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CLINICAL RESEARCH

Accuracy of cardiac magnetic resonance imaging to rule out significant coronary artery disease in patients with systolic heart failure of unknown aetiology: Single-centre experience and comprehensive meta-analysis

Intérêt de l'imagerie par résonance magnétique cardiaque pour exclure la présence d'une coronaropathie sous-jacente chez les patients avec insuffisance cardiaque systolique d'étiologie inconnue : expérience monocentrique et méta-analyse

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Abbreviations: CA, coronary angiogram/angiography; CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; HF, heart failure; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NLR, negative likelihood ratio; PLR, positive likelihood ratio; st-LGE, subendocardial or transmural late gadolinium enhancement.

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KEYWORDS
Coronary artery disease;
Magnetic resonance imaging;
Late gadolinium enhancement;
Coronary angiogram;
Heart failure

Summary
Background. — Coronary artery disease (CAD) is the leading cause of systolic heart failure (HF). Cardiac magnetic resonance imaging (CMR) is a non-invasive technique that detects a myocardial infarction scar as subendocardial or transmural late gadolinium enhancement (st-LGE).
Aim. — We sought to evaluate whether a lack of st-LGE could rule out CAD in new-onset systolic HF of unknown aetiology.
Methods. — We included 232 consecutive patients with new-onset HF and left ventricular ejection fraction $\leq$ 35% who underwent both coronary angiography and CMR to assess HF aetiology. CAD was defined as the presence of coronary artery stenosis $\geq$ 50% on a coronary angiogram. We assessed sensitivity, specificity, and positive and negative likelihood ratios (PLR and NLR) of the presence of st-LGE to detect underlying CAD. A complementary meta-analysis of 11 studies (including ours) was also performed.
Results. — In our study, 49 (21.1%) patients had CAD. The sensitivity and specificity of the presence of st-LGE to detect CAD were 69 and 92%, respectively. PLR and NLR were 8.47 and 0.33, respectively. In the meta-analysis, 1227 patients were included, and the prevalence of CAD ranged from 19.2 to 68.3%. Sensitivity, specificity, PLR and NLR were 87% (95% confidence interval [CI] 0.80—0.92), 93% (95% CI 0.89—0.96), 12.91 (95% CI 7.70—21.64) and 0.14 (95% CI 0.09—0.22), respectively. Altogether, 55 patients presented CAD with no st-LGE; inversely, 75 patients presented st-LGE with no CAD.
Conclusion. — With a CMR specificity of 93%, the absence of st-LGE rules out significant underlying CAD in patients with systolic HF of unknown aetiology in most cases.

MOTS CLÉS
Coronaropathie ;
Imagerie par résonance magnétique ;
Rehaussement tardif ;
Angiographie coronaire ;
Insuffisance cardiaque

Résumé
Contexte. — La coronaropathie est la principale cause d'insuffisance cardiaque (IC) systolique. L'imagerie par résonance magnétique cardiaque (IRM-C) est une technique non invasive qui permet de détecter les cicatrices d'infarctus du myocarde sous la forme d'un rehaussement tardif sous-endocardique ou transmural après injection de gadolinium (st-RT).
Objectif. — L'objectif de cette étude est d'évaluer si l'absence de st-RT peut exclure la coronaropathie chez les patients présentant une IC systolique d'étiologie inconnue.
Méthodes. — Au total, 232 patients consécutifs présentant une IC avec une fraction d'éjection ventriculaire gauche $\leq$ 35 % et qui ont eu à la fois une angiographie coronaire et une IRM-C ont été inclus. La coronaropathie était définie par la présence d'une sténose coronaire $\geq$ 50 % en angiographie. La sensibilité, la spécificité, les rapports de vraisemblance positifs et négatifs (RVP et RVN) de la présence d'un st-RT à l'IRM-C pour détecter la coronaropathie ont été évalué. Une méta-analyse complémentaire de 11 études (dont la nôtre) a également été réalisée.
Résultats. — Dans notre étude, 49 (21,1 %) patients avaient une coronaropathie. La sensibilité et la spécificité de la présence de st-RT pour détecter cette dernière étaient de 69 et 92 %, respectivement. Les RVP et RVN étaient respectivement de 8,47 et 0,33. La méta-analyse a inclus 1227 patients. La prévalence de la coronaropathie variait de 19,2 à 68,3 %. La sensibilité, la spécificité, le RVP et le RVN étaient respectivement de 87 % (IC95 % 0,80—0,92), 93 % (IC95 % 0,89—0,96), 12,91 (IC95 % 7,70—21,64) et 0,14 (IC95 % 0,09—0,22). Au total, 55 patients ne présentaient pas de st-RT mais une coronaropathie ; inversement 75 patients présentaient une st-LGE sans coronaropathie.
Conclusion. — Avec une spécificité de l'IRM cardiaque de 93 %, l'absence de st-RT exclut une coronaropathie chez les patients présentant une IC systolique d'étiologie inconnue dans la plupart des cas.

Background

Coronary artery disease (CAD) is currently the leading cause of systolic heart failure (HF), and impacts patient prognosis and care in practice [1]. In this context, the need to systematically perform a coronary angiogram (CA), which is an invasive procedure, in patients with systolic HF of unknown aetiology has been challenged by new techniques. Cardiac magnetic resonance imaging (CMR) has emerged as a non-invasive technique that provides high-resolution images of the heart in any desired plane and without radiation; it assesses cardiac morphology and function, and the presence and extent of myocardial infarction scar, by showing subendocardial or transmural late gadolinium enhancement (st-LGE) [2]. Recent small-scale investigations have suggested that late gadolinium enhancement (LGE) can distinguish whether HF is related to CAD [3—14]. Therefore, the inclusion of CMR in the clinical management of patients with systolic HF of unknown aetiology might avoid unnecessary invasive diagnostic coronary angiography (CA) procedures.

