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Impact of Late Gadolinium Enhancement on mortality, sudden death and major adverse cardiovascular events in ischemic and nonischemic cardiomyopathy: A systematic review and meta-analysis

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ABSTRACT

Background: The central role of left ventricular ejection fraction (LVEF) as the definitive risk marker of adverse outcomes in ischemic and nonischemic cardiomyopathy is increasingly uncertain. The current study aimed to conduct a systematic review and meta-analysis with the objective of evaluating the prognostic importance of Late Gadolinium Enhancement (LGE) in ischemic cardiomyopathy (ICM) and non-ischemic cardiomyopathy (NICM) on the key endpoints of all-cause mortality, cardiovascular mortality and sudden death.

Methods: The study was prospectively registered in PROPSERO (CRD 42016039034). Electronic databases and reference lists were searched for studies evaluating the impact of LGE-CMR on all-cause mortality, cardiovascular mortality, ventricular arrhythmia or sudden death, or major adverse cardiovascular events. Data were extracted from 36 studies including $n = 7882$ patients.

Results: LGE was strongly associated with all-cause mortality HR 2.96 (95%CI: 2.37, 3.70, $P < 0.001$), cardiovascular mortality HR 3.27 (95% CI: 2.05, 5.22, $P < 0.001$), ventricular arrhythmia and sudden cardiac death HR 3.76 (95% CI: 3.14, 4.52, $P < 0.001$), and major adverse cardiovascular events HR 3.24 (95% CI: 2.32, 4.52, $P < 0.001$). In subgroup analyses, LGE was associated with all-cause mortality and cardiovascular mortality in both LVEF ≤ 35% and LVEF > 35% patients ($P < 0.001$ all endpoints), as well as in nonischemic and ischemic cardiomyopathy.

Conclusion: Late Gadolinium Enhancement (LGE) in CMR predicts all-cause mortality, cardiovascular mortality, ventricular arrhythmia and sudden death, and major adverse cardiovascular events, independent of LVEF. Future trials of investigational therapies in NICM and ICM should consider the utilization of LGE to identify patients at risk of adverse outcomes.

1. Introduction

Left ventricular ejection fraction (LVEF) is at present the cornerstone of prognostic assessment in nonischemic and ischemic cardiomyopathy (NICM/ICM), based on its utilization as an entry criterion into randomized controlled trials of defibrillators to prevent sudden death [1,2]. In this respect, LVEF has been utilised as a surrogate marker for ventricular scar, believed to be the key substrate for ventricular arrhythmia [3,4].

In the past decade, there has been growing awareness that LVEF-based stratification as currently practised may have potentially significant deficiencies in its ability to identify at risk populations in ICM and NICM [2,4–6]. Multiple epidemiological studies have suggested that the majority of sudden deaths occur in patients with LVEF > 35% [7–10]. More recently, in a landmark clinical trial, ICD placement in an NICM population identified by LVEF < 35%, failed to demonstrate benefit for defibrillator therapy in terms of all-cause and cardiovascular mortality, despite reducing sudden death [11]. Together, these data are consistent with the idea that LVEF may in many circumstances fail to delineate those patients at high risk for adverse clinical outcomes. Hence there is an urgent need for alternative parameters to LVEF, to identify sub-populations at risk of all-cause mortality, cardiovascular mortality and sudden death.

In this regard, over the last 15 years, Late Gadolinium Enhancement (LGE) Cardiovascular Magnetic Resonance (CMR) has emerged as a widely available technique to enable visualization and quantitation of myocardial scar [12,13]. LGE CMR has evolved as an accurate and reproducible technique to directly measure replacement fibrosis in patients with both ICM and NICM [14,15,16]. A growing body of observational

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evidence has shown that LGE in ICM/NICM patients may be associated with a variety of adverse outcomes including ventricular arrhythmia and sudden cardiac death (SCD) [17–19], heart failure [20], and increased mortality [21–24].

The most definitive means of evaluating LGE-CMR as a prognostic tool would be a demonstration that its application improves clinical outcomes in a prospective, multi-centre randomized controlled trial (RCT) [5,25,26]. To date, however, the only RCT addressing the specific prognostic importance of LGE-CMR in patients with ICM and preserved LVEF > 35%, DETERMINE (DEfibrillators To REduce Risk by MagnetIc ResoNance Imaging), was terminated after it failed to reach its enrolment target [5].

Therefore, at present, the most readily available objective way to determine the prognostic role of LGE-CMR on mortality is by aggregation of existing observational clinical data in a systematic review and meta-analysis [27]. Previous meta-analyses analysing the impact of LGE on clinical outcomes have predominantly focused on the ventricular arrhythmia or sudden death. In the current study, we sought to conduct a systematic review and meta-analysis examining the prognostic impact of LGE-CMR in both NICM and ICM on all-cause mortality, cardiovascular mortality, sudden cardiac death and major adverse cardiovascular events. The study sought to aggregate available clinical data, to test the hypothesis that LGE scar is associated with an underlying propensity towards increased morbidity and mortality in NICM/ICM.

2. Methods

2.1. Study search, inclusion/exclusion criteria, data extraction

The study was registered in PROSPERO (CRD 42016039034). We conducted a systematic search of PubMed, with the search grid outlined in the Supplemental Information. The search was conducted with the assistance of a research librarian, and included studies up to 6/6/2017. Abstracts were reviewed independently by two reviewers (AG, JG), with differences resolved by consensus. The primary inclusion criterion was studies in which dichotomized clinical outcome data was reported in ICM or NICM patients stratified by either the presence or threshold of LGE-CMR.

