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SYSTEMATIC REVIEW AND META-ANALYSIS

Association of Isolated Coronary Microvascular Dysfunction With Mortality and Major Adverse Cardiac Events: A Systematic Review and Meta-Analysis of Aggregate Data

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BACKGROUND: The impact of coronary microvascular dysfunction (CMD), as diagnosed by reduced coronary flow reserve, on the outcomes of patients with symptoms of myocardial ischemia and nonobstructive coronary artery disease is poorly understood. We performed a systematic review and meta-analysis of observational studies to determine the association of CMD with outcomes.

METHODS AND RESULTS: We searched online databases for studies where coronary flow reserve was measured invasively or noninvasively, clinical events were recorded after determination of coronary flow reserve, and the frequency of those events was reported for patients with and without CMD. The primary outcome was all-cause mortality. The secondary outcome was major adverse cardiac events, including cardiac or cardiovascular death, nonfatal myocardial infarction, cardiac hospitalization, or coronary revascularization. Estimates of effect were calculated from crude event rates with a random-effects model. There were 122 deaths in the 4661 patients without CMD (2.6%) and 183 deaths in the 1970 patients with CMD (9.3%). The odds ratio for mortality in patients with CMD compared with those without CMD was 3.93 (95% CI, 2.91–5.30; $P<0.001$). There were 167 major adverse cardiac events in the 3742 patients without CMD (4.5%) and 245 events in the 1447 patients with CMD (16.9%). The odds ratio for major adverse cardiac events in patients with CMD compared with those without CMD was 5.16 (95% CI, 2.81–9.47; $P<0.001$).

CONCLUSIONS: CMD is associated with a nearly 4-fold increase in mortality and a 5-fold increase in major adverse cardiac events. Future studies are needed to identify effective strategies to diagnose and treat CMD.

Key Words: coronary flow reserve ■ coronary microvascular dysfunction ■ meta-analysis ■ outcomes

Chest pain is among the most common symptoms evaluated in emergency departments and outpatient clinical settings. Although the differential diagnosis is extensive, most evaluations of adults with risk factors for cardiovascular disease focus on the diagnosis of obstructive atherosclerosis of the epicardial coronary arteries, which is often considered the leading cause of myocardial ischemia and the primary driver of adverse outcomes. However, patients presenting with chest pain and found not to have obstructive coronary artery disease (CAD) on coronary angiography are increasingly recognized.[1–3] It is estimated that 3 to 4 million men and women in the United States have symptoms of myocardial

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CLINICAL PERSPECTIVE

What Is New?

- In this systematic review and meta-analysis of >5000 patients with suspected ischemia, nonobstructive epicardial coronary artery disease on coronary angiography, or absence of myocardial ischemia on stress testing, ≈30% of patients, equally divided between men and women, had abnormally reduced coronary flow reserve diagnostic of coronary microvascular dysfunction.
- In these patients, we observed a nearly 4-fold higher mortality and a 5-fold increase in major adverse cardiac events among individuals with coronary microvascular dysfunction compared with those with normal coronary microvascular function.

What Are the Clinical Implications?

- These results support the need to integrate the totality of the coronary circulation, both macrovascular and microvascular, when conceptualizing the pathophysiological characteristics, treatment, and prognosis of patients with symptoms of ischemic heart disease.

Nonstandard Abbreviations and Acronyms

CFR	coronary flow reserve
CMD	coronary microvascular dysfunction
MACE	major adverse cardiac event(s)
PET	positron emission tomography

ischemia with no obstructive CAD.[4,5] This population of patients has an elevated risk of mortality and major adverse cardiac events (MACE).[2] One potential cause of angina without obstructive CAD is coronary microvascular dysfunction (CMD), a disorder affecting the structure and/or function of the coronary microcirculation, resulting in reduced coronary flow reserve (CFR). CMD is associated with known cardiovascular risk factors, including hypertension,[6,7] diabetes mellitus,[8–10] hypercholesteremia,[11] and smoking.[12–15] However, only ≈17% of variance in CFR is explained by traditional risk factors and <1% is explained by sex.[16] Camici and Crea classified CMD into 4 main types based on their different pathophysiological characteristics: type 1, CMD in the absence of myocardial disease and obstructive CAD; type 2, CMD in myocardial disease; type 3, CMD in obstructive CAD; and type 4, iatrogenic CMD.[3]

In the absence of obstructive CAD, CFR, the ratio of coronary flow achieved at maximal coronary vasodilation/flow under baseline conditions, reflects coronary microvascular function; an abnormally reduced CFR indicates CMD.[3] CFR can be measured invasively as an adjunct to coronary angiography or noninvasively, using positron emission tomography (PET) or transthoracic Doppler echocardiography of the left anterior descending coronary artery.[17]

Patients presenting with angina and found not to have obstructive CAD are often given reassurance that their symptoms are noncardiac[18] and do not place them at an increased risk of adverse events. However, these patients, if found to have CMD on the basis of an abnormal CFR, have been shown in several single-center studies to have increased rates of all-cause or cardiac mortality and MACE. To better understand the impact of isolated CMD on outcomes, we performed a systematic review and meta-analysis of published studies to determine the association of CMD with mortality and MACE in type 1 patients without obstructive CAD or other cardiac pathological characteristics.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Protocol and Registration

We conducted a systematic review and meta-analysis of published studies, according to the Meta-Analysis of Observational Studies in Epidemiology guidelines.[19] This study was registered at the International Prospective Register of Systematic Reviews (CRD42019117036).

Information Sources

The search was implemented in April 2019 by a medical librarian (M.D.) in Ovid Medline 1946-, Embase.com 1947-, Scopus 1960-, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Cochrane Database of Systematic Reviews, and Clinicaltrials.gov using controlled vocabulary and keywords for the following: coronary flow reserve, measurement, diagnostic imaging, thermodilution, follow-up, hospitalization, MACE, and death. Articles were restricted to the English language and published literature. The full search strategy is provided in Data S1.

Study Eligibility

Studies were included in the meta-analysis if CFR was prospectively measured either invasively or

noninvasively; clinical events, including death, cardiovascular death, cardiac death, myocardial infarction, hospital admission, and/or coronary revascularization, that occurred after determination of CFR were recorded and the frequency of those events were compared between patients with normal and abnormal CFR. The definition of abnormal CFR was that used in each study and had to be defined prospectively. To limit the study population to isolated or type 1 CMD, only studies of patients with nonobstructive CAD on invasive coronary angiography (or who had a negative stress test for myocardial ischemia if coronary angiography was not performed) were included and studies of patients with a history of heart transplantation, cardiomyopathy, or aortic stenosis were excluded.