In the present study, we sought to assess the diagnostic accuracy of st-LGE on CMR to rule out significant underlying CAD in patients with new-onset systolic HF of unknown aetiology, and to include our data in a comprehensive meta-analysis of its diagnostic accuracy compared with invasive CA as a reference standard.

Methods

Patient population

An ongoing registry of catheter-based coronary procedures is maintained at our institution. From February 2005 to December 2016, all consecutive patients who underwent CA for new-onset systolic HF (left ventricular ejection fraction [LVEF] $\leq$ 35% on transthoracic echocardiography) were screened. Those who had no clinical or electrical evidence suggestive of CAD, and for whom CMR was available, were included in the present analysis. During the study period, patients presenting with new-onset HF and reduced LVEF were routinely referred for both CA and CMR. Lack of evidence suggestive of CAD was considered in cases of no clinical evidence (no history of documented CAD [history of unstable angina and/or history of myocardial infarction and/or previous percutaneous coronary intervention and/or previous coronary bypass and/or previous CA showing > 50% diameter luminal stenosis in any epicardial coronary artery] or presence of typical chest pain), and no electrocardiogram evidence (pathological Q waves). Regional wall motion alteration on transthoracic echocardiography was not considered to be discriminating for CAD, because this variable is known to be non-specific [15]. The final study population consisted of 232 patients with new systolic HF.

CA

Conventional techniques were used to perform the CA. Patients were considered to have CAD when $\geq$ 50% diameter luminal stenosis in any epicardial coronary artery (with a diameter > 2 mm) was observed. Two experienced interventional cardiologists (A.M. and C.D.) reviewed the CA in blinded conditions. In cases of discrepancy, consensus was reached by discussion with a third experienced interventional cardiologist (G.L.).

CMR

All patients were examined using a 1.5 Tesla MR system (Achieva™; Philips Healthcare, Best, The Netherlands). Detailed information about the CMR is available in Appendix B. LGE imaging was performed 10 minutes after an intravenous bolus of 0.4 mL/kg (0.2 mmol/kg) of gadoteratemeglumine (Dotarem®; Guerbet, Roissy, France), with optimization of inversion times using inversion recovery pulses to null the signal from the normal myocardium. Images were evaluated independently by two experienced radiologists (F.P. and P.L.), who were blinded to the clinical variables and the CA results. In cases of discrepancy, consensus was reached by discussion with a third radiologist (M.R.). End-diastolic and end-systolic volumes were calculated from manual contouring. The left myocardium was analysed in 17 segments according to standardized reported segmentation. To be validated, LGE must be present in the same myocardial segment in at least two different planes. When present, st-LGE was then described using a three-point scale, according to the myocardial thickness involved (1 = < 25%; 2 = 25—75%; 3 = > 75%). Only st-LGE was considered for the present analysis to assess the accuracy of CMR to detect underlying CAD in patients with HF of unknown aetiology. However, subepicardial or intramyocardial enhancement without any coronary artery distribution was also reported and included with patients with no LGE in the group of patients with no st-LGE, according to the previous literature [16].

Meta-analysis

The PubMed database was searched for eligible studies, with no time restriction, on 5 April 2017, by using the combined medical subject headings for ''coronary artery disease, left ventricular dysfunction, heart failure, ischaemic, late gadolinium enhancement and magnetic resonance imaging''. The complete search used for PubMed was: (coronary artery disease[Title/Abstract] OR left ventricular dysfunction[Title/Abstract] OR heart failure[Title/Abstract] OR ischaemic[Title/Abstract]) AND late gadolinium enhancement[Title/Abstract] OR magnetic resonance imaging[Title/Abstract]) AND english[Language]. Two investigators (G.L. and C.D.) independently checked retrieved titles and abstracts for eligibility, and relevant full texts were systematically retrieved for further detailed assessment. Major reviews regarding the place of CMR in HF were also hand searched. Cross-references and quoted papers were checked, and experts were contacted to identify other relevant studies. The retrieved studies were examined to exclude duplicate or overlapping data. Unpublished data were not considered for the present analysis, because results could not be considered as certain and definitive. Meeting abstracts were also excluded, because they could not provide adequately detailed data and their results might not have been final.

Studies were eligible for inclusion in the final analysis:

- if they included patients with systolic HF of unknown aetiology;
- if they reported st-LGE by the presence of significant CAD status on CA;
- if they reported a clear definition of significant CAD;
- if the absolute numbers of true positives, false positives, true negatives and false negatives were reported or could be derived.

Studies were excluded:

- if they focused on patients with known specific cardiomyopathy as post-partum cardiomyopathy, hypertrophic cardiomyopathy, amyloid, sarcoidosis or mitochondrial cardiomyopathy, right ventricular dysplasia or congenital heart disease;
- if they focused on patients with CAD only;
- if they focused on patients without CAD;
- if they focused on patients with LVEF > 50%;
- if a clear definition of significant CAD was not reported;
- if st-LGE was not reported by CAD status;
- if they were performed with no final report and only abstracts available;
- if they were performed in animals.

The information that was systematically searched for and extracted from each study is presented in Appendix B. Three investigators (G.L., C.D. and A.M.) performed the data extraction independently; discrepancies were solved by consensus. Two investigators (G.L. and C.D.) independently assessed the quality of all included studies using the revised quality assessment of diagnostic accuracy studies (QUADAS-2) tool [17]. Any disagreement was resolved by consensus.

Statistical analysis

Continuous variables are expressed as means ± standard deviations, except for delays, which are expressed as medians [25th—75th percentiles]. Categorical variables are expressed as numbers (percentages). Student's *t* test was used to compare continuous variables, and the χ^2 test or Fisher's exact test was used to compare categorical variables. Delays between groups were compared using the Mann-Whitney U test.

