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Outcomes after inappropriate nuclear myocardial perfusion imaging: A meta-analysis

Islam Y Elgendy, MD[a], **Ahmed Mahmoud, MD**[a], **Jonathan J Shuster, PhD**[b], **Rami Doukky, MD,MSc**[c], and **David E Winchester, MD,MS**[d]

[a]Department of Medicine, University of Florida College of Medicine, Gainesville, FL

[b]Department of Health Outcomes and Policy, University of Florida, Gainesville, FL

[c]Division of Cardiology, Rush University Medical Center, Chicago, IL

[d]Division of Cardiovascular Medicine, University of Florida College of Medicine, Gainesville, FL

Abstract

Background—The relationship between inappropriate MPI and cardiovascular outcomes is poorly understood. We sought to systematically review the literature on appropriate use criteria (AUC) for MPI, including temporal trend of inappropriate testing and resulting cardiovascular outcomes.

Methods—We searched the MEDLINE database for studies related to AUC and MPI. The co-primary outcomes were abnormal test results and the presence of cardiac ischemia. Random effects odds ratios (OR) were constructed using DerSimonian-Laird method.

Results—A total of 22 studies with 23,443 patients were included. The prevalence of inappropriate testing was 14.8 % [95% confidence interval (CI) 11.6–18.7%]. Inappropriate MPI studies were less likely to be abnormal (OR 0.41 95% CI 0.35–0.49, p<0.0001) and to demonstrate ischemia (OR 0.40, 95% CI 0.24–0.67, p<0.0001) compared to appropriate testing. No difference in the rate of inappropriate tests was detected based on the midpoint of the enrollment year (p=0.54). The pattern of ordering inappropriate studies was not different between cardiology and non-cardiology providers (OR 0.74, 95% CI 0.51–1.06, p=0.10).

Conclusion—Inappropriate MPI studies are less likely to yield abnormal results or demonstrate myocardial ischemia. The rate of inappropriate MPI has not decreased over time.

Introduction

Myocardial perfusion imaging (MPI) remains a cornerstone for diagnosis and risk stratification in patients with coronary artery disease.[1,2] The volume of MPI grew for the past 3 decades.[3–5] Substantial growth in the use of MPI has generated concerns for overuse of this technology.[6,7] To address this concern, the American College of Cardiology (ACC)

Corresponding author: David E Winchester, MD MS, 1600 SW Archer Rd, Box 100277, Gainesville, FL 32610, david.winchester@medicine.ufl.edu.

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and other specialty societies developed appropriate use criteria (AUC) for MPI in 2005, which was later revised in 2009.[8,9]

Since the development of the AUC for MPI, several studies have described the prevalence of inappropriate MPI. Most of these studies were conducted in single centers yielding variable rates of inappropriate MPI testing.[10–19] The process of rating indications as "inappropriate" is supposed to account for low clinical utility in those scenarios; however, few studies have reported on the relationship between inappropriate MPI and cardiovascular outcomes.[15,20–22] A recent analysis of appropriateness across imaging modalities showed a decrease in trans-thoracic echocardiography and computerized tomography angiography, but not with stress echocardiography or SPECT; however this study did not evaluate all studies in temporal sequence and did not address the relationship between inappropriate studies and cardiovascular outcomes.[23]

We conducted this systematic review and meta-analysis to demonstrate the relationship between inappropriate MPI and the frequency of abnormal test results and myocardial ischemia. Secondarily, we intended to test the hypothesis that inappropriate MPI testing is less common when ordered by cardiology providers.

Methods

Data sources

We performed a computerized literature search of the MEDLINE database without language restriction from January 2005 until December 2014 using the search strategy shown in Figure 1. To ensure that no potentially important studies were missed, the reference lists from the retrieved articles were also checked.

Selection criteria

We selected studies that: 1) reported the prevalence of appropriate and inappropriate MPI testing according to either the 2005 or 2009 AUC for MPI, 2) described clinical outcomes among both groups, or 3) reported the variation among clinicians in ordering MPI tests. If the individual study used both criteria for evaluation of the MPI tests ordered, we utilized the data based on the 2009 AUC. We excluded studies that reported only a single arm (either appropriate or inappropriate MPI testing). If multiple reports were made from the same data, we preferentially used reports that included report of cardiovascular outcomes.