Study Selection

The study selection process is presented in Figure 1. Two independent reviewers (M.A.G., D.L.B.) initially screened the retrieved citations for potential relevance by assessment of the title and abstract to determine eligibility. The full text of the article was reviewed if the content was not clear from the abstract. Agreement was 100%. If a study was potentially relevant, the full report was assessed using the selection criteria for inclusion. In cases where there was overlap of the study

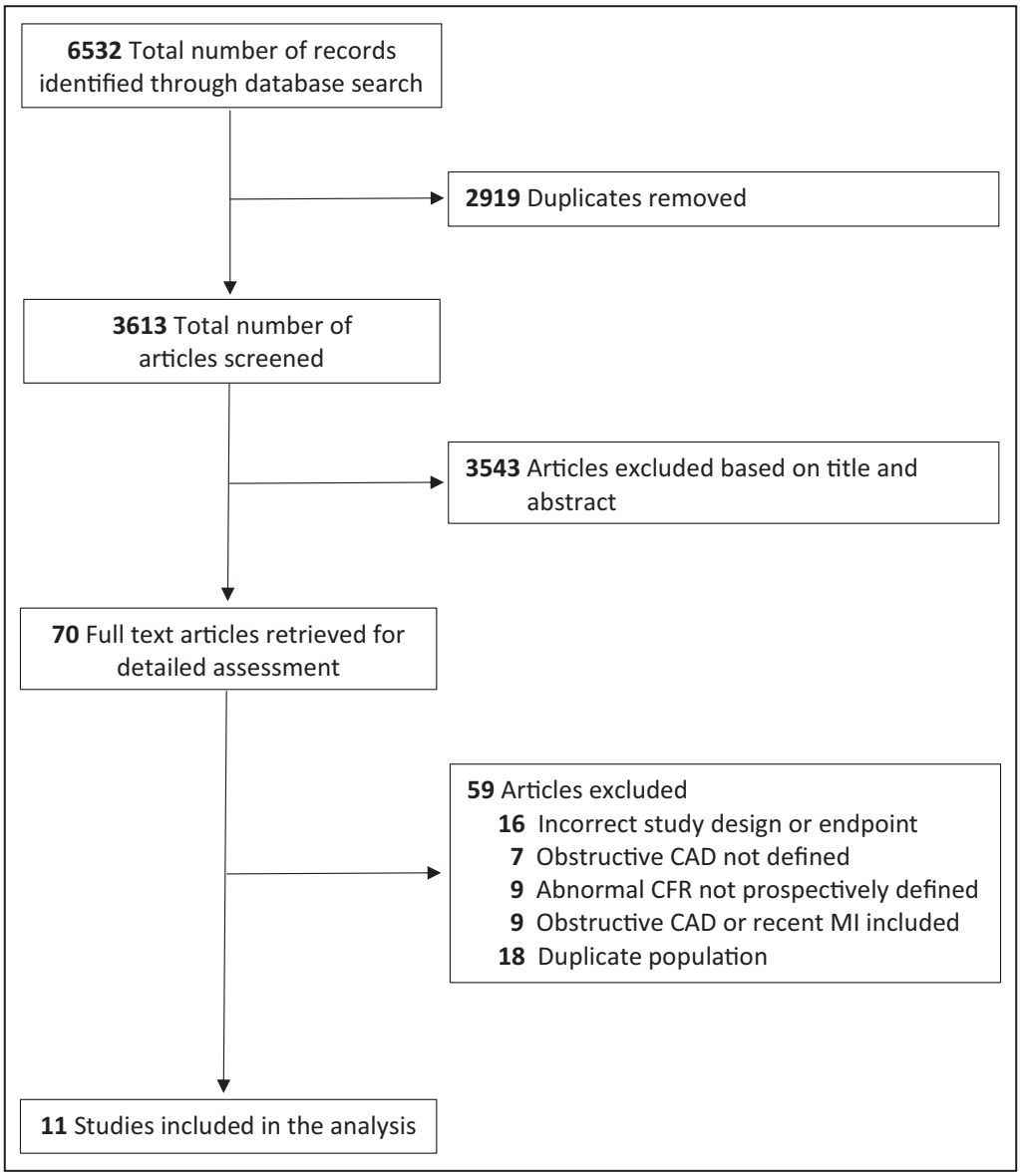

Figure 1. Flow diagram of included studies.
CAD indicates coronary artery disease; CFR, coronary flow reserve; and MI, myocardial infarction.

population or enrollment period in articles published by the same investigators, the article with the greatest number of patients was used for the analysis.

Data Extraction

The following information was extracted from each article: editorial information (lead author, publication year, study size, and duration of follow-up), study population information (number of patients for each study, percentage of female population, and age), risk factors, such as smoking, hypertension, hyperlipidemia, and diabetes mellitus, method of CFR determination, outcomes using raw data and expressed as crude event rates, and adjusted time-to-event data, expressed as hazard ratios (HRs) that dichotomized CFR as normal or abnormal, if available. If results were presented for >1 time point, the latest results were extracted. Studies reporting the HR using CFR as a continuous variable were not included. For studies that reported HRs for subgroups, but not for the overall cohort, the HRs and 95% CIs for each subgroup were extracted. When relevant information was not included in the article, the authors were contacted to obtain the data.

Outcomes

The primary outcome was all-cause mortality (or cardiac death or cardiovascular death if all-cause mortality was not provided). The secondary outcome of interest was MACE, including cardiac or cardiovascular death, nonfatal myocardial infarction, coronary revascularization, or cardiac hospitalization.

Quality Assessment

Two investigators (M.A.G., D.L.B). assessed the risk of bias using the Newcastle-Ottawa Scale[20] for cohort studies. A quality score was calculated on the basis of 3 major components of cohort studies: selection of study groups (0–4 points), comparability of study groups (0–2 points), and ascertainment of the outcome of interest (0–3 points). A higher score represents better methodologic quality. Disagreements in quality assessment were resolved by consensus.

Statistical Analysis

A meta-analysis of summary statistics from each article was performed using Comprehensive Meta-Analysis 2.0 (Biostat, Inc) software. Estimates of effect for both all-cause mortality (unless only cardiac or cardiovascular mortality was reported) and MACE were calculated from crude event rates with a random-effects model using inverse variance weighting, expressed as odds ratios (ORs) with 95% CIs, and presented in forest plots. The random-effects model provides more conservative results than a fixed-effects model and assumes that each sample comes from a different population and that the effects in these populations may also differ. Estimates of time-to-event data for mortality and MACE were calculated using a random-effects model and were expressed as HRs with 95% CIs. Statistical significance was set at $P \leq 0.05$ (2 tailed). Heterogeneity was assessed by the I^2 test. An I^2 of <25% is considered no statistical heterogeneity, 25% to 50% is considered as low statistical heterogeneity, 50% to 75% is considered as medium statistical heterogeneity, and >75% is considered as high statistical heterogeneity. Planned sensitivity analyses included the leave-one-out analysis as well as stratified analyses to assess any potential differences in method of measurement of CFR, for angiographic exclusion of obstructive CAD compared with exclusion based on lack of ischemia on stress testing, and for different numerical definitions of abnormal CFR. Because the number of studies was <10 for both mortality and MACE end points, a funnel plot assessment for publication bias was not performed as the power of the tests is too low to distinguish chance from real asymmetry.[21]

RESULTS

Study Selection and Characteristics

The electronic search identified 3613 citations that were screened by reviewing the title and abstract. A total of 70 articles were assessed in full text and 11 studies were included in the meta-analysis (Figure 1). For the calculation of ORs for mortality, 8 articles were included in the meta-analysis.[16,22–28] For the calculation of ORs for MACE, 9 articles were included in the meta-analysis.[16,23,25–31]Characteristics of included studies are presented in Table 1.

