

Appropriateness Criteria for Coronary Angiography in Angina: Reliability and Validity

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Background: Evaluated criteria for tailoring the decision to perform coronary angiography in specific clinical scenarios are lacking.

Objective: To determine the reliability and prognostic validity of patient-specific appropriateness criteria for coronary angiography among patients with suspected angina pectoris.

Design: Prospective observational study. Two independent panels of clinicians scored 2400 patient-specific indications for coronary angiography as inappropriate, uncertain, or appropriate. Using a simple computer algorithm, patients were matched to 1 of these indications.

Setting: 6 urban ambulatory care clinics in the United Kingdom.

Patients: 9356 consecutive patients with recent-onset chest pain in whom stable angina was suspected.

Measurements: Appropriateness ratings and clinical outcomes (coronary death and acute coronary syndrome events) over a median of 3 years of follow-up.

Results: 660 coronary deaths or acute coronary syndrome events occurred. Agreement between the 2 panels (reliability) on appropriateness category was moderate (weighted $\kappa = 0.58$; $P < 0.001$).

Use of subsequent angiography was strongly related to appropriateness category (P for linear trend <0.001) according to scores from either panel. Among patients judged as appropriate candidates for angiography, underuse was common (57% according to panel A and 71.3% according to panel B), and not undergoing coronary angiography was associated with higher coronary event rates than was undergoing the procedure. The hazard ratio after adjustment for age, sex, exercise electrocardiography result, and secondary prevention medication was similar according to panel A (2.78 [95% CI, 1.77 to 4.37]) and panel B (2.47 [CI, 1.72 to 3.55]).

Limitation: The study was too small to assess the relationship of angiography with coronary death and did not assess the reasons why patients did not receive angiography.

Conclusion: Appropriateness scores offer prognostically valid criteria for judging which specific patients might benefit from coronary angiography. Patient-specific appropriateness scores help pinpoint areas where judgments diverge and are a promising tool for making guidelines more effective.

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The decision to perform diagnostic and prognostic investigations in clinical medicine is uncommonly supported by evidence from randomized trials, yet it has major consequences in terms of cost and clinical outcomes when treatments are contingent on investigation results. Deciding which patients with suspected chronic stable angina pectoris should undergo coronary angiography is an important example of this general phenomenon. Although broad conventional clinical guideline recommendations (1, 2) and patient-specific appropriateness criteria (3) have been developed, 3 key questions about their clinical value remain unanswered. First, are the recommendations for investigation reliable, in the sense of being reproducible by independent groups? Good levels of agreement are essential for clinical credibility and accurate measurement of the frequency of underuse. Second, are the recommendations graded? Although the decision to perform angiography is binary (it either is or is not done), many decisions in clinical medicine are made in the “gray zone,” where understanding thresholds of benefit is crucial (4). For revascularization, prognostically important underuse was found not only among patients rated as appropriate candidates for revascularization but also among patients with scores denoting uncertainty about the appropriateness of this procedure (5). Third, and most important, are the recommendations valid in terms of prognosis? If so, then coronary event rates should be higher among patients not under-

going the recommended procedure (reflecting underuse). This might occur if medical or invasive management were optimized (6) in patients with the more definitive diagnosis that angiography offers. Although some studies have reported that angiography for suspected angina is underused (7–9), they have not reported whether such underuse has prognostic consequences. In the setting of acute myocardial infarction, patients not undergoing angiography that was considered necessary had worse outcomes (4, 10), but studies among ambulatory patients with chest pain at the point of diagnosis are lacking.

We sought to address these 3 questions in the ARIA (Appropriateness of Referral and Investigation of Angina) study, in which 2 independent panels rated the appropriateness of patient-specific clinical indications by using the RAND appropriateness method. These appropriateness

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Context

Can patient-specific appropriateness criteria developed by experts validly determine which patients with suspected angina should undergo coronary angiography?

Contribution

In this study, expert panels scored hundreds of patient-specific scenarios for coronary angiography as inappropriate, uncertain, or appropriate. Using a computer algorithm, researchers matched the devised appropriateness indications to 9356 clinic patients with recent-onset chest pain. They found that many patients judged as appropriate candidates did not undergo angiography and that this group had more subsequent coronary events than did patients who “appropriately” did have angiography.

Implication

Patient-specific appropriateness criteria are a promising tool for improving care of patients with suspected angina.