Randomized controlled trials, cohort studies, and case series data from patients with ICM or NICM were included. Studies exclusively in patients in individual disease-specific sub-populations of NICM (e.g. hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, sarcoidosis, amyloidosis, myocarditis) were excluded. No upper limit of LVEF for study entry was placed. Review articles, letters to the editor, commentary, conference papers, and case reports were excluded. The baseline characteristics of included studies are shown in Table 1, with full reference citations for included studies in the Supplemental Information.

Data on the following endpoints were extracted: (i) all-cause mortality; (ii) cardiovascular mortality; (ii) ventricular arrhythmia and SCD events; and (iii) major adverse cardiovascular events (MACE). Where MACE was reported, the definition of this endpoint was accepted as those defined in the original manuscripts. In studies in which MACE was not reported, MACE was computed as the composite of all-cause mortality, ventricular arrhythmia/SCD events, and heart failure events.

Pre-specified subgroup analyses were the impact of LGE on clinical outcomes in NICM and ICM patients, and the impact of LGE on clinical outcomes in study populations with LVEF ≤ 35% and LVEF > 35%. As a supplementary analysis, meta-regression was performed to assess the impact of LVEF as a continuous variable on the clinical outcomes of all-cause mortality, cardiovascular mortality, major adverse cardiac events, and ventricular arrhythmia/sudden cardiac death.

Individual study-level definitions of the cutoff for an LGE positive test were accepted as in previous systematic reviews [28,29]. As a sensitivity analysis, all-cause mortality, cardiovascular mortality, sudden death and MACE were analysed in the subgroup of studies where the cutoff was defined by the presence of absence of LGE.

2.2. Statistical analysis

Statistical analysis was performed with Comprehensive Meta-Analysis 2 (Biostat, NJ). For included studies, hazard ratios (HR) were derived from univariate Cox proportional hazards analysis where these data were available. In studies reporting raw event data dichotomized by the presence or quantity of LGE, hazard ratios were estimated as previously described [30,31]. The I^2 statistic was used as a measure of variability in observed effect estimates attributable to between study heterogeneity [32]. Pooled hazard ratio estimates were derived with random effects models [33].

3. Results

A total of 6042 citations were retrieved. 5815 citations were excluded after initial screening of abstracts and titles on general criteria, with 228 citations selected for a secondary review. From these citations, 33 journal articles were identified, referencing observational cohort studies reporting endpoint data stratified by the presence or extent of LGE-CMR.

3.1. Baseline characteristics of included studies

The baseline characteristics of included studies are presented in Tables 1 and 2. A total of 7397 patients were included from $n = 33$ studies. Included studies were published from 2006 to 2015. Sample size varied from $n = 32$ patients to $n = 1148$ patients. Follow-up varied from 9 months to 64 months. The mean age of patients varied from 48 to 68 years. The mean LV ejection fraction varied from 21% to 65%. The proportion of female patients varied from a range of 12% to 41%.

3.2. Impact of LGE on all-cause mortality

All-cause mortality was reported in 19 out of 36 studies (53%). In these studies, the HR for all-cause mortality with an LGE positive test was 2.96 (95% CI: 2.37, 3.70, $P < 0.001$) (Fig. 1A). Heterogeneity for this outcome was low ($I^2 = 19.0\%$). In the subgroup of 13 studies where outcomes were dichotomized by the presence or absence of LGE, the HR for all-cause mortality was 2.88 (95% CI: 2.15, 3.87, $P < 0.001$). In the subgroup of 8 studies with pooled LVEF ≤ 35%, HR for mortality was 2.89 (95% CI: 1.72, 4.85, $P < 0.001$). In the subgroup of 11 studies with pooled LVEF > 35%, the HR for all-cause mortality was 2.99 (95% CI: 2.32, 3.86, $P < 0.001$). The P-value for the difference between the LVEF ≤ 35% and LVEF > 35% subgroup was not significant at 0.90.

3.3. Impact of LGE on cardiovascular mortality

Cardiovascular mortality was reported in 13 studies (36%). The HR for all-cause mortality with an LGE positive test was 3.27 (95% CI: 2.05, 5.22, $P < 0.001$, Fig. 1B). I^2-was significant at 70.6%. In the subgroup of 12 studies where outcomes were dichotomized by the presence or absence of LGE the HR was 3.72 (95% CI: 2.56, 5.39, $P < 0.001$). The HR for mortality in the 5 studies with pooled LVEF ≤ 35% was 4.10 (95% CI: 1.63, 10.29, $P = 0.003$). The HR for cardiovascular mortality in the 8 studies with pooled LVEF > 35% was 2.99 (95% CI: 1.70, 5.24, $P = 0.002$). The P-value for the difference between the LVEF ≤ 35% and LVEF > 35% subgroup was not significant at 0.57.

3.4. Impact of LGE on ventricular arrhythmia and sudden cardiac death

Ventricular arrhythmia and sudden cardiac death was reported in 24/36 studies (67%). The hazard ratio for VA/SCD with an LGE positive test was 3.76 (95% CI: 3.14, 4.52, $P < 0.001$, Fig. 1C). Heterogeneity for