Sensitivity and specificity were calculated using true positive, true negative, false positive and false negative rates. Sensitivity was calculated as the number of patients with CAD and st-LGE divided by the number of patients with CAD; specificity was calculated as the number of patients without CAD and no st-LGE divided by the number of patients without CAD. Also calculated were the likelihood ratios, which express how much the odds of CAD change in the presence of st-LGE (positive likelihood ratio [PLR] = sensitivity/[1 − specificity]) or in the absence of st-LGE (negative likelihood ratio [NLR] = [1 − sensitivity]/specificity). Post-test probability odds expressed in percentages with 95% confidence intervals (CIs) were calculated, defined by the probability of CAD after a positive test and after a negative test, represented in a Fagan diagram.

All these measures of diagnostic accuracy were also calculated for each individual study included in the meta-analysis, and were reported as point estimates with 95% CIs. Pooled results for the meta-analysis were calculated with STATA software, version 14.0 (StataCorp, College Station, TX, USA) using the MIDAS command. Between-study statistical heterogeneity was assessed by using the Cochran Q χ^2 test and the I^2 test. The study was performed according to established methods, and in compliance with the quality of reporting of meta-analyses (QUORUM) guidelines [18].

All statistical analyses were performed with STATA software version 14.1 (StataCorp). Statistical significance was assumed at a P value < 0.05.

Results

Single-centre experience

Population

The baseline characteristics of the patients are summarized in Table 1. In the overall population, the mean age was 57.3 ± 12.3 years. Altogether, 79.3% of cases were male, and 15.1% had diabetes. The mean LVEF was 22.5 ± 7.5%, as assessed by transthoracic echocardiography. The median delay between CA and CMR was 2 [1—6] days.

Significant obstructive CAD was found in 49 patients (21.1%). Patients with CAD were older (62.4 vs 56 years; $P = 0.001$) and more often had diabetes (26.5% vs 12.0%; $P = 0.012$) and hypertension (49.0% vs 32.2%; $P = 0.03$) than those without CAD at inclusion.

Regarding CMR data, st-LGE was found in 49 patients (21.1%) in the overall population. Patients with st-LGE were more often male (91.8% vs 76.0%; $P = 0.015$) than those without st-LGE at inclusion.

Diagnostic accuracy of st-LGE

Altogether, st-LGE was found in 34 (true positives, 69.4%) of the 49 patients with CAD, and in 15 (false positives, 8.2%) of the 183 patients without CAD. CMR did not report any st-LGE in 15 (false negatives, 30.6%) of the 49 patients with CAD (Table 2). Repartition of the patients according to st-LGE and CAD status is depicted in Fig. 1. Therefore, in our population, the sensitivity and specificity of the presence of st-LGE on CMR to detect CAD were 69% and 92%, respectively. PLR and NLR were 8.47 and 0.33, respectively. The description of the underlying CAD in the 15 patients with significant obstructive CAD but no st-LGE on CMR is available in Table 3. Of note, 11 patients had single-vessel disease (including only one with severe [> 70%] stenosis), three patients had two-vessel disease and one patient had three-vessel disease.

Meta-analysis

Search results and study selection

We found 3232 citations in PubMed and other data sources. There were 113 relevant studies, for which a detailed assessment of the full text was performed. We finally included 11 studies (including our own) [3—12] and excluded 102 others. The reasons for exclusion were study focused on patients with CAD only ($n = 23$); study focused on patients with no CAD ($n = 53$); study did not focus on patients with systolic HF ($n = 9$); study did not report st-LGE by CAD status ($n = 17$); and study had duplicate data ($n = 9$). A study could be excluded

Table 1 Baseline characteristics of our population.

	Total population ($n=232$)	With CAD ($n=49$)	Without CAD ($n=183$)	*P*	With st-LGE ($n=49$)	Without st-LGE ($n=183$)	*P*
Demographics							
Age (years)	57.3 ± 12.3	62.4 ± 11.9	56 ± 12	0.001	57.3 ± 10.9	57.3 ± 12.6	0.987
Male sex	184 (79.3)	43 (87.8)	141 (77.0)	0.100	45 (91.8)	139 (76.0)	0.015
Risk factors							
Body mass index (kg/m^2)	26.6 ± 5.8	26 ± 4.5	26.8 ± 6.1	0.399	25.9 ± 4.1	26.9 ± 6.2	0.291
Diabetes mellitus	35 (15.1)	13 (26.5)	22 (12.0)	0.012	10 (20.4)	25 (13.7)	0.248
Hypertension	83 (35.8)	24 (49.0)	59 (32.2)	0.030	19 (38.8)	64 (35.0)	0.622
Active smoker	149 (64.2)	35 (71.4)	114 (62.3)	0.236	35 (71.4)	114 (62.3)	0.236
Hypercholestero-laemia	60 (25.9)	15 (30.6)	45 (24.6)	0.393	11 (22.4)	49 (26.8)	0.539
Familial history of CAD	40 (17.2)	8 (16.3)	32 (17.5)	0.849	8 (16.3)	32 (17.5)	0.849
Peripheral arterial disease or carotid disease	20 (8.6)	6 (12.2)	14 (7.7)	0.309	7 (14.3)	13 (7.1)	0.112
Initial clinical presentation							
Acute pulmonary oedema	42 (18.1)	12 (24.5)	30 (16.4)	0.191	13 (26.5)	29 (15.8)	0.085
Other congestive symptoms[a]	190 (81.9)	37 (75.5)	153 (83.6)	—	36 (73.5)	154 (84.2)	—
Electrocardiogram findings							
Atrial fibrillation	42 (18.1)	9 (18.4)	33 (18.0)	0.970	5 (10.2)	37 (20.2)	0.103
Left bundle branch block	49 (21.1)	14 (28.6)	35 (19.1)	0.156	12 (24.5)	37 (20.2)	0.527
LVEF by echocardiography (%)	22.5 ± 7.5	23.3 ± 7.6	22.3 ± 7.5	0.407	21.7 ± 7	22.7 ± 7.7	0.382
Delay between CA and CMR (days)	2 [1—6]	2 [1—4]	3 [1—6]	0.036	1 [1—5]	3 [1—6]	0.099
CA data							
Obstructive CAD	49 (21.1)	49 (100)	—	—	34 (69.4)	15 (8.2)	< 0.0001
One-vessel CAD	28 (12.1)	28 (57.1)	—	—	16 (32.7)	12 (6.6)	< 0.0001
Multivessel CAD	21 (9.0)	21 (42.9)	—	—	18 (36.7)	3 (1.6)	—
Delay between symptom onset and CA (days)	12 [9—21]	12 [9—19]	12 [9—21]	0.911	12 [9—21]	12 [9—21]	0.815
CMR data							
st-LGE	49 (21.1)	34 (69.4)	15 (8.2)	< 0.0001	49 (100)	—	—
Subepicardial or nodular (atypical) LGE	14 (6.0)	1 (2.0)	13 (7.1)	0.184	—	14 (7.7)	—
Delay between symptom onset and CMR (days)	11 [7—15]	6 [11—14]	7 [11—15]	0.305	6 [11—15]	7 [11—15]	0.511