Data Extraction

Two authors (IYE and AM) independently extracted data on sample characteristics, sample size, intervention strategies, outcome measures, and other study characteristics from the included studies using a standardized form. Any discrepancies were resolved by consensus of the authors. For all clinical outcomes, we tabulated the number of events that occurred in each cohort within the study.

Outcomes and Definitions

The co-primary outcomes were the rate of abnormal test results and the presence of cardiac ischemia compared between inappropriate and appropriate or uncertain MPI. We used the definition of cardiac ischemia as reported in the individual studies. Other outcomes included all-cause mortality, non-fatal myocardial infarction (MI), the combined outcome of mortality or MI, cardiac catheterization, and revascularization.

Statistical Analysis

Since none of the studies had low event rates (arbitrarily defined as an expected event rate in any cell below 5.0), summary random effects odds ratio (OR) were constructed using the DerSimonian-Laird method.[32] This meta-analysis was conducted based on the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[33] An inverse variance weighted meta-regression for the rate of inappropriate testing versus the midpoint of the enrolment period in the individual studies was conducted. All p-values were 2-tailed, with statistical significance declared at P≤0.025. All overall estimates are accompanied by 95% confidence intervals (CI). All meta-analyses were performed using Comprehensive Meta-Analysis version 3.0 (Biostat; Englewood, New Jersey), and the meta-regression was conducted using SAS 9.3 (SAS Institute, Cary NC).

Results

A total of 22 studies with 23,443 patients were included in our analysis.[10–20,34–44] The results of our search strategy are illustrated in Figure 1. The 2005 AUC were used by 6 studies,[16,18,19,39,42,44] and the remainder used the 2009 AUC.[10–15,17,20,34–38,40,41,43] Single-photon emission computed tomography (SPECT) was the modality utilized in most of the studies,[13–20,34–36,38,39,41–44] one study reported using positron emission tomography (PET),[12] while the remainder of the studies did not specify.[10,11,37,40] Among the included studies, 5 were conducted outside the United States.[11,17,34,38,41] Patients were recruited from the outpatient setting in 3 studies,[20,35,37] from an inpatient setting in 1 study,[10] and from both settings in 13 studies.[11–16,19,34,36,38,40,42,43] Overall, the summary rate for inappropriate testing was 14.8% (95% CI 11.6–18.7%). The baseline characteristics and the percentage of inappropriate testing among the included studies are reported in Table 1. In Table 2, we summarize the quality of the studies included and report the most common reason for inappropriate MPI in the individual studies.

Primary outcomes

The relationship between inappropriate MPI and abnormal test results were reported by 8 studies reported the incidence of abnormal test results,[10,12,17,18,20,34,40,41] while 6 studies described on myocardial ischemia.[10,12,20,34,36,40] Individual study definitions for ischemia are supplied in supplemental Table 1. Inappropriate MPI studies were less likely to be abnormal 15.6% vs 42.0% (OR 0.41 95% CI 0.35–0.49, p<0.0001) compared to appropriate tests (Figure 2). Additionally, inappropriate MPI testing was less likely to demonstrate cardiac ischemia 6.1% vs 18.5 % (OR 0.40, 95% CI 0.24–0.67, p<0.0001) when compared to appropriate testing (Figure 3).

Additional analyses

No significant difference was observed in the pattern of ordering inappropriate tests between cardiology and non-cardiology providers (OR 0.74, 95% CI 0.51–1.06, p=0.10) (Figure 4). No significant correlation was observed between the rate of inappropriate testing and the midpoint of the enrollment year (0.52%, 95% CI -1.16% to -2.20% per year, p=0.54) (Figure 5). Meta-analysis could not be performed for the risk of all-cause mortality, MI, the combined outcome of mortality or MI, cardiac catheterization, or revascularization due to the limited number of studies reporting these outcomes. In Table 3, we summarize the rate of all-cause mortality, MI, the combined outcome of mortality or MI, cardiac catheterization, and revascularization in the individual studies. The study by Doukky et al was both large and had a notably different point estimate for inappropriate MPI.[20] To evaluate the impact of this study on our investigation, we excluded it in a sensitivity analysis. Doing this, the summary estimate of inappropriate testing was 14.0% (95% CI 12.1% to 16.2%) and estimates for the co-primary outcomes were not changed; (OR 0.41, 95% CI 0.33–0.50, p< 0.0001) for abnormal test results, and (OR 0.35, 95% CI 0.18–0.62, p=0.002) for ischemia.