The 8 articles that reported mortality enrolled 6631 patients, of whom 1970 had CMD (30%). CFR was measured invasively in 2 studies, by PET in 3 studies, and by transthoracic Doppler echocardiography of the left anterior descending coronary artery in 3 studies. Most patients were men (52%), and the mean age of subjects ranged from 51 to 67 years.

The 9 articles that reported MACE enrolled 5189 patients, of whom 1447 had CMD (28%). CFR was measured invasively in 1 study, by PET in 4 studies, and by transthoracic Doppler echocardiography of the left anterior descending coronary artery in 4 studies. Most patients were women (52%), and the mean age ranged from 51 to 67 years. Characteristics of patients included in each study are presented in Table 2. We evaluated each study using the Newcastle-Ottawa Scale quality assessment criteria for cohort studies. Study quality is presented in Table S1. Of 9 possible points, the median score was 8 (range, 8–9).

Table 1. Characteristics of Included Studies

Author and Year	No. of Subjects	Method	Outcomes Extracted	Follow-up (mean or median), years	Abnormal CFR Cutoff
Marks et al,[22] 2004	168	Intracoronary CFR Doppler flow wire	Death	8.5	3.0
Herzog et al,[23] 2009	103	Adenosine 13N–ammonia PET	Cardiac death, nonfatal MI, cardiac hospitalization, PCI/CABG	5.5	2.0
Cortigiani et al,[29] 2010	1660	Dipyridamole stress TTE (LAD)	Nonfatal STEMI, NSTEMI, coronary revascularization	1.6	2.0
Ziadi et al,[30] 2011	414	Dipyridamole rubidium-82 PET	Cardiac death, MI, PCI/CABG, cardiac hospitalization	1.1	2.0
Cortigiani et al,[24] 2012	3548	Dipyridamole stress TTE (LAD)	Death	1.6	2.0
Lowenstein et al,[25] 2014	651	Dobutamine or dipyridamole stress TTE (LAD)	Cardiovascular death, AMI, PCI/CABG	2.9	2.0
Murthy et al,[16] 2014	1218	Vasodilator rubidium-82 PET	Cardiovascular death, AMI, PCI/CABG, hospitalization for CHF	1.3	2.0
Dikic et al,[31] 2015	200	Adenosine stress TTE (LAD)	Cardiovascular death, stroke, AMI, unstable angina, PCI/CABG	1.2	2.0
Gan et al,[26] 2017	233	Adenosine stress TTE (LAD)	Cardiovascular death, AMI, PCI/CABG	4.5	2.0
Lee et al,[27] 2018	631	Intracoronary CFR guide wire	Cardiac death, vessel-oriented composite outcomes (vessel-related death, MI, PCI)	5.1	2.0
Monroy-Gonzalez et al,[28] 2019	79	Vasodilator 13N–ammonia PET	All-cause mortality, hospitalization attributable to heart failure, late revascularization	8	2.0

13N indicates nitrogen-13; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CFR, coronary flow reserve; CHF, congestive heart failure; LAD, left anterior descending; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation MI; PCI, percutaneous coronary intervention; PET, positron emission tomography; STEMI, ST-segment–elevation MI; and TTE, transthoracic echocardiogram.

Quantitative Results

Of the 6631 patients included in the 8 studies reporting mortality, there were a total of 305 deaths. There were 122 deaths in the 4661 patients without CMD (2.6%) and 183 deaths in the 1970 patients with CMD (9.3%). Of the 8 studies, 5 reported cardiac or cardiovascular mortality only[16,23,25–27] and the remaining 3 reported all-cause mortality.[22,24,28] The median follow-up ranged from 19 months to 8.5 years. The OR for mortality in patients with CMD compared with those without CMD was 3.93 (95% CI, 2.91–5.30; P<0.001; I^2=11.7%) (Figure 2A). Three studies presented adjusted HRs for mortality.[16,23,24] The summary HR for mortality among patients with CMD was 3.62 (95% CI, 2.45–5.35; P<0.001; I^2=17.2%) (Figure 2B).

A total of 5189 patients were included in the 9 studies that reported MACE, with 412 events reported. There were 167 events in the 3742 patients with normal coronary microvascular function (4.5%) and 245 events in the 1447 patients with CMD (16.9%). The median follow-up ranged from 1 to 8 years. The OR for MACE in patients with CMD compared with those with normal coronary microvascular function was 5.16 (95% CI, 2.81–9.47; P<0.001; I^2=82.5%) (Figure 3A). Seven studies presented adjusted HRs for MACE.[23,25–27,29–31] The summary HR for MACE among patients with CMD was 4.42 (95% CI, 2.79–7.01; P<0.001; I^2=75.2%) (Figure 3B).

Sensitivity Analysis

Sensitivity analyses to assess the potential impact of qualitative differences in study design and patient selection showed that exclusion of any single trial from the analyses for mortality or MACE did not alter the overall findings of the analysis and demonstrated that no individual study had a disproportionate influence on between-study heterogeneity. Likewise, the overall findings were not modified by an analysis stratified by method of CFR measurement, use of angiography to exclude obstructive CAD, or definition of abnormal CFR (data not shown).

DISCUSSION

In this systematic review and meta-analysis of >5000 patients with suspected ischemia, nonobstructive epicardial CAD on coronary angiography, or absence of myocardial ischemia on stress testing, ≈30% of patients, equally divided between men and women, had abnormally reduced CFR diagnostic of CMD. In these patients, we observed a nearly 4-fold higher mortality

Table 2. Patient Characteristics

Study	Women, %	Mean Age, y	Diabetes Mellitus, %	Hypertension, %	Hyperlipidemia, %	Smoking, %
Marks 2004[22]						
Overall	65	52	21	85	N/A	N/A
Normal CFR	60	53	15	82	N/A	N/A
Abnormal CFR	73	51	33	88	N/A	N/A
Herzog 2009[23]						
Overall	31	60	18	60	59	42
Cortigiani 2010[29]						
Overall	55	63	19	63	46	25
Ziadi 2011[30]						
Overall	39	64	29	68	69	64
Cortigiani 2012[24]						
Overall	43	66	22	65	54	30
Normal CFR	44	64	19	64	52	30
Abnormal CFR	35	68	30	72	60	31
Lowenstein 2014[25]						
Overall	49	67	13	45	36	12
Normal CFR	49	66	11	44	37	10
Abnormal CFR	51	70	25	52	34	17
Murthy 2014[16]						
Overall	67	62	30	73	54	10
Dikic 2015[31]						
Overall	55	58	50	70	63	24
Gan 2017[26]						
Overall	53	62	12	12	50	49
Normal CFR	43	62	11	13	48	46
Abnormal CFR	61	65	17	13	55	59
Lee 2018[27]						
Overall	29	61	29	59	64	18
Normal CFR	28	61	28	58	65	19
Abnormal CFR	33	64	31	61	60	17
Monroy-Gonzalez 2019[28]						
Overall	74	51	4	34	28	18
Normal CFR	71	51	4	36	27	9
Abnormal CFR	79	51	3	32	29	29

CFR indicates coronary flow reserve and N/A, not available.

and a 5-fold increase in MACE among individuals with CMD compared with those with normal coronary microvascular function. CMD was not simply a marker for other atherogenic risk factors as synthesis of covariate-adjusted time-to-event data showed similar increases in HRs for mortality and MACE. The increased risk associated with CMD was similar across 9 countries on 4 continents, different patient populations, and regardless of the modality used to detect it, including invasive assessment during coronary angiography or noninvasive testing with PET scans or Doppler echocardiography.