Data are expressed as mean ± standard deviation, number (%) or median [25th—75th percentiles]. CA: coronary angiogram; CAD: coronary artery disease; CMR: cardiac magnetic resonance imaging; LGE: late gadolinium enhancement; LVEF: left ventricle ejection fraction; NYHA: New York Heart Association; st-LGE: subendocardial or transmural late gadolinium enhancement.

[a] NYHA class II/III dyspnoea and leg oedema.

Table 2 Numbers of true positive, false positive, true negative and false negative patients in the 11 studies included in the meta-analysis.

Study	All patients	TPs (patients with CAD and st-LGE)	FNs (patients with CAD and no st-LGE)	FPs (patients with no CAD and st-LGE)	TNs (patients with no CAD and no st-LGE)
McCrohon et al. (2003)	90	27	0	8	55
Casolo et al. (2006)	60	40	1	3	16
Soriano et al. (2007)	123	39	11	8	65
Schietinger et al. (2007)	26	2	3	0	21
Le Polain de Waroux et al. (2008)	71	24	7	5	35
Valle-Munoz et al. (2009)	100	18	3	6	73
Krittayaphong et al. (2011)	98	53	5	0	40
Gao et al. (2012)	124	59	0	8	57
Di Bella et al. (2016)	187	77	9	6	95
Thompson et al. (2017)	116	73	1	16	26
Manchuelle et al. (2018)	232	34	15	15	168

Data are expressed as number. CAD: coronary artery disease; FN: false negative; FP: false positive; st-LGE: subendocardial or transmural late gadolinium enhancement (at least one segment); TN: true negative; TP: true positive.

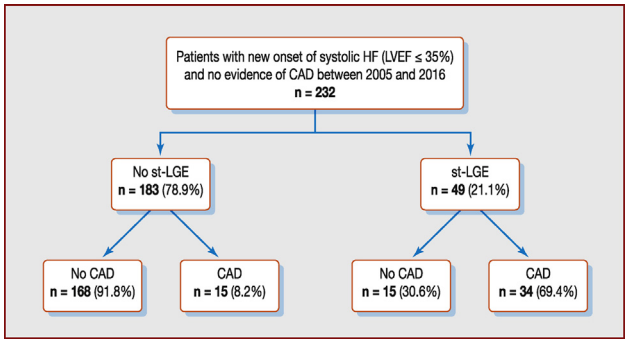

Figure 1. Study population according to the presence of subendocardial or transmural late gadolinium enhancement (st-LGE) and coronary artery disease (CAD). HF: heart failure; LVEF: left ventricular ejection fraction.

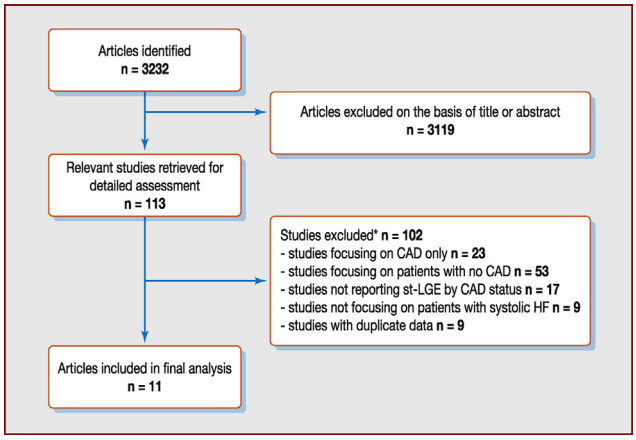

Figure 2. Flow chart of the study selection process. CAD: coronary artery disease; HF: heart failure; st-LGE: subendocardial or transmural late gadolinium enhancement. *: a single study could be excluded for several reasons.

for several reasons. The flow chart of the study selection process is shown in Fig. 2.

Study and patient characteristics

Altogether, 11 studies and 1227 patients were included in the meta-analysis. Detailed information about the 11 included studies is presented in Table 3 and Table 4: eight studies were prospective registries and three were retrospective studies. The year of publication ranged from 2003 to 2017. The median age of included patients ranged from 49 to 66.4 years. The rate of male sex ranged from 65 to 80.6%, and the rate of diabetes mellitus ranged from 11.5 to 42.9% among in the eight studies that reported this information. The median LVEF ranged from 25 to 40%. The median time between CAD assessment by CA and st-LGE assessment by CMR ranged from 2 days to 3.4 years in the eight studies that reported these data. The definition of obstructive CAD differed across the studies. The prevalence of CAD ranged from 19.2 to 68.3%.