Discussion

AUC are based on the premise that MPI testing for inappropriate indications will not benefit patients. In this meta-analysis of 22 studies including 23,443 patients, inappropriate MPI are consistently less likely to be abnormal or demonstrate ischemia as compared to appropriate studies. Using currently available data, we were unable to analyze relationship between inappropriate MPI and more substantial cardiovascular outcomes, such as catheterization, MI, and death. While the data for these outcomes were not sufficient to meta-analyze, individual studies demonstrated a substantial effect.[20,21] Doukky et al showed a dramatic difference in cardiac events despite having a notably higher rate of inappropriate MPI as compared to other studies.[20] Our analysis suggests that systems such as the AUC are valid strategies for focusing limited health care resources on those patients with the most to benefit from testing. It is important to mention that the 2013 AUC for stable ischemic heart disease now uses the term rarely appropriate as opposed to inappropriate"; 18 out of 80 indications are rated as "rarely appropriate".[45]

Since the first AUC for MPI were published 10 years ago, a reasonable assumption is that growing awareness of recommendations about inappropriate testing might alter patterns of care. Although Fonseca et al analyzed the temporal trends in AUC for SPECT,[23] our analysis included 7 additional studies.[10,11,13,14,34–36] Using meta-regression, we analyzed our data for any change in the rate of inappropriate testing over time. If any change has occurred, the magnitude of change (0.52%, 95% CI -1.16% to -2.20 in our analysis). Larger scale real world data from programs such as FOCUS and ImageGuide™ may make it possible to ascertain such temporal trends in the future.[46,47] We observed a wide range of rates of inappropriate MPI. In one study with the highest inappropriate rate, the patient population was based on multiple community practices, in contrast to the vast majority of the studies included in this analysis which were conducted in single-tertiary care centers. Differences in patient populations and behavior of ordering physicians may have contributed

to this difference. In our sensitivity analysis excluding this study, our results did not change.[20]

Compared with non-cardiology providers, cardiology providers did not order significantly fewer inappropriate MPI in our analysis. The publications addressing this question have shown mixed results with some finding a difference,[16,42] and other with no difference.[12,24] Doukky et al were able to demonstrate that if a difference does exist, the likely explanation relates to the patient population being tested and not to an enhanced knowledge base by cardiology providers.[24] The data were insufficient to make other comparisons about practice setting, such as geographic differences, US versus non-US investigations, academic versus community institutions, and inpatient versus outpatient setting. This last comparison may become more challenging as the next iteration of AUC shift away from modality based rating systems to multimodality ratings based on patient presentations.

Few studies on interventions to reduce inappropriate testing have been published. Some of the heterogeneous approaches attempted include education, peer review and feedback, and point-of-care decision support systems.[19,29,35] Among these studies, education alone appeared insufficient to reduce inappropriate MPI while the addition of other system changes resulted in a decrease. These findings are in accord with recent investigations and systematic reviews, which demonstrate that decision support systems can reduce unnecessary imaging.[48–50] Another strategy that has been considered is prior authorization, although a recent analysis on this strategy suggests no effect on the rate of inappropriate MPI among patients insured by private carriers as compared to Medicare which does not implement prior authorization measures.[51]

Meta-analysis of AUC is subject to a number of limitations. We relied on the AUC classification systems used by the original authors. Multiple studies have demonstrated that inter-rater and intra-rater variation is not negligible; however, we could not ascertain in which direction this might bias our results.[19,30] One study showed the AUC inter-rater variation for non-cardiologists raters was modest compared to cardiologists (κ= 0.51).[52] As noted previously, we could not comment on the risk of cardiac events due to the limited number of studies reporting these outcomes. Because we lacked access to patient level data, we could not analyze appropriateness of MPI based on patient characteristics such as sex, obesity, or diabetes since this has been described to increase the risk of bias.[53] Publication bias is a potential limitation to meta-analyses. Finally, we included studies that used 2 different AUC (2005 & 2009), however; only one study utilizing the 2005 AUC was included in the analysis of the co-primary outcomes.[18]

New Knowledge Gained

Inappropriate MPI are less likely to yield abnormal results or determine myocardial ischemia. There has not been a significant reduction in the rates of inappropriate MPI testing with time. No differences were observed in the pattern of ordering inappropriate MPI between cardiology and non-cardiology providers.