—The Editors

ratings were then matched to a large consecutive ambulatory cohort of patients with first-presentation chest pain who were followed for coronary events.

METHODS

Design

The study involved 3 stages: development of new appropriateness ratings (on which full details are published elsewhere [11]), matching these ratings to a patient cohort, and following the cohort for clinical outcomes (Figure 1).

Panel Members

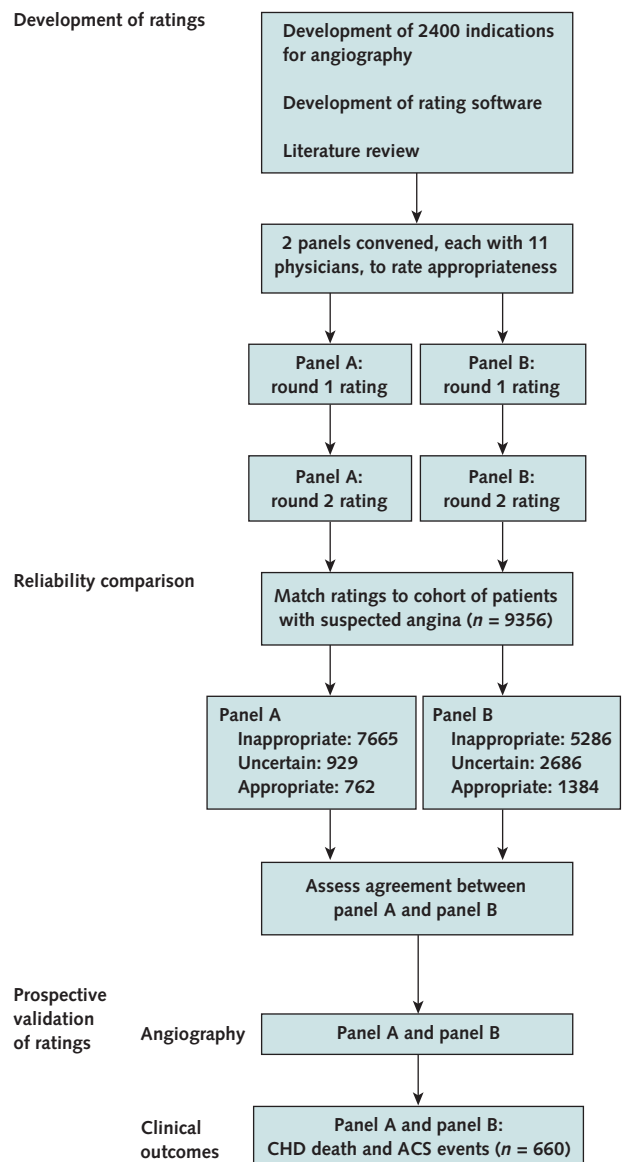
We convened 2 independent panels with different moderators, who at each stage were unaware of the other’s ratings. Twenty-two physicians from 9 centers in England, Ireland, and Scotland took part in these panels, rating the appropriateness of angiography by using the RAND appropriateness method (12). Only 1 of the 9 centers was also involved in the 6 centers for patient recruitment. We sought nominations within centers to reflect a balance of experience (years since qualification); sex; and, among specialists, invasive and noninvasive practice. Sixteen of the clinicians had published research on the management of coronary disease. Each panel consisted of 5 cardiologists, 5 family physicians, and 1 cardiothoracic surgeon.

Indications for Angiography

Panelists judged appropriateness of angiography on a 9-point scale, on which scores of 1 to 3 denoted inappropriate use (no benefit of angiography, possible harms), 4 to 6 denoted uncertainty about use (when harms and benefits were judged as approximately equal, or when the best available evidence did not support a judgment either way), and 7 to 9 denoted appropriate use (benefits were judged to

outweigh harms). Combinations of routinely assessed clinical factors were used to define specific clinical indications (scenarios) spanning the range of pretest probability of coronary disease from very low (<5%) to very high (>95%). Eight clinical descriptors were identified that influence the decision to perform angiography in people with suspected angina (but in the absence of previous definite coronary disease); Table 1 shows how these descriptors were combined into clinical indications. The descriptors are age (<40, 40 to 49, 50 to 59, 60 to 74, or 75 to 84 years), sex, typicality of symptoms, severity of symptoms (Canadian Cardiovascular Society class), medication for symptoms (submaximal or maximal), coronary risk factors (low, me-

Figure 1. Study flow diagram.