Although CMD is scarcely mentioned in the American College of Cardiology/American Heart Association guideline for stable ischemic heart disease, with no recommendations provided for diagnosis or treatment,[32] it is not uncommon. Approximately 4 million Americans receive a new diagnosis of angina annually.[33,34] Up to 40% of these patients are found to have nonobstructive CAD[35] and 30% to 70% of such patients, equating to from ≈500 000 to 1 million Americans, have been demonstrated to have CMD.[36] Unfortunately, stress testing and computed tomography coronary angiography, both of which are recommended in various guidelines[37,38] for the evaluation of patients with symptoms consistent with myocardial ischemia and are

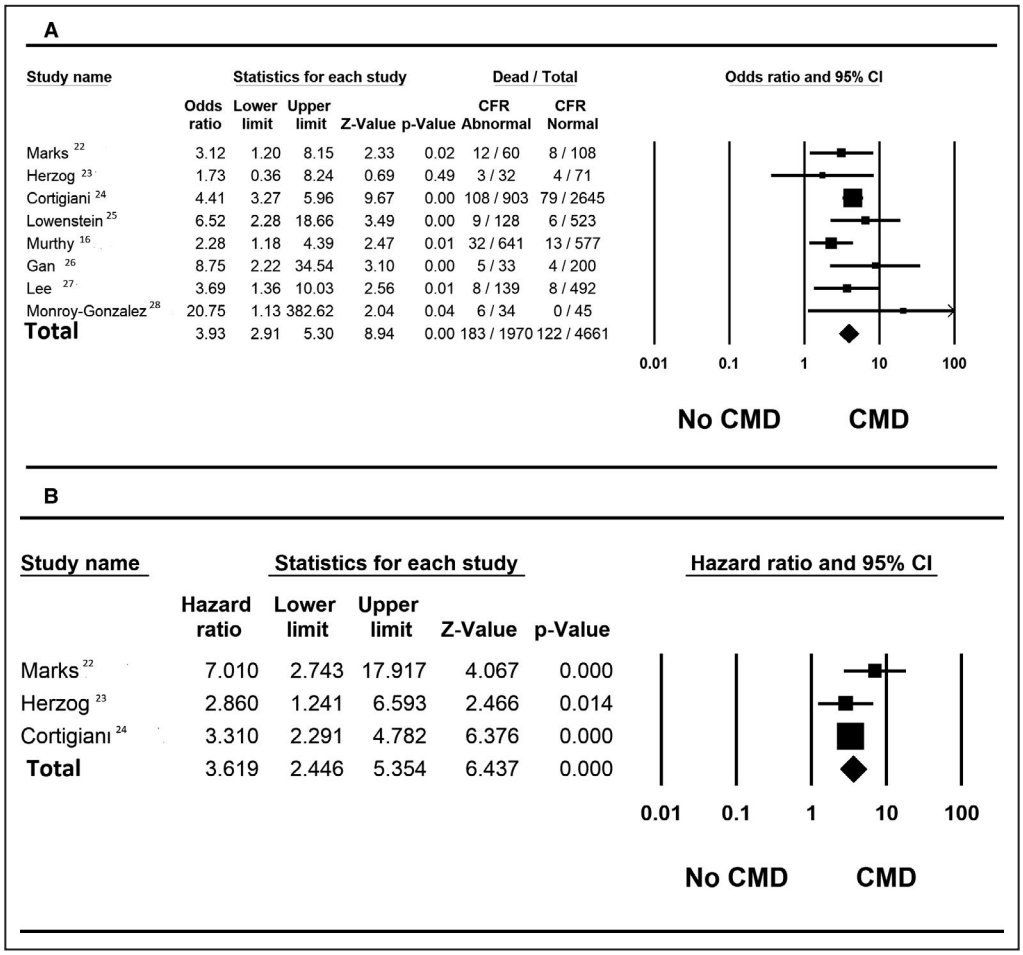

Figure 2. Meta-analysis of mortality with and without coronary microvascular dysfunction (CMD). **A**, Crude event rates. **B**, Covariate adjusted time-to-event data. Point estimates of the effect sizes are shown for individual studies. Odds ratios or hazard ratios for individual studies are indicated by squares, and 95% CIs are indicated by horizontal lines. Pooled estimates and their 95% CIs are represented by diamonds. The sizes of the squares and the diamonds are proportional to the weight assigned to the relative effect sizes. CFR indicates coronary flow reserve.

intended to diagnose obstructive epicardial CAD, fail to detect CMD.

The only prior systematic review on the prognostic value of CMD[39] included studies of patients with hypertrophic obstructive cardiomyopathy, heart failure, and aortic stenosis (type 2 CMD) who were excluded in the present analysis that was limited to type 1 CMD. Nevertheless, the findings were similar, with a relative risk for cardiovascular events of 4.58 in patients with CMD for studies measuring CFR using echocardiography and 2.44 for studies using PET.

The mechanisms by which CMD leads to adverse outcomes are poorly understood and are likely multifactorial. Coronary blood flow, in healthy individuals, is regulated at the level of the arterioles to meet myocardial oxygen demand. At rest, myocardial oxygen extraction is near maximal and, thus, adequate oxygen delivery to the myocardium is dependent on coronary blood flow. The coronary circulation coordinates the resistance in the microcirculation to maintain sufficient coronary blood flow throughout the myocardium to prevent myocardial ischemia in response to exercise or other stressful stimuli. In patients with CMD, the microcirculation is unable to adequately respond to stress, leading to myocardial ischemia as a result of functional abnormalities, such as endothelial and smooth muscle cell dysfunction, as well as structural abnormalities, including external compression and arteriolar rarefaction.[40,41] These mechanisms likely contribute to the increased mortality and MACE seen in patients with CMD compared with patients with normal coronary microvascular function. Furthermore, CMD is usually associated with mild diffuse atherosclerosis and the combination of the 2 may have important clinical implications.[40] Recent evidence suggests that CMD may also play a pivotal role in the development of heart failure with preserved ejection fraction.[42]