Conclusions

We observed a wide range of inappropriate MPI rates, and estimate the overall rate among published studies to be 14.8%. Inappropriate MPI tests are consistently less likely to be abnormal or demonstrate ischemia than appropriate MPI, thus limiting their clinical utility. Currently available literature is insufficient to meta-analyze the relationship between death, MI, and inappropriate MPI. The rate of inappropriate MPI does not appear to have changed significantly over the time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACC	American College of Cardiology
AUC	appropriate use criteria
CI	confidence interval
MI	myocardial infarction
MPI	myocardial perfusion imaging
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
OR	odds ratio
PET	positron emission tomography
SPECT	single-photon emission computed tomography

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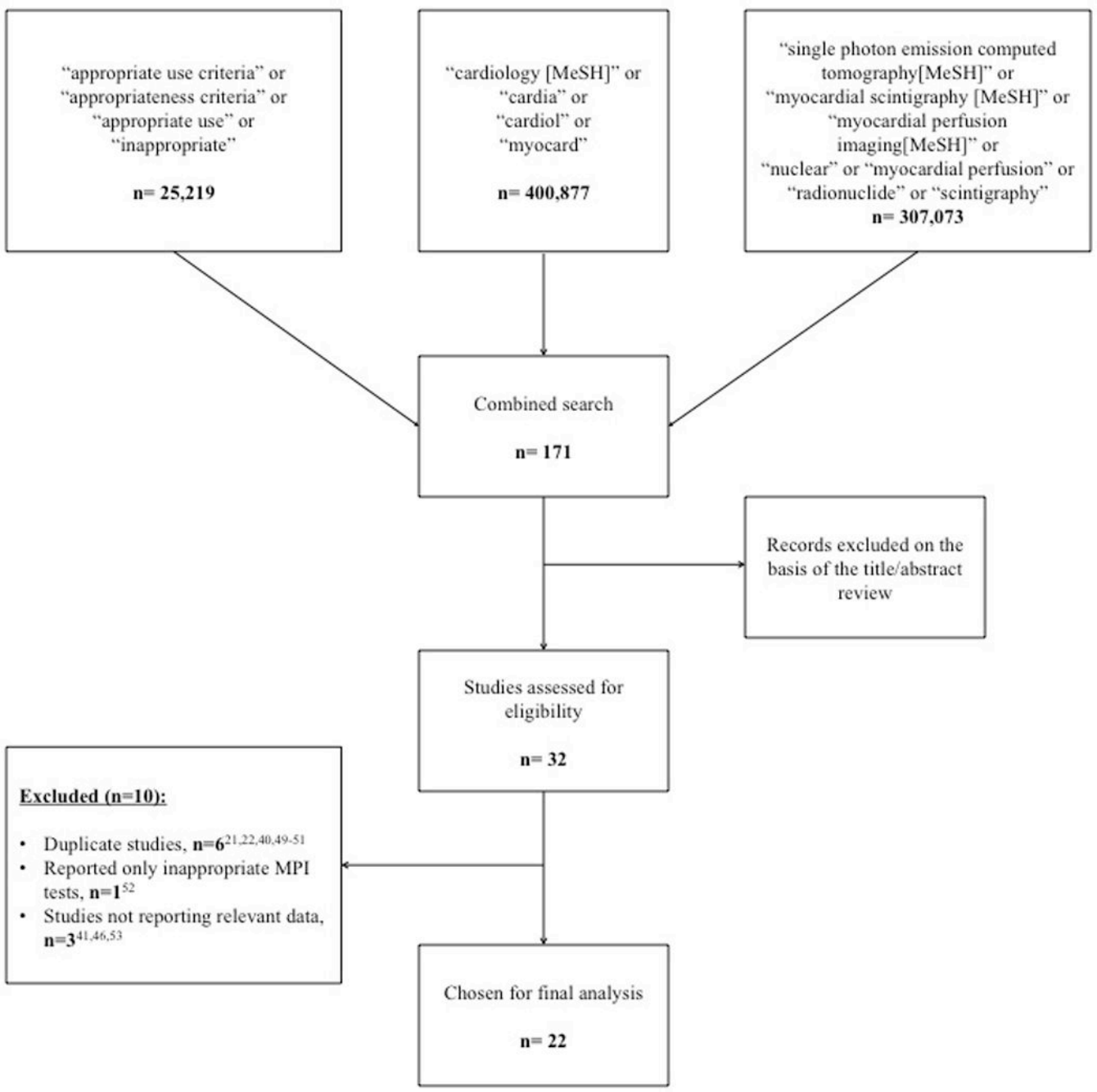