Table 3 Main patient characteristics in the 11 studies included in the meta-analysis.

Study	Patients (*n*)	Age (years)	Men	Diabetes mellitus	LVEF	Prevalence of obstructive CAD	Prevalence of st-LGE	Prevalence of atypical LGE	Description of underlying CAD in patients with CAD and no st-LGE
McCrohon et al. (2003)	90	54 in NIDCM vs 67 in IDCM	41 (65.0)	NA	39% in NIDCM vs 33% in IDCM assessed by CMR	27 (30.0)	35 (38.9)	18 (20.0)	No patient with CAD and no st-LGE
Casolo et al. (2006)	60	66.4	44 (73.3)	12 (20.0)	35% assessed by TTE	41 (68.3)	56 (93.0)	0 (0)	One patient: severe lesion of the LM
Soriano et al. (2007)	123	60	99 (80.5)	32 (26.0)	28% assessed by TTE	50 (40.7)	47 (38.2)	NA	11 patients: nine with single vessel disease and two with two-vessel disease, not involving the LM or proximal LAD in all cases
Schietinger et al. (2007)	26	49	19 (73.1)	3 (11.5)	25% assessed by CMR	5 (19.2)	2 (7.7)	2 (7.7)	Three patients: all with significant stenosis of the LAD and at least one other major coronary artery
Le Polain de Waroux et al. (2008)	71	Mean 56–63	50 (70.0)	NA	Mean 25–29% assessed by CMR	31 (43.6)	28 (39.4)	11 (15.5)	Seven patients: one with single proximal LAD stenosis; one with proximal LAD and distal LCx stenosis; four with three-vessel disease; one with dominant RCA stenosis
Valle-Munoz et al. (2009)	100	60.4	68 (68.0)	33 (33.0)	29.1% assessed by CMR	21 (21.0)	24 (24.0)	7 (7.0)	Three patients: one with 80% stenosis of the mid LAD and 70% in the first marginal branch; one with 80% in the proximal non-dominant RCA and 70% stenosis of the distal segment of the LCx; one with 70% stenosis of the mid LAD

Table 3 (*Continued*)

Study	Patients (*n*)	Age (years)	Men	Diabetes mellitus	LVEF	Prevalence of obstructive CAD	Prevalence of st-LGE	Prevalence of atypical LGE	Description of underlying CAD in patients with CAD and no st-LGE
Krittayaphong et al. (2011)	98	59.4 in NIDCM vs 61.5 in IDCM	66 (67.3)	42 (42.9)	32.8% in IDCM vs 27.1% in NIDCM assessed by CMR	58 (59.2)	53 (54.1)	10 (10.2)	Five patients: no information on CAD pattern
Gao et al. (2012)	124	61	100 (80.6)	30 (24.2)	26% assessed by CMR	59 (47.6)	67 (54.0)	38 (30.6)	No patient with CAD and no st-LGE
Di Bella et al. (2016)	187	61	135 (72.2)	37 (19.8)	37% assessed by CMR	86 (46.0)	83 (44.4)	48 (25.7)	Nine patients: no information on CAD pattern
Thompson at al. (2017)	116	64	90 (77.6)	NA	40% assessed by CMR	73 (62.9)	89 (76.7)	15 (12.9)	One patient: total occlusion of an epicardial vessel, not involving the LM or LAD
Manchuelle et al. (2018)	232	57	184 (79.3)	35 (15.1)	22.5% assessed by TTE	49 (21.1)	49 (21.1)	14 (6.0)	15 patients: 11 with single vessel disease (including 50—70% stenosis of the distal RCA [*n* = 1], mid LAD [*n* = 5] and LCx [*n* = 3]; 80—90% stenosis of the mid RCA [*n* = 2]); three with two-vessel disease (including 60% stenosis of the mid LAD and 50—70% stenosis of the LCx [*n* = 2]; 80% stenosis of the mid LAD and CTO of the mid RCA [*n* = 1]); one with three-vessel disease (LAD, 90%; LCx, 80%; and CTO of the RCA)

Data are expressed as number (%) unless otherwise indicated. CAD: coronary artery disease; CMR: cardiac magnetic resonance imaging; CTO: chronic total occlusion; IDCM: ischaemic cardiomyopathy LAD: left anterior descending artery; LCx: left circumflex artery; LGE: late gadolinium enhancement; LM: left main coronary artery; LVEF: left ventricular ejection fraction; NA: not available; NIDCM: non-ischaemic dilated cardiomyopathy; RCA: right coronary artery; st-LGE: subendocardial or transmural late gadolinium enhancement; TTE: transthoracic echocardiography.

Table 4 Description of the 11 studies included in the meta-analysis.

Study	Design	Period of inclusion	Consecutive patients	Main inclusion criteria	Main exclusion criteria	Technique to assess LGE	Technique to assess underlying CAD	Definition of obstructive CAD	Interval between CAD evaluation and CMR
McCrohon et al. (2003)	Prospective registry	NA	Yes	Clinical presentation of HF, documented LV dilation and dysfunction by TTE or radionucleotide imaging	Suspected infiltrative heart disease, hypertrophic cardiomyopathy, previous revascularization, significant valve disease, history of myocarditis	Assessed blindly	CA in all patients, assessed blind by a single cardiologist	> 50% stenosis of any epicardial vessel	2.2 years in NIDCM vs 3.4 years in IDCM
Casolo et al. (2006)	Retrospective study	NA	Yes	Clinical symptoms, LVEF < 40% by TTE and LV dilatation by TTE with volume > 2 SDs of the sex/body surface area	Severe congestive symptoms, previous revascularization, significant valvular disease, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, myocarditis	Two operators, blinded to clinical data	CA in all patients	$\geq$ 75% stenosis in at least one major epicardial vessel	Maximum 30 days
Soriano et al. (2007)	Prospective registry	NA	Yes	Clinical evidence of HF, LV dysfunction documented by TTE < 50%	ACS in previous 3 months, secondary causes of HF, including valve disease, constrictive pericarditis, hypertrophic cardiomyopathy, restrictive cardiomyopathy, myocarditis	Two physicians blinded to CA data	CA in all patients, assessed blind by a single expert	$\geq$ 50% stenosis of any epicardial vessel	5 months