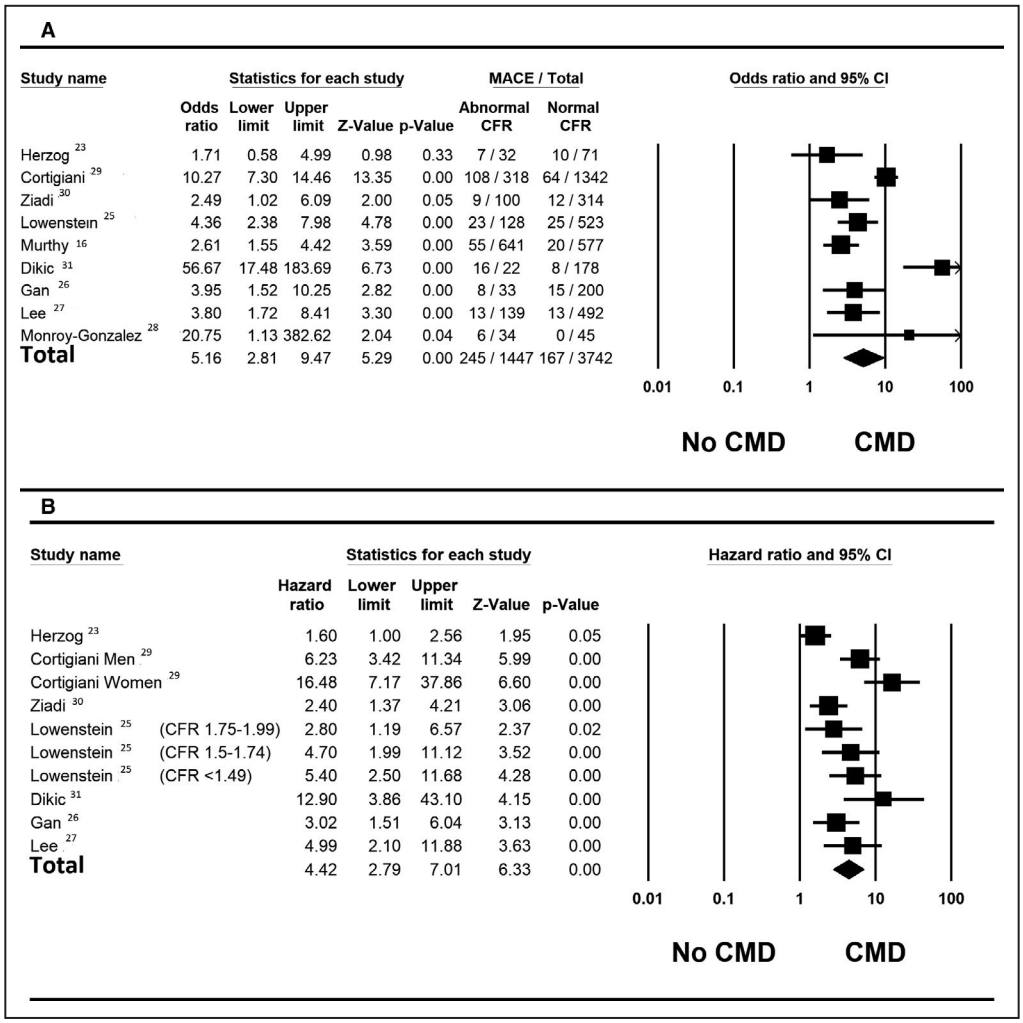

Figure 3. Meta-analysis of major adverse cardiac events (MACE) with and without coronary microvascular dysfunction (CMD).
A, Crude event rates. **B**, Covariate-adjusted time-to-event data. Point estimates of the effect sizes are shown for individual studies. Odds ratios or hazard ratios for individual studies are indicated by squares, and 95% CIs are indicated by horizontal lines. Pooled estimates and their 95% CIs are represented by diamonds. The sizes of the squares and the diamonds are proportional to the weight assigned to the relative effect sizes. CFR indicates coronary flow reserve.

The precise number of patients who undergo testing for CMD is unknown but is likely to be extremely low relative to the number of patients with ischemic symptoms and nonobstructive CAD, given the belief that ruling out obstructive CAD or myocardial ischemia identifies low-risk patients, the lack of widespread availability of cardiac PET scanners and their myocardial perfusion tracers, lack of familiarity with the use of Doppler echocardiography to interrogate the left anterior descending coronary artery, and the negative impact of invasive measurement of CFR on workflow in catheterization laboratories. The significant underdiagnosis of CMD has likely dampened the incentive to develop diagnostic algorithms and targeted therapies and has been a major hurdle even for the validation of existing therapeutics for modification of prognosis in patients with CMD. Although some existing therapies have been shown in small studies to reduce angina or improve CFR, specific treatment options that improve outcomes of patients with CMD beyond treatment of established risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, and smoking cessation, are lacking.[43]

LIMITATIONS

There are several limitations of our study. First, CFR is a continuous measure, but most studies dichotomize it using various cutoffs for normal and abnormal. Second, caution is appropriate in interpreting the results of this meta-analysis because the results are

based on data from observational studies. Although our meta-analysis of covariate-adjusted HRs found similar magnitudes of increased death and MACE as with the unadjusted crude event rates, the possibility of unequal distribution of important measured and unmeasured prognostic variables remains. Third, most of the included studies were performed at referral centers, which raises the possibility that the patients studied were not representative of the overall population. A more precise estimate of the prognostic implications of CMD will require testing in unselected populations. Fourth, we accepted absence of myocardial ischemia on stress testing as a surrogate for the absence of obstructive CAD demonstrated by coronary angiography. Although patients with CMD do not uniformly have ischemia on stress testing because of the diffuse nature of CMD, some patients do, and those patients would have been excluded by our selection criteria. Fifth, we cannot exclude the possibility that some patients with type 2 CMD were included in the cohorts analyzed. Fifth, medical therapies, including β blockers, angiotensin-converting enzyme inhibitors, aspirin, and statins, were inconsistently reported. Differential use of medical therapy could potentially influence outcomes and confound the results of the study. Sixth, we were unable to perform sex-specific analysis of CMD because of the lack of sex-specific frequency and outcomes data in the included studies. Finally, we did not include emerging technologies, such as magnetic resonance imaging as, to our knowledge, there are no magnetic resonance imaging studies of the population of interest that have prospectively defined abnormal CFR and followed up patients for adverse outcomes.

CONCLUSIONS

This systematic review and meta-analysis of aggregate data suggests that patients with isolated CMD, as demonstrated by abnormally reduced CFR, measured invasively or noninvasively, are at substantially increased risk of mortality and MACE when compared with those without CMD. These results support the need to integrate the totality of the coronary circulation, both macrovascular and microvascular, when conceptualizing the pathophysiological characteristics, treatment, and prognosis of patients with symptoms of ischemic heart disease. The recently reported CorMicA (Coronary Microvascular Angina) study demonstrated an improvement in quality of life among angina patients without obstructive CAD who underwent vasoreactivity testing and were treated on the basis of those results compared with standard care.[44] Furthermore, multiple knowledge gaps exist in our understanding of CMD, which require an intensified research agenda to establish evidence-based approaches to the diagnostic evaluation and management of patients with CMD.[45]

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Data S1
Table S1
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Supplemental Material

Data S1.

Supplemental Methods

Systematic review search strategy

Ovid Medline

08/17/17
1,184 results

Updated search = 168 results after limit to yr= “2017-Current” on 12/26/18
Updated search = 39 results after limit to yr="2019 -Current" on 04/18/19

Coronary flow reserve.mp. OR Coronary flow reserves.mp. OR coronary flow velocity reserve.mp. OR coronary flow velocity reserves.mp. OR coronary flow reserve velocity.mp. OR myocardial flow reserve.mp. OR CFVR.mp. OR (("Myocardial blood flow" adj8 (stress OR hyperemia)) AND rest).mp.