Figure 1.

Study Selection Flow Diagram.

Summary of how the systematic search was conducted and eligible studies were identified.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Events / Total: Inappropriate	Events / Total: Appropriate
Winchester	0.215	0.076	0.609	-2.893	0.004	4 / 53	114 / 414
Mahajan	0.410	0.223	0.752	-2.883	0.004	15 / 118	70 / 267
Medolago	0.355	0.249	0.506	-5.731	0.000	49 / 149	1040 / 1793
Doukky	0.444	0.312	0.631	-4.527	0.000	48 / 688	119 / 823
Nelson	0.551	0.254	1.197	-1.506	0.132	9 / 58	53 / 212
Gholamrez	0.227	0.086	0.598	-3.004	0.003	5 / 49	73 / 219
Koh	0.560	0.389	0.805	-3.129	0.002	44 / 162	532 / 1331
Mehta	0.382	0.266	0.549	-5.204	0.000	49 / 154	517 / 940
	0.416	0.352	0.492	-10.270	0.000		

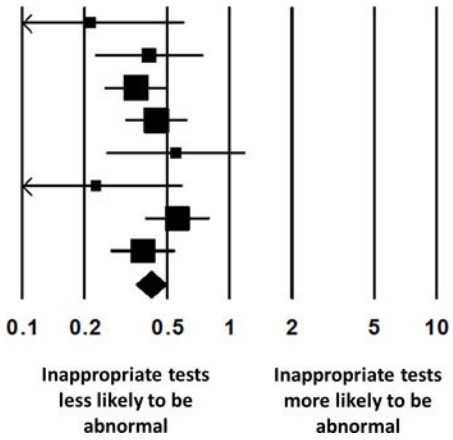

Figure 2.

Summary plot for abnormal test results.

The relative size of the data markers indicates the weight of the sample size from each study.

CI = confidence interval

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Events / Total: Inappropriate	Events / Total: Appropriate
Winchester	0.128	0.017	0.947	-2.014	0.044	1 / 53	54 / 414
Mahajan	0.452	0.204	1.003	-1.952	0.051	8 / 118	37 / 267
Medolago	0.148	0.069	0.318	-4.886	0.000	7 / 149	448 / 1793
Khawaja	0.534	0.223	1.277	-1.410	0.158	7 / 66	32 / 176
Doukky	0.565	0.382	0.838	-2.842	0.004	40 / 688	81 / 823
Nelson	0.700	0.276	1.773	-0.752	0.452	6 / 58	30 / 212
	0.401	0.241	0.668	-3.515	0.000		

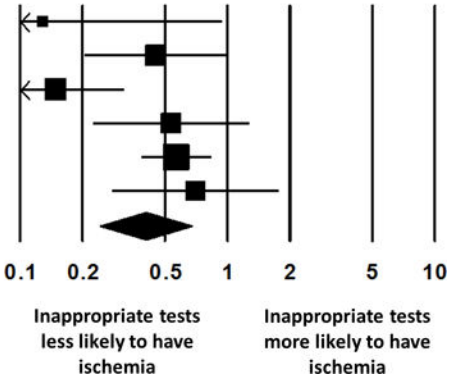

Figure 3.