Table 4 (*Continued*)

Study	Design	Period of inclusion	Consecutive patients	Main inclusion criteria	Main exclusion criteria	Technique to assess LGE	Technique to assess underlying CAD	Definition of obstructive CAD	Interval between CAD evaluation and CMR
Schietinger et al. (2007)	Prospective registry	NA	NA	New-onset HF and LV systolic dysfunction, symptom duration < 3 months	Age < 18 years, known CAD, previous positive stress test, previous ACS, previous revascularization, valvular heart disease	One reader blinded to all clinical and CA data	CA in all patients	> 50% stenosis of any epicardial vessel	14 days
Le Polain de Waroux et al. (2008)	Prospective registry	NA	Yes	LVEF < 50%, referred for HF aetiology	Previously established diagnosis of LVSD, haemodynamic instability, atrial fibrillation	One reader blinded to all clinical and CA data	CA in all patients	> 50% stenosis of any epicardial vessel with diameter > 1.5 mm	Maximum 1 month
Valle-Munoz et al. (2009)	Prospective registry	NA	Yes	Acute new-onset HF with LVSD (LVEF < 40% and increased LVEDD > 95th percentile on TTE), with no previous history of CAD, no Q waves on ECG and no clinical data at time of diagnosis to suggest CAD	Clinical data suggesting hypertrophic cardiomyopathy, infiltrative heart disease or myocarditis	Two independent observers; discrepancies resolved by consensus	CA performed by one cardiologist blinded to CMR results	$\geq$ 70% stenosis of any epicardial vessel	NA

Table 4 (*Continued*)

Study	Design	Period of inclusion	Consecutive patients	Main inclusion criteria	Main exclusion criteria	Technique to assess LGE	Technique to assess underlying CAD	Definition of obstructive CAD	Interval between CAD evaluation and CMR
Krittayaphong et al. (2011)	Prospective registry	NA	NA	Age > 30 years, history of HF within 6 months, LVEF < 50% on TTE, CMR or ventriculogram	Clinically unstable, history of revascularization, HF from valvular or pericardial causes	Experienced cardiologist unaware of CA results	CA in all patients	$\geq$ 50% stenosis of any epicardial vessel	Maximum 1 year
Gao et al. (2012)	Prospective registry	NA	Yes	LVEF $\leq$ 35% on TTE, stable for 3 months under maximal tolerated therapies, referred for ICD implantation	-	Assessed blind by a single expert	CA or computed tomography angiography	$\geq$ 70% stenosis of any epicardial vessel	NA
Di Bella et al. (2016)	Prospective registry	June 2007 to January 2013	Yes	Newly-diagnosed LV dysfunction (LVEF < 45% by ambulatory TTE evaluation) and NYHA $\leq$ 2	Chest pain, history of CAD, history of secondary causes of HF (primary valve disease, constrictive pericarditis, hypertrophic cardiomyopathy, restrictive cardiomyopathy, myocarditis), cardiac hospitalization, atrial fibrillation	Consensus of three CMR expert cardiologists	CA in all patients	$\geq$ 50% stenosis in the LM and/or $\geq$ 70% in any other epicardial vessel	NA

Table 4 (*Continued*)

Study	Design	Period of inclusion	Consecutive patients	Main inclusion criteria	Main exclusion criteria	Technique to assess LGE	Technique to assess underlying CAD	Definition of obstructive CAD	Interval between CAD evaluation and CMR
Thompson at al. (2017)	Retrospective study	2006 to April 2013	NA	LVEF < 50% or LVEDV $\geq$ 97 mL/m^2 on CMR or previous LV dysfunction on TTE	History of revascularization	Assessed independently of CA	Assessed independently of CMR	$\geq$ 50% stenosis in the LM and/or $\geq$ 70% in any other epicardial vessel	42 days
Manchuelle et al. (2018)	Retrospective study	Feb 2005 to Nov 2016	Yes	New-onset HF with LVEF $\leq$ 35% measured by TTE AND no clinical, electrical or biological evidence of CAD	History of CAD or presence of typical chest pain, pathological Q waves on ECG, troponin elevation	Two readers blinded to clinical variables and CA results; consensus with a third if discrepancy	CA in all patients; blind review of CA by two experienced interventional cardiologists; consensus with a third if discrepancy	$\geq$ 50% stenosis in any epicardial coronary artery with diameter $\geq$ 2 mm	2 days

ACS: acute coronary syndrome; CA: coronary angiogram; CAD: coronary artery disease; CMR: cardiac magnetic resonance imaging; ECG: electrocardiogram; HF: heart failure; ICD: implantable cardioverter defibrillator; IDCM: ischaemic cardiomyopathy; LGE: late gadolinium enhancement; LM: left main coronary artery; LV: left ventricular; LVEF: left ventricular ejection fraction; LVEDD; left ventricular end-diastolic diameter; LVEDV; left ventricular end-diastolic volume; LVSD: left ventricular systolic dysfunction; NA: not available; NIDCM: non-ischaemic dilated cardiomyopathy; NYHA: New York Heart Association; SD: standard deviation; TTE: transthoracic echocardiography.

