n/i	HR: 3.92 CI: 2.07; 7.43 <i>p</i> : <0.0001
35 % ≤ LVEF <50 %	n/i	n/i	n/i	HR: 2.92 CI: 1.54; 5.51 <i>p</i> : 0.001
<i>X</i> ²	40.388	47.770	46.309	41.310

Table 4 continued

	Model 1	Model 2	Model 3	Model 4
<i>p</i>	<0.0001	<0.0001	<0.0001	<0.0001
Addition of LGE	HR: 2.63 CI: 1.19; 5.79 <i>p</i> : <0.0001	HR: 3.22 CI: 1.42; 7.31 <i>p</i> : <0.0001	HR: 2.70 CI: 1.21; 6.01 <i>p</i> : 0.015	HR: 2.80 CI: 1.25; 6.25 <i>p</i> : 0.012
X^2	46.828	55.311	56.693	48.186
<i>p</i>	<0.0001	<0.0001	<0.0001	<0.0001
Addition of LGE affected segments normalized	HR: 0.8389 CI: 0.21; 6.74 <i>p</i> : 0.84	HR: 1.08 CI: 0.18; 6.47 <i>p</i> : 0.93	HR: 0.98 CI: 0.17; 6.18 <i>p</i> : 0.98	HR: 1.09 CI: 0.18; 6.51 <i>p</i> : 0.92
X^2	40.429	46.777	46.310	41.320
<i>p</i>	<0.0001	<0.0001	<0.0001	<0.0001

BMI body mass index, *CI* confidence interval, *HR* hazard ratio, *n/i* not included, *n/s* not significant, *LVEF* left ventricular ejection fraction, *LGE* late gadolinium enhancement

Table 5 Hazard ratios and annual event rates of different LVEF categories

	Number of subjects in this category	Hazard ratio, confidence interval, <i>p</i>	Event rate (%)	Number of events in this category
Model 2				
LVEF <35 %	<i>n</i> = 143 (6.1 %)	HR: 3.94, CI: 2.54; 6.10, <i>p</i> : <0.0001	7.06	26
35 % ≤ LVEF < 45 %	<i>n</i> = 213 (9.0 %)	HR: 3.30, CI: 2.22; 4.91, <i>p</i> : <0.0001	5.94	34
45 % ≤ LVEF < 55 %	<i>n</i> = 407 (17.3 %)	HR: 1.41, CI: 0.94; 2.10, <i>p</i> : 0.09	2.74	33
55 % ≤ LVEF	<i>n</i> = 1591 (67.6 %)		1.92	91
Model 3				
LVEF <30 %	<i>n</i> = 89 (3.8 %)	HR: 3.35, CI: 1.91; 5.87, <i>p</i> : <0.0001	5.95	14
30 % ≤ LVEF < 40 %	<i>n</i> = 129 (5.5 %)	HR: 4.52, CI: 2.95; 6.94, <i>p</i> : <0.0001	7.86	27
40 % ≤ LVEF < 50 %	<i>n</i> = 288 (12.2 %)	HR: 2.81, CI: 1.94; 4.08, <i>p</i> : <0.0001	4.88	39
50 % ≤ LVEF	<i>n</i> = 1848 (78.5 %)		1.89	104
Model 4				
LVEF <35 %	<i>n</i> = 143 (6.1 %)	HR: 4.07, CI: 2.64; 6.28, <i>p</i> : <0.0001	7.06	26
35 % ≤ LVEF < 50 %	<i>n</i> = 363 (15.4 %)	HR: 3.05, CI: 2.19; 4.26, <i>p</i> : <0.0001	5.35	54
50 % < LVEF	<i>n</i> = 1848 (78.5 %)		1.89	104