AND

(Measure*.mp. OR Quantif*.mp. OR heart output determination.mp. OR cardiac output determination.mp. OR Exp diagnostic imaging/ OR Diagnostic imaging.mp. OR Diagnostic imaging.fs. OR ((intracardiac OR EKG OR cardiac) adj2 imaging).mp. OR angiocardiograph*.mp. OR angio cardiography.mp. oR angiocardiogram.mp. OR cardioangiography.mp. OR heart angiography.mp. OR heart arteriography.mp. OR scintiangiocardiography.mp. OR cineangiocardiography.mp. OR (coronary adj1 (angiograph* OR arteriograp* OR arteriogram)).mp. OR Exp echocardiography/ OR echocardiograph*.mp. OR echocardiogram.mp. OR cardiac echography.mp. OR cardiac scanning.mp. OR cardial echography.mp. OR cardioechography.mp. OR echo cardiogram.mp. OR echo cardiography.mp. OR echocardiogram.mp. OR heart echo sounding.mp. OR heart echography.mp. OR heart scanning.mp. OR myocardium scanning.mp. OR myocardial perfusion imaging.mp. OR myocardial scintigraphy.mp. OR radionuclide ventriculography.mp. OR ("myocardial perfusion" adj7 assess*).mp. OR ("myocardial blood flow" adj7 assess*).mp. OR Exp Thermodilution/ OR thermodilution.mp. OR thermal dilution.mp. OR adenosine.mp. OR dipyridamole.mp. OR Dipyridamol.mp. OR dipyridimole.mp. oR dipiridamole.mp. OR (Doppler adj1 tte).mp. OR ((transthoracic OR flowmetry OR method OR system OR Technique) adj1 doppler).mp. OR vasodilator*.mp. OR nuclear stress test.mp. OR Exp Positron-Emission Tomography/ OR positron emission tomography.mp. OR (PET adj2 scan*).mp. OR positron emission tomographic scan.mp. OR positron emission tomographic scanning.mp. OR positron tomography.mp. OR positron-emission tomography.mp. OR magnetic resonance.mp. OR mri.mp. OR Exp ultrasonography/ OR ultrasound.mp.)

AND

(Follow-up.mp. OR Follow*.mp. OR Predictor*.mp. OR Outcome*.mp. OR Exp death/ OR Death.mp. OR Exp myocardial infarction/ OR ((myocardi* OR cardiac OR heart) adj1 infarct*).mp. OR (cardiovascular adj1 stroke*).mp. OR (heart adj1 attack*).mp. OR Exp hospitalization/ OR hospitalization.mp. OR ((hospital OR patient*) adj2 admi*).mp. OR ((hospital or patient*) adj2 readmi*).mp. OR major adverse

cardiovascular events.mp. OR major adverse cardiovascular event.mp. OR MACE.mp. OR MACEs.mp. OR Exp heart failure/ OR ((cardiac OR heart OR myocardial) adj1 failure).mp. OR ((prospective OR longitudinal) adj1 stud*).mp. OR years after.mp.)

Embase

08/18/17

2,401 results

Updated search = 390 results after limit to [18-8-2017]/sd NOT [27-12-2018]/sd on 12/26/18
Updated search = 104 results after limit to [26-12-2018]/sd NOT [19-4-2019]/sd on 04/18/19

('coronary flow reserve'/exp OR 'Coronary flow reserve':ti,ab,kw,de OR 'Coronary flow reserves':ti,ab,kw,de OR 'coronary flow velocity reserve':ti,ab,kw,de OR 'coronary flow velocity reserves':ti,ab,kw,de OR 'coronary flow reserve velocity':ti,ab,kw,de OR 'myocardial flow reserve':ti,ab,kw,de OR 'CFVR':ti,ab,kw,de OR (('Myocardial blood flow' near/8 (stress OR hyperemia)) AND rest):ti,ab,kw,de)

AND

('cardiac imaging'/exp OR 'angiocardiography'/exp OR 'echocardiography'/exp OR 'ultrasound'/exp OR 'doppler flowmetry'/exp OR 'positron emission tomography'/exp OR Measure*:ti,ab,kw,de OR Quantif*:ti,ab,kw,de OR 'heart output determination':ti,ab,kw,de OR 'cardiac output determination':ti,ab,kw,de OR 'diagnostic imaging'/exp OR 'Diagnostic imaging':ti,ab,kw,de OR ((intracardiac OR EKG OR cardiac) near/2 imaging):ti,ab,kw,de OR 'angiocardiograph*':ti,ab,kw,de OR 'angio cardiography':ti,ab,kw,de oR 'angiocardiogram':ti,ab,kw,de OR 'cardioangiography':ti,ab,kw,de OR 'heart angiography':ti,ab,kw,de OR 'heart arteriography':ti,ab,kw,de OR 'scintiangiocardiography':ti,ab,kw,de OR 'cineangiocardiography':ti,ab,kw,de OR (coronary near/1 (angiograph* OR arteriograp* OR arteriogram)):ti,ab,kw,de OR echocardiograph*:ti,ab,kw,de OR echocardiogram:ti,ab,kw,de OR 'cardiac echography':ti,ab,kw,de OR 'cardiac scanning':ti,ab,kw,de OR 'cardial echography':ti,ab,kw,de OR 'cardioechography':ti,ab,kw,de OR 'echo cardiogram':ti,ab,kw,de OR 'echo cardiography':ti,ab,kw,de OR 'echocardiogram':ti,ab,kw,de OR 'heart echo sounding':ti,ab,kw,de OR 'heart echography':ti,ab,kw,de OR 'heart scanning':ti,ab,kw,de OR 'myocardium scanning':ti,ab,kw,de OR 'myocardial perfusion imaging':ti,ab,kw,de OR 'myocardial scintigraphy':ti,ab,kw,de OR 'radionuclide ventriculography':ti,ab,kw,de OR ('myocardial perfusion' near/7 assess*):ti,ab,kw,de OR ('myocardial blood flow' near/7 assess*):ti,ab,kw,de OR 'Thermodilution'/exp OR 'thermodilution':ti,ab,kw,de OR 'thermal dilution':ti,ab,kw,de OR 'adenosine':ti,ab,kw,de OR 'dipyridamole':ti,ab,kw,de OR 'Dipyridamol':ti,ab,kw,de OR 'dipyridimole':ti,ab,kw,de oR 'dipiridamole':ti,ab,kw,de OR (Doppler near/1 tte):ti,ab,kw,de OR ((transthoracic OR flowmetry OR method OR system OR Technique) near/1 doppler):ti,ab,kw,de OR vasodilator*:ti,ab,kw,de OR 'nuclear stress test':ti,ab,kw,de OR 'positron emission tomography':ti,ab,kw,de OR (PET near/2 scan*):ti,ab,kw,de OR 'positron emission tomographic scan':ti,ab,kw,de OR 'positron emission tomographic scanning':ti,ab,kw,de OR 'positron tomography':ti,ab,kw,de OR 'positron-emission tomography':ti,ab,kw,de OR 'magnetic resonance':ti,ab,kw,de OR 'mri':ti,ab,kw,de OR 'ultrasound':ti,ab,kw,de)