Table A.1 shows the overall quality of the included studies, according to QUADAS-2 recommendations [17].

Diagnostic accuracy of no st-LGE

As shown in Table 2, 55 (false negative) patients presented no st-LGE on CMR, but significant CAD; inversely, 75 (false positive) patients presented st-LGE on CMR and no CAD. The diagnostic performance of the presence of st-LGE is summarized in Fig. 3, with pooled results. Sensitivity and specificity were 87% (95% CI 0.80—0.92) and 93% (95% CI 0.89—0.96), respectively. PLR and NLR were 12.91 (95% CI 7.70—21.64) and 0.14 (95% CI 0.09—0.22), respectively. According to the Fagan diagram, and using a pre-test probability of CAD (prevalence of the disease in the tested population) of 25%, the post-test probability of CAD when st-LGE was present on CMR was 81%, and the post-test probability of CAD when no st-LGE was found on CMR

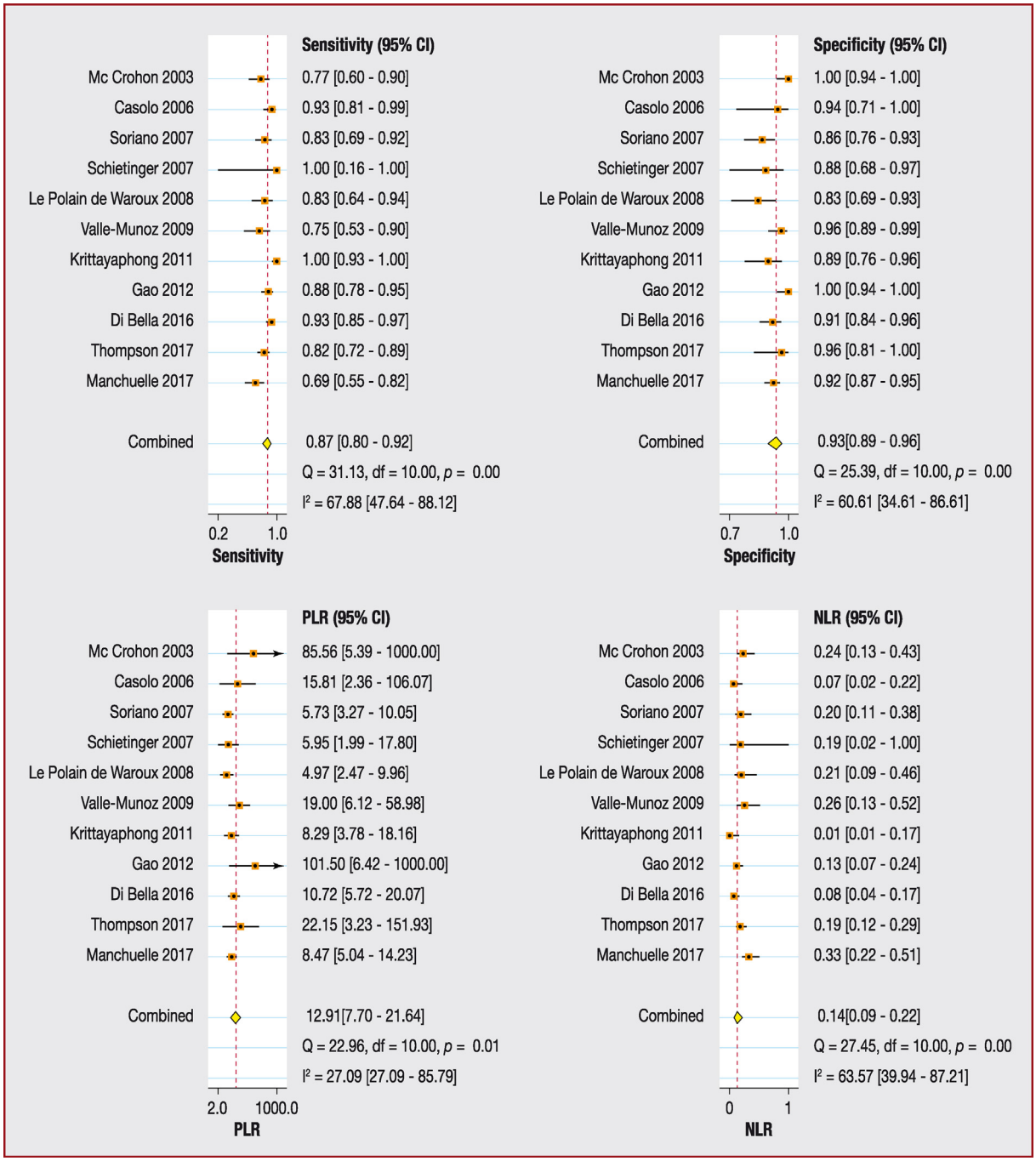

Figure 3. Diagnostic accuracy of the presence of subendocardial or transmural late gadolinium enhancement on cardiac magnetic resonance imaging to detect coronary artery disease. CI: confidence interval; NLR: negative likelihood ratio; PLR: positive likelihood ratio.

was 4% (Fig. A.1). When reported in original studies, the description of the underlying CAD in the 55 patients with significant CAD but no st-LGE on CMR is given in Table 3.

Discussion

In patients with new-onset systolic HF, CAD is known to be a leading cause, and may have important therapeutic and prognostic implications [1,19]. In some cases, angina together with electrocardiogram signs (Q waves) make the diagnosis of CAD very likely; CA is thus recommended, with the objectives of adapting medical treatment and identifying patients suitable for coronary artery revascularization, both of which may favour the recovery of myocardium contractile function affected by hibernation or stunning [20,21] and improve the patient's condition and outcomes [22].