Summary plot for detection of cardiac ischemia.

The relative size of the data markers indicates the weight of the sample size from each study.

CI = confidence interval

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Events / Total NonCardio	Events / Total Cardio
Doukky	1.899	1.244	2.900	2.970	0.003	654 / 1363	34 / 104
Winchester	1.063	0.604	1.873	0.213	0.831	36 / 360	21 / 222
Lalude	0.701	0.360	1.365	-1.045	0.296	42 / 303	14 / 75
Singh	0.828	0.318	2.159	-0.385	0.700	8 / 149	10 / 156
Gupta	1.997	0.897	4.446	1.694	0.090	25 / 178	9 / 119
Druz	1.938	1.169	3.213	2.564	0.010	58 / 256	26 / 198
	1.357	0.944	1.952	1.649	0.099		

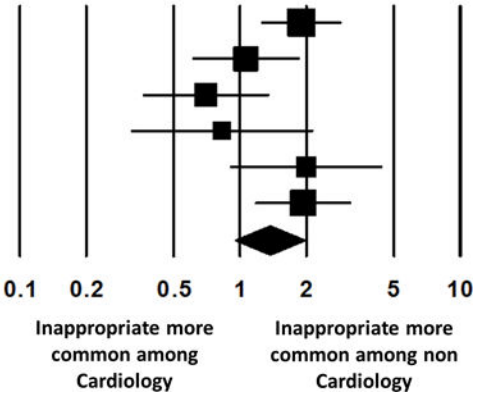

Figure 4.

Summary plot for the rate of inappropriate testing according to provider.

The relative size of the data markers indicates the weight of the sample size from each study.