AND

('follow up'/exp OR 'outcome assessment'/exp OR 'patient assessment'/exp OR 'heart infarction'/exp

OR ‘major adverse cardiac event’/exp OR ‘Follow-up’:ti,ab,kw,de OR ‘Follow*’:ti,ab,kw OR ‘Predictor*’:ti,ab,kw,de OR ‘Outcome*’:ti,ab,kw,de OR ‘death’/exp OR ‘Death’:ti,ab,kw,de OR ((myocardi* OR cardiac OR heart) near/1 infarct*):ti,ab,kw,de OR (cardiovascular near/1 stroke*):ti,ab,kw,de OR (heart near/1 attack*):ti,ab,kw,de OR ‘hospitalization’/exp OR ‘hospitalization’:ti,ab,kw,de OR ((hospital OR patient*) near/2 admi*):ti,ab,kw,de OR ((hospital or patient*) near/2 readmi*):ti,ab,kw,de OR ‘major adverse cardiovascular events’:ti,ab,kw,de OR ‘major adverse cardiovascular event’:ti,ab,kw,de OR ‘MACE’:ti,ab,kw,de OR ‘MACEs’:ti,ab,kw,de OR ‘heart failure’/exp OR ((cardiac OR heart OR myocardial) near/1 failure):ti,ab,kw,de OR ((prospective OR longitudinal) near/1 stud*):ti,ab,kw,de OR ‘years after’:ti,ab,kw,de OR 'major adverse cardiac and cerebrovascular events':ti,ab,kw OR 'major adverse cardiac and cerebrovascular event':ti,ab,kw OR 'macce':ti,ab,kw OR ‘macces’:ti,ab,kw)

Cochrane Library

08/18/17

Cochrane Database of Systematic Reviews– 0 results
Cochrane Central Register of Controlled Trials – 170 results
Database of Abstracts of Reviews of Effect – 0 results

Updated search for Cochrane Central Register of Controlled Trials (Central) = 32 results after limit to “Year first published 2017 to 2018” on 12/26/18

Updated search for Cochrane Database of Systematic Reviews = 0 results after limit to “Year first published 2017 to 2018” on 12/26/18

Updated search for Cochrane Central Register of Controlled Trials (Central) = 43 results after limit to Date added to CENTRAL trials database 26/12/2018 to 18/04/2019 on 12/26/18

Updated search for Cochrane Database of Systematic Reviews = 0 results after limit to “Year first published 2017 to 2018” on 12/26/18

(“Coronary flow reserve”:ti,ab,kw OR “Coronary flow reserves”:ti,ab,kw OR “coronary flow velocity reserve”:ti,ab,kw OR “coronary flow velocity reserves”:ti,ab,kw OR “coronary flow reserve velocity”:ti,ab,kw OR “myocardial flow reserve”:ti,ab,kw OR CFVR:ti,ab,kw OR ((“Myocardial blood flow” near/8 (stress OR hyperemia)) AND rest):ti,ab,kw)

AND

(Measure*:ti,ab,kw OR Quantif*:ti,ab,kw OR “heart output determination”:ti,ab,kw OR “cardiac output determination”:ti,ab,kw OR [mh “diagnostic imaging”] OR “Diagnostic imaging”:ti,ab,kw OR [mh “Diagnostic imaging”/ae] OR ((intracardiac OR EKG OR cardiac) near/2 imaging):ti,ab,kw OR angiocardiograph*:ti,ab,kw OR “angio cardiography”:ti,ab,kw OR “angiocardiogram”:ti,ab,kw OR “cardioangiography”:ti,ab,kw OR “heart angiography”:ti,ab,kw OR “heart arteriography”:ti,ab,kw OR “scintiangiocardiography”:ti,ab,kw OR “cineangiocardiography”:ti,ab,kw OR (coronary near/1 (angiograph* OR arteriograp* OR arteriogram)):ti,ab,kw OR [mh echocardiography] OR echocardiograph*:ti,ab,kw OR “echocardiogram”:ti,ab,kw OR “cardiac echography”:ti,ab,kw OR “cardiac scanning”:ti,ab,kw OR “cardial echography”:ti,ab,kw OR “cardioechography”:ti,ab,kw OR “echo cardiogram”:ti,ab,kw OR “echo cardiography”:ti,ab,kw OR “echocardiogram”:ti,ab,kw OR “heart echo

sounding":ti,ab,kw OR "heart echography":ti,ab,kw OR "heart scanning":ti,ab,kw OR "myocardium scanning":ti,ab,kw OR "myocardial perfusion imaging":ti,ab,kw OR "myocardial scintigraphy":ti,ab,kw OR "radionuclide ventriculography":ti,ab,kw OR ("myocardial perfusion" near/7 assess*):ti,ab,kw OR ("myocardial blood flow" near/7 assess*):ti,ab,kw OR [mh Thermodilution] OR "thermodilution":ti,ab,kw OR "thermal dilution":ti,ab,kw OR "adenosine":ti,ab,kw OR "dipyridamole":ti,ab,kw OR "Dipyridamol":ti,ab,kw OR "dipyridimole":ti,ab,kw OR "dipiridamole":ti,ab,kw OR (Doppler near/1 tte):ti,ab,kw OR ((transthoracic OR flowmetry OR method OR system OR Technique) near/1 doppler):ti,ab,kw OR vasodilator*:ti,ab,kw OR "nuclear stress test":ti,ab,kw OR [mh "Positron-Emission Tomography"] OR "positron emission tomography":ti,ab,kw OR (PET near/2 scan*):ti,ab,kw OR "positron emission tomographic scan":ti,ab,kw OR "positron emission tomographic scanning":ti,ab,kw OR "positron tomography":ti,ab,kw OR "positron-emission tomography":ti,ab,kw OR "magnetic resonance":ti,ab,kw OR "mri":ti,ab,kw OR [mh ultrasonography] OR ultrasound:ti,ab,kw)

AND

(Follow-up:ti,ab,kw OR Follow*:ti,ab,kw OR Predictor*:ti,ab,kw OR Outcome*:ti,ab,kw OR [mh death] OR Death:ti,ab,kw OR [mh "myocardial infarction"] OR ((myocardi* OR cardiac OR heart) near/1 infarct*):ti,ab,kw OR (cardiovascular near/1 stroke*):ti,ab,kw OR (heart near/1 attack*):ti,ab,kw OR [mh hospitalization] OR hospitalization:ti,ab,kw OR ((hospital OR patient*) near/2 admi*):ti,ab,kw OR ((hospital or patient*) near/2 readmi*):ti,ab,kw OR "major adverse cardiovascular events":ti,ab,kw OR "major adverse cardiovascular event":ti,ab,kw OR MACE:ti,ab,kw OR MACEs:ti,ab,kw OR [mh "heart failure"] OR ((cardiac OR heart OR myocardial) near/1 failure):ti,ab,kw OR ((prospective OR longitudinal) near/1 stud*):ti,ab,kw OR "years after":ti,ab,kw)

Scopus

08/18/17

1,756 results

Updated search = 129 results after the limit: LIMIT-TO (PUBYEAR , 2018) on 12/26/18