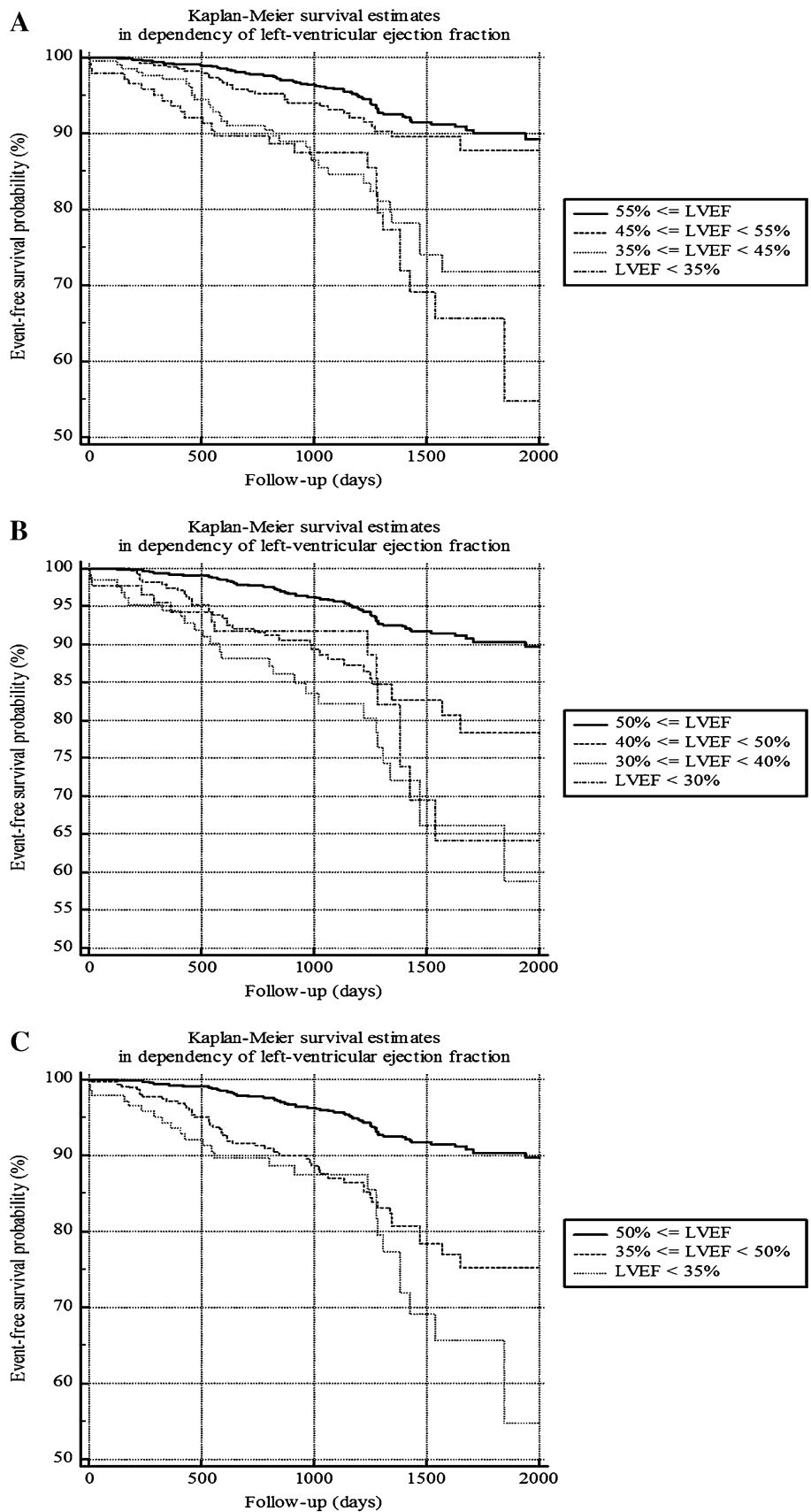
CI confidence interval, *HR* hazard ratio, *LVEF* left ventricular ejection fraction

reported thresholds for LVEF of ≤30 % and for LGE of ≥45 % of left ventricular mass as being most predictive [19]. Patients fulfilling both criteria exhibited annual event rates of 43 %, which rather can be called an ultra-high-risk group and does not account for high-risk patients in clinical routine. In a larger single-center study following up 908 patients for 2.6 ± 1.2 years, patients with abnormal LVEF (defined <50 %) or any presence of LGE had annual event rates of 5.6–6.1 % [20]. Annual event rates in these patients were slightly higher when both parameters were fulfilled (6.5–7.0 %). This study showed an incremental predictive power of these variables when added to risk models containing conventional clinical risk factors.

Recently, annual event rates have been proposed to correctly identify patient risk groups with comparable risks throughout different studies and imaging modalities [21]. A general recommendation derived from these results is to set the threshold for high-risk patients at an annual event rate of 5 % whilst patients with low risk should exhibit event rates of about 1 %.