CI = confidence interval; MPI= myocardial perfusion imaging

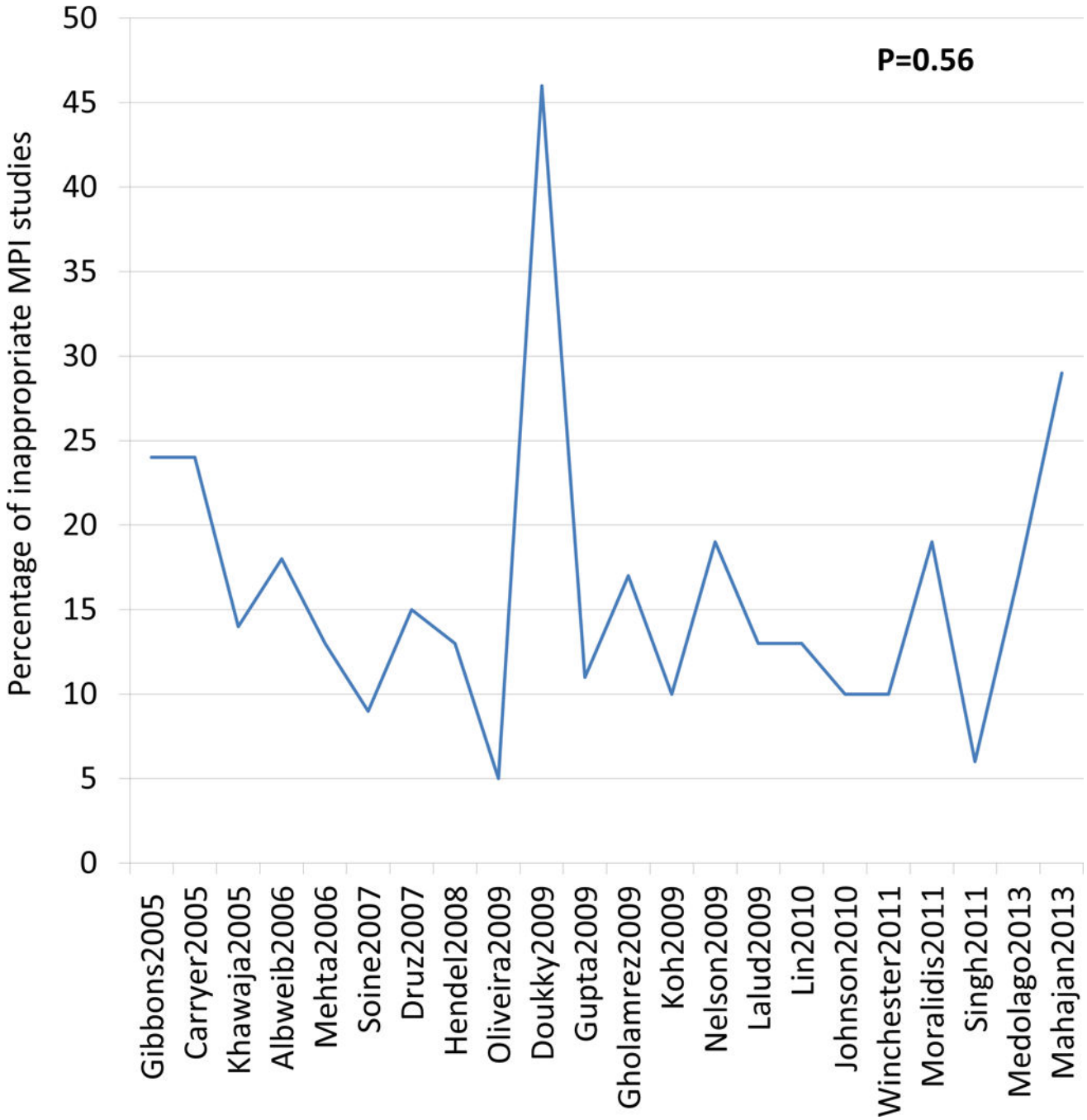

Figure 5.

Rate of inappropriate studies over time

On the X-axis, studies were arranged chronologically based on the midpoint of patient enrollment for their study.

MPI= myocardial perfusion imaging

Table 1

Baseline characteristics of the included studies

Study (Ref#)	Year	AUC used	Patients, n	Age, years mean (SD)	DM, %	Obesity, % †	CAD, %	Inappropriate testing, %
Mahajan et al[10]	2014	2009	403	62 (14)	31	50	27	29.3
Medolago et al[34]	2014	2009	866	67 (10)	NR	NR	49	17.2
Oliveira et al[11]	2014	2009 *	367	65 (12)	27	20	NR	5.2
Johnson et al[35]	2014	2009	206	NR	NR	NR	NR	10.2
Winchester et al[12]	2014	2009	582	NR	41	68	41	9.8
Lalude et al[13]	2014	2009	420	56	39	51	NR	12.9
Singh et al[14]	2014	2009	328	67	33	NR	38	5.5
Khawaja et al[36]	2013	2009	280	67 (11)	26	NR	NR	23.6
Doukky et al[20]	2013	2009	1,511	59 (13)	22	NR	NR	45.5
Aldweib et al[15]	2013	2009	1,105	64 (13)	28	45	18	18.0
Lin et al[37]	2013	2009	338	57 (8)	25	NR	49	13.0
Moralidis et al[38]	2013	2009	3,032	66 (11)	NR	NR	44	19.2
Soine et al[39]	2012	2005	2,782	59 (12)	28	NR	NR	9.2
Nelson et al[40]	2012	2009	300	48 (11)	28	NR	NR	19.3
Gholamrezanezhad et al[41]	2011	2009 *	291	55 (10)	22	NR	NR	16.8
Gupta et al[16]	2011	2005	314	62 (14)	24	NR	33	10.8
Druz et al[42]	2011	2005	570	64 (13)	NR	NR	28	14.7
Koh et al[17]	2011	2009	1,623	61 (11)	31	NR	NR	10.0
Carryer et al[43]	2010	2009 *	281	67 (11)	27	41	NR	24.2
Hendel et al[44]	2010	2005	6,351	66 (12)	23	NR	NR	13.4
Mehta et al[18]	2008	2005	1,209	61	NR	NR	NR	12.7
Gibbons et al[19]	2007	2005	284	67 (11)	27	41	NR	14.1

* Studies that utilized both the 2009 and 2005 AUC, data reported is for the 2009 AUC

† Body mass index ≥ 30

AUC= appropriate use criteria, CAD= coronary artery disease, DM= diabetes mellitus, NR= not reported, SD= standard deviation