Updated search = 41 results after the limit: LIMIT-TO (PUBYEAR , 2019) on 04/18/19

((TITLE-ABS-KEY ("Follow-up")) OR (TITLE-ABS-KEY (follow*)) OR (TITLE-ABS-KEY (predictor*)) OR (TITLE-ABS-KEY (outcome*)) OR (TITLE-ABS-KEY ("Death")) OR (TITLE-ABS-KEY ((myocardi* OR cardiac OR heart) W/1 infarct*)) OR (TITLE-ABS-KEY (cardiovascular W/1 stroke*)) OR (TITLE-ABS-KEY (heart W/1 attack*)) OR (TITLE-ABS-KEY ("hospitalization")) OR (TITLE-ABS-KEY ((hospital OR patient*) W/2 admi*)) OR (TITLE-ABS-KEY ((hospital OR patient*) W/2 readmi*)) OR (TITLE-ABS-KEY ("major adverse cardiovascular events")) OR (TITLE-ABS-KEY ("major adverse cardiovascular event")) OR (TITLE-ABS-KEY ("MACE")) OR (TITLE-ABS-KEY ("MACEs")) OR (TITLE-ABS-KEY ((cardiac OR heart OR myocardial) W/1 failure)) OR (TITLE-ABS-KEY ((prospective OR longitudinal) W/1 stud*)) OR (TITLE-ABS-KEY ("years after"))) **AND** ((TITLE-ABS-KEY (measure*)) OR (TITLE-ABS-KEY (quantif*)) OR (TITLE-ABS-KEY ("heart output determination")) OR (TITLE-ABS-KEY ("cardiac output determination")) OR (TITLE-ABS-KEY ("Diagnostic imaging")) OR (TITLE-ABS-KEY ((intracardiac OR ekg OR cardiac) W/2 imaging)) OR (TITLE-ABS-KEY ("angiocardiograph*")) OR (TITLE-ABS-KEY ("angio cardiography")) OR (TITLE-ABS-KEY ("angiocardiogram")) OR (TITLE-ABS-KEY ("cardioangiography")) OR (TITLE-ABS-KEY ("heart

angiography")) OR (TITLE-ABS-KEY ("heart arteriography")) OR (TITLE-ABS-KEY ("scintiangiocardiography")) OR (TITLE-ABS-KEY ("cineangiocardiography")) OR (TITLE-ABS-KEY (coronary W/1 (angiograph* OR arteriograp* OR arteriogram))) OR (TITLE-ABS-KEY (echocardiograph*)) OR (TITLE-ABS-KEY (echocardiogram)) OR (TITLE-ABS-KEY ("cardiac echography")) OR (TITLE-ABS-KEY ("cardiac scanning")) OR (TITLE-ABS-KEY ("cardial echography")) OR (TITLE-ABS-KEY ("cardioechography")) OR (TITLE-ABS-KEY ("echo cardiogram")) OR (TITLE-ABS-KEY ("echo cardiography")) OR (TITLE-ABS-KEY ("echocardiogram")) OR (TITLE-ABS-KEY ("heart echo sounding")) OR (TITLE-ABS-KEY ("heart echography")) OR (TITLE-ABS-KEY ("heart scanning")) OR (TITLE-ABS-KEY ("myocardium scanning")) OR (TITLE-ABS-KEY ("myocardial perfusion imaging")) OR (TITLE-ABS-KEY ("myocardial scintigraphy")) OR (TITLE-ABS-KEY ("radionuclide ventriculography")) OR (TITLE-ABS-KEY ("myocardial perfusion" W/7 assess*)) OR (TITLE-ABS-KEY ("myocardial blood flow" W/7 assess*)) OR (TITLE-ABS-KEY ("thermodilution")) OR (TITLE-ABS-KEY ("thermal dilution")) OR (TITLE-ABS-KEY ("adenosine")) OR (TITLE-ABS-KEY ("dipyridamole")) OR (TITLE-ABS-KEY ("Dipyridamol")) OR (TITLE-ABS-KEY ("dipyridimole")) OR (TITLE-ABS-KEY ("dipiridamole")) OR (TITLE-ABS-KEY (doppler W/1 tte)) OR (TITLE-ABS-KEY ((transthoracic OR flowmetry OR method OR system OR technique) W/1 doppler)) OR (TITLE-ABS-KEY (vasodilator*)) OR (TITLE-ABS-KEY ("nuclear stress test")) OR (TITLE-ABS-KEY ("positron emission tomography")) OR (TITLE-ABS-KEY (pet W/2 scan*)) OR (TITLE-ABS-KEY ("positron emission tomographic scan")) OR (TITLE-ABS-KEY ("positron emission tomographic scanning")) OR (TITLE-ABS-KEY ("positron tomography")) OR (TITLE-ABS-KEY ("positron-emission tomography")) OR (TITLE-ABS-KEY ("magnetic resonance")) OR (TITLE-ABS-KEY ("mri")) OR (TITLE-ABS-KEY ("ultrasound"))) **AND** ((TITLE-ABS-KEY ("Coronary flow reserve")) OR (TITLE-ABS-KEY ("Coronary flow reserves")) OR (TITLE-ABS-KEY ("coronary flow velocity reserve")) OR (TITLE-ABS-KEY ("coronary flow velocity reserves")) OR (TITLE-ABS-KEY ("coronary flow reserve velocity")) OR (TITLE-ABS-KEY ("myocardial flow reserve")) OR (TITLE-ABS-KEY ("CFVR")) OR (TITLE-ABS-KEY (("Myocardial blood flow" W/8 (stress OR hyperemia)) AND rest)))

Clinicaltrials.gov

8/17/17
45 results

Updated search = 11 results after limit “First posted from 08/01/2017 to 12/26/2018” on 12/26/18
Updated search = 19 results after limit “First posted from 12/26/2018 to 04/18/2019” on 12/26/18

(coronary flow reserve OR coronary flow velocity) AND follow up

Table S1. Results of quality appraisal using the Newcastle-Ottawa scale.

Study	Selection				Compara-bility	Outcome			Total Score
	Representative-ness of the exposed cohort	Select-ion of the non-exposed cohort	Ascertain-ment of exposure	Demonstra-tion that outcome was not present at start of study	Compara-bility of the cohorts	Assess-ment	Adequa-cy of follow-up duration	Complete-ness of follow-up	
Marks 2004[21]	*	*	*	*	**	*	*		8
Herzog 2009[22]	*	*	*	*	**	*	*	*	9
Cortigiani 2010[29]	*	*	*	*	**	*	*		8
Ziadi 2011[30]	*	*	*	*	**	*	*	*	9
Cortigiani 2012[23]	*	*	*	*	**	*	*		8
Lowenstein 2014[24]	*	*	*	*	**	*	*		8
Murthy 2014[25]	*	*	*	*	**	*	*		8
Dikic 2015[31]	*	*	*	*	**	*	*		8
Gan 2017[26]	*	*	*	*	**	*	*	*	9
Lee 2018[27]	*	*	*	*	**	*	*		8
Monroy-Gonzalez 2018[28]	*	*	*	*	**	*	*	*	9