Within our study, several LVEF thresholds and categories have been evaluated in a multi-model approach. Model 3 which defined a threshold between normal and mildly impaired LVEF at <50 % proved to be superior in correctly identifying patients at increased risk in comparison to model 2 which used the more common threshold at <55 %. Hence,

Fig. 1 Kaplan–Meier-plot depicting event-free survival in dependency of left ventricular ejection fraction. **a** LVEF categories corresponding to model 2 (LVEF <35 %, 35 % ≤ LVEF <45 %, 45 % ≤ LVEF <55 %, 55 % ≤ LVEF); **b** LVEF categories corresponding to model 3 (LVEF <30 %, 30 % ≤ LVEF <40 %, 40 % ≤ LVEF <50 %, 50 % ≤ LVEF); **c** LVEF categories corresponding to model 4 (LVEF <35 % and 35 % ≤ LVEF <50 %, 50 % ≤ LVEF). *LVEF* left-ventricular ejection fraction



annual event rates for patients with normal LVEF in model 3 (e.g. $\geq 50\%$) were similar to those in model 2 (e.g. $\geq 55\%$). In these models, annual event rates for patients with “normal” LVEF were 1.92 % (model 2) and 1.89 % (model 3), which was in concordance with the above mentioned definition for low risk. On the other hand, model 2 showed better results in the high-risk area: a threshold of LVEF at $<35\%$ (event rate 7.06 %, model 2) proved to be superior concerning the identification of patients at very high risk than a threshold at $<30\%$ (event rate 5.95 %, model 3). In conclusion, we set up model 4, which only used 3 LVEF categories (normal: LVEF $\geq 50\%$, moderately impaired: $35\% \leq \text{LVEF} < 50\%$, severely impaired: LVEF $<35\%$). Within this model, it was possible to include the advantages of the former models which translated into proper risk stratification according to the current recommendations (event rates for patients with LVEF $\geq 50\%$: 1.89 %, for patients with $35\% \leq \text{LVEF} < 50\%$: 5.35 %; for patients with LVEF $<35\%$: 7.06 %). Whether these three LVEF categories will form a sufficient basis for decision making in any situation CAD patients will possibly experience obviously remains to be clarified in other studies with designated design.

Presence of LGE is known to be a strong predictor of clinical events in patients with stable CAD [3, 4]. In our study, this finding could be confirmed. By adding presence of LGE to the former elaborated risk prediction models, a significant improvement in prognostic power could be observed. In the past, several attempts have been made to evaluate the potential benefit that would arise from quantification of this important variable [22]. Still, the studies available provide inconclusive results and a uniform way of assessing and reporting the extent of LGE could not be elaborated, yet. One study evaluating the prevalence and prognosis of LGE in 1148 patients with known or suspected CAD and normal wall motion defined a study-specific median size of LGE of 6.25 % of myocardium [23]. Patients with LGE lower than the median had no significant increase in risk for cardiac death and non-fatal myocardial infarction on multivariate testing compared to patients without LGE. LGE greater than the median resulted in a hazard ratio of 7.96 which was a significant increase ($p = 0.001$). It is of note, that only patients with normal wall motion score, and thus normal LVEF were included in this study. Another study evaluating the prognostic value of LGE in a comparable cohort of 1644 patients came to similar results pointing out the strong association between LGE and hard clinical events. Moreover, it could be demonstrated that an increase in LGE resulted in a further increase of risk (patients with LGE $\leq 20\%$: hazard ratio 2.49, $p = 0.032$; patients with LGE $>20\%$: hazard ratio 7.77, $p < 0.001$) [24]. In our study, quantification of LGE was performed on a segmental basis in a subgroup of 655 patients. According to general

recommendations, the number of LGE affected segments were normalized to the total number of myocardial segments [25]. Quantification of LGE yielded highly significant results on univariate testing (hazard ratio 12.76, $p < 0.0001$). Interestingly, it lost its significance on multivariate testing when added to models that contained the variable LVEF. It could be supposed that this finding could be explained because of the strong collinearity between these variables, nevertheless, presence of LGE remained a strong predictor of clinical endpoints in this large cohort of CAD patients.

Limitations

Our study exhibits several limitations that need to be addressed. Because of its retrospective character, it is not possible to conclude information beyond risk stratification. Especially, consequences concerning patient management could not be drawn, yet. It has to be mentioned that information on quantification of LGE only was available in a subgroup of patients and that no quantitative assessment of the extent of LGE or evaluation of transmural extent was performed. Nevertheless, the subgroup consisted of 655 patients that were representative for the whole study cohort. Thus, above described analysis can be considered to be acceptable and rational. Anticipatory, emerging techniques, such as T1- and T2-mapping are thought to have the potential to improve automatic quantification of injured myocardium, and thus might further ameliorate the understanding of the complex interactions concerning prognosis prediction and patient management [26].

Conclusion

In this study, a large cohort of patients with stable CAD derived from three experienced CMR centers was analyzed. LVEF thresholds at 50 and 35 % could be defined as being most useful and predictive concerning risk stratification. These LVEF thresholds in combination with the assessment of LGE allowed for excellent discrimination between low, mid and high risk prognosis.

Compliance with ethical standards

Conflict of interest The authors state that there neither exists a conflict of interest nor that there are financial information to disclose.

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