Table 2

Assessment of study components

Study (Ref#)	Study design	Outpatient/ inpatient	Institution	Single/ multi-center	Restrictive inclusion criteria	Commonest reason for inappropriate testing
Mahajan et al[10]	Retrospective	Inpatient	Academic	Single	No	Non acute chest pain
Medolago et al[34]	Prospective	Both	Academic	Multi	No	Non acute chest pain
Oliveira et al[11]	Retrospective	Both	Academic	Single	No	Asymptomatic patient until 1 year after revascularization
Johnson et al[35]	Prospective	Outpatient	Community	Multi	No	Low risk symptomatic patients
Winchester et al[12]	Retrospective	Both	Academic	Single	No	Low risk asymptomatic patients
Lalude et al[13]	Retrospective	Both	Academic	Single	No	Low pretest probability of CAD, ECG interpretable, and able to exercise
Singh et al[14]	Retrospective	Both	Academic	Single	No	Pre-operative assessment
Khawaja et al[36]	Retrospective	Both	Academic	Single	Yes	NR
Doukky et al[20]	Prospective	Outpatient	Community	Multi	No	NR
Aldweib et al[15]	Retrospective	Both	Academic	Single	No	Pre-operative assessment
Lin et al[37]	Prospective	Outpatient	Community	Multi	Yes	Low risk asymptomatic patients
Moralidis et al[38]	Prospective	Both	Academic	Multi	No	Pre-operative assessment
Soine et al[39]	Retrospective	NR	Academic	Multi	No	NR
Nelson et al[40]	Retrospective	Both	Academic	Multi	No	Asymptomatic patients < 2 years after PCI
Gholamrezanezhad et al[41]	Prospective	NR	Community	Multi	No	NR
Gupta et al[16]	Retrospective	Both	Community	Single	No	NR
Druz et al[42]	Prospective	Both	Academic	Single	No	Low risk asymptomatic patients
Koh et al[17]	Prospective	NR	Academic	Single	No	Pre-operative assessment
Carryer et al[43]	Retrospective	Both	Academic	Single	No	Low risk asymptomatic patients
Hendel et al[44]	Prospective	NR	Academic	Multi	No	Low risk asymptomatic patients
Mehta et al[18]	Retrospective	NR	Academic	Single	No	Low risk symptomatic patients
Gibbons et al[19]	Retrospective	Both	Academic	Single	No	Low risk asymptomatic patients

CAD= coronary artery disease

ECG= electrocardiogram

NR= not reported

PCI= percutaneous coronary intervention

Table 3

Cardiac events

Study (ref#)	Appropriate, n	Event, n (%)	Inappropriate, n	Event, n (%)	Follow-up duration, m
All-cause mortality					
Winchester et al[12]	414	13 (3.1)	53	0 (0)	12
Doukky et al[20]	823	29 (3.5)	688	5 (0.7)	27*
Aldweib et al[15]	685	68 (9.9)	199	10 (5.0)	100
Koh et al[17]	106	3 (2.8)	70	0 (0)	3
Death or MI					
Winchester et al[12]	414	15 (3.6)	53	1 (1.9)	12
Doukky et al[20]	823	37 (4.5)	688	7 (1.0)	27*
MI					
Winchester et al[12]	414	3 (0.7)	53	1 (1.9)	12
Koh et al[17]	106	6 (5.7)	70	1 (1.4)	3
Cardiac catheterization					
Mahajan et al[10]	267	NR	118	11 (9.3)	4
Winchester et al[12]	414	68 (16.4)	53	1 (1.9)	12
Singh et al[14]	287	NR	18	6 (33.3)	6
Khawaja et al[36]	176	25 (14)	66	2 (0.3)	6
Doukky et al[20]	823	72 (8.7)	688	34 (4.9)	27*
Revascularization					
Mahajan et al[10]	267	NR	118	6 (5.1)	4
Winchester et al[12]	414	31 (7.5)	53	1 (1.9)	12
Singh et al[14]	287	NR	18	3 (16.7)	6
Khawaja et al[36]	176	NR	66	0 (0)	6
Doukky et al[20]	823	40 (4.9)	688	21 (3.1)	27*
Druz et al[42]	359	13 (3.6)	84	NR	12

*mean is reported

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MI= myocardial infarction, NR= not reported