To date, guidelines propose performing CA in patients with systolic HF in case of angina or when a non-invasive stress test is positive for ischaemia/viability in asymptomatic patients [1]. However, in practice, the interpretation of a non-invasive stress test can be highly challenging in such patients with depressed left ventricular systolic function and a remodelled left ventricle [23]. Because the aetiology of systolic HF has been shown to be CAD in about 30% of angina-free patients with no previous coronary event, several teams routinely continue to perform CA, which is considered to be the gold standard for assessing underlying CAD in this specific subset [24].

CA is, however, an invasive technique and may lead to complications — although these are rare when no percutaneous coronary intervention is performed (< 1% in current practice) [25,26]. Therefore, several authors have proposed alternative strategies for CAD detection in these patients, and CMR has been shown to be an interesting technique in this context. In addition, CMR also provides useful information about cardiac morphology and function. The present study is the largest in the field; it included 232 patients with new-onset systolic HF of unknown aetiology, who underwent both CA and CMR evaluation at a median interval of 2 days, which is the shortest ever reported. In previous literature, this delay often lasted several months or years, and sometimes was not even available [8,10]. In our study, the presence of st-LGE on CMR had a sensitivity of 69%, a specificity of 92%, a PLR of 8.47 and an NLR of 0.33 to detect the presence of significant underlying CAD.

Importantly, and as in previous studies, the definition we used for significant CAD may have affected our results; significant CAD was defined, as in most previous literature focusing on CAD [27], as the presence of a coronary artery stenosis $\geq$ 50% in any epicardial vessel with a diameter of > 2 mm. Our objective here was to not underestimate the presence of underlying CAD by choosing too stringent a definition. Of note, all CAs were assessed blind by two experienced interventional cardiologists, and consensus was reached with a third in case of discrepancies. Among the 15 patients identified as having no st-LGE but significant CAD in our study, 11 had single-vessel disease (including two with severe narrowing [> 80%]) and four had multivessel CAD. The presence of a single mild and/or distal coronary artery stenosis probably cannot solely explain the severity and extent of the left ventricular dysfunction in some cases [21]. Indeed, as suggested by Soriano et al. [10], who previously reported a correlation between the extent of st-LGE and a standardized definition of ischaemic cardiomyopathy (history of myocardial infarction and/or coronary revascularization; or stenosis $\geq$ 75% in the left main coronary artery and/or in the anterior descending coronary artery before the first diagonal branch; or two or more stenoses $\geq$ 75% in epicardial coronary arteries) [19], it could be speculated that this was a fortuitous association in some cases. However, beyond the therapeutic and prognostic implications of the presence of a ''real'' ischaemic cardiomyopathy, we believe that the presence of any CAD may also carry relevant individual information for patients with systolic HF (medical treatment, follow-up, prognostic evaluation, etc.).

To definitively assess whether the absence of st-LGE can rule out significant CAD, we also performed a comprehensive meta-analysis of the previous literature, which reported, overall, very consistent results with our study (sensitivity 69 vs 87, specificity 92 vs 93, PLR 8.47 vs 12.9, NLR 0.33 vs 0.14). The definition used for significant obstructive CAD varied across the 11 included studies, but the one used in our study was the most commonly used (Table 4) [3—12]. According to the results of this meta-analysis, the presence of st-LGE on CMR had a sensitivity of 87%, a specificity of 93%, a PLR of 12.91 and an NLR of 0.14 to detect CAD in patients with systolic HF of unknown aetiology. Of the 1227 included patients, 55 with no st-LGE had, in fact, significant CAD. PLR (''good at ruling in the disease'') and NLR (''good at ruling out the disease'') describe the discriminatory properties of positive and negative test results, respectively (i.e. the presence or absence of st-LGE). Of note, both likelihood ratios are roughly independent of prevalence rates, and state how many times more likely particular test results are in patients with disease than in those without disease (i.e. CAD). There is consensus that a PLR > 10 and an NLR < 0.1 provide highly convincing diagnostic evidence, whereas a PLR > 5 and an NLR < 0.2 provide strong diagnostic evidence [28]. When applied to our results, CMR looks useful for excluding significant CAD in most cases (NLR 0.14). Interestingly, some authors have additionally suggested that coupling CMR to a stress test or to magnetic resonance coronary angiography may further improve its diagnostic accuracy in this context [13]. In the same way, coupling CMR to a coronary computed tomography scan may also provide useful information, and may offer, in our view, the best non-invasive strategy [7].

Finally, it should be emphasized that LGE might be related to numerous causes other than CAD, and that LGE discovery on CMR may also carry relevant diagnostic (sarcoidosis, inflammatory disease, etc.) and prognostic information outside the context of CAD. As specified in our Methods section, we focused on st-LGE, which is highly specific for myocardial infarction scar.

Our study population belongs to an observational cohort of patients with new-onset HF. Nevertheless, it is the largest series including patients who underwent both CMR and CA. When focusing on our meta-analysis, a publication bias could not be ruled out, as only small-scale studies have focused on this topic in the past. Therefore, studies with low sensitivity and/or specificity may not have been

submitted by investigators or accepted by editors for futility reasons. However, Fig. A.2 is reassuring regarding this issue.

The presence of st-LGE on CMR had a sensitivity of 87% and a specificity of 93% to detect the presence of CAD in a selected population of patients with new-onset HF with LVEF $\leq$ 35% and no clinical and/or electrical evidence of CAD. Our results therefore suggest that CMR is a rather good non-invasive alternative to the systematic use of CA in such a population. However, CMR was unable to detect significant CAD in a few cases, and coupling CMR to magnetic resonance angiography or to a coronary computed tomography scan may further improve diagnostic performance. Our data and the cost-effectiveness of this approach should, however, be confirmed in a larger cohort of patients.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2018.04.004.

Disclosure of interest

The authors declare that they have no competing interest.

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