ACS = acute coronary syndrome; CHD = coronary heart disease.

Table 1. Most Frequent Indications for Angiography and Guideline Recommendations, by Angiography Appropriateness Rating and Symptom Typicality*

Type of Chest Pain	Angiography Appropriateness Rating		
	Inappropriate	Uncertain	Appropriate
Typical angina			
Modal indication	Normal exercise ECG, age 50–59 y, female, CCS I/II, medium risk, submaximal therapy	Normal exercise ECG, age 60–74 y, male, CCS I/II, medium risk, submaximal therapy	Abnormal exercise ECG, age 60–74 y, female, CCS I/II, medium risk, submaximal therapy
ACC/AHA guideline recommendation	No close match; not included in any class III recommendation	Not identified as a specific group; closest match suggests class IIa or IIb recommendation	Not identified as a specific group; closest match suggests class IIa or IIb recommendation
Patients with indications of typical pain/patients presenting with typical pain, <i>n/n</i>	52/712	46/803	28/585
Patients with modal indication, <i>n</i>	61	84	130
Atypical angina			
Modal indication	Normal exercise ECG, age 40–49 y, female, mild functional impairment, medium risk, submaximal therapy	Abnormal exercise ECG, age 60–74 y, female, mild functional impairment, low risk, submaximal therapy	Abnormal exercise ECG, age 60–74 y, female, mild functional impairment, medium risk, submaximal therapy
ACC/AHA guideline recommendation	No recommendations for use of angiography in patients with atypical symptoms	No recommendations for use of angiography in patients with atypical symptoms	No recommendations for use of angiography in patients with atypical symptoms
Patients with indications of typical pain/patients presenting with typical pain, <i>n/n</i>	94/5090	16/119	15/171
Patients with modal indication, <i>n</i>	333	26	63
Nonspecific			
Modal indication	No exercise ECG, age <40 y, women, mild to moderate functional impairment, medium risk, normal resting ECG, submaximal therapy	Abnormal exercise ECG, age 50–59 y, women, mild to moderate functional impairment, low risk, submaximal therapy	Abnormal exercise ECG, age 60–74 y, female, mild to moderate functional impairment, medium risk, submaximal therapy
ACC/AHA guideline recommendation	"All other patients with nonspecific chest pain"; not further specified	No statement	"High risk findings on non-invasive testing"; not further specified
Patients with indications of typical pain/patients presenting with typical pain, <i>n/n</i>	83/1767	2/2	2/2
Patients with modal indication, <i>n</i>	137	1	1

ACC = American College of Cardiology; AHA = American Heart Association; CCS = Canadian Cardiovascular Society; ECG = electrocardiogram.

*As assessed by panel A. For definitions of all variables, see the study protocol (11). ACC/AHA grading of recommendations: class I, useful and effective; class IIa, weight of evidence/opinion is in favor of usefulness/efficacy; class IIb, usefulness/efficacy is less well established by evidence/opinion; class III, not useful or effective.

dium, or high), resting electrocardiography (ECG) findings (normal or abnormal), and exercise ECG findings (none, normal, abnormal, or very abnormal). Indications were grouped in 3 broad clinical presentations: typical angina symptoms (900 indications), atypical angina symptoms (900 indications), and nonspecific chest pain (600 indications).

Appropriateness Scores

We developed software for the panel members to enter and review their own scores for each patient indication and access definitions of terms. Panelists were invited to base their ratings on peer-reviewed research evidence and were given a literature review with evidence tables, narrative synopses, and graded strength of evidence (11). We identified key articles on the role of angiography in the diagnosis of

coronary artery disease from existing guidelines, systematic reviews, and MEDLINE, and then performed forward citation tracking in the Science Citation Index until March 2003.

Panel members did the first round of rating independently. Panels then met over 2 days in July 2003, during which they followed an identical protocol. Each panelist was given a personalized report containing their own first-round ratings; the medians of their whole panel; and the range, with areas of disagreement highlighted. Panel members had the opportunity to change their ratings in light of the panel discussion, but in accordance with the RAND appropriateness method (12); no attempt was made to force the panel to consensus. **Table 1** shows the most frequently occurring indications according to symptom typi-

cality and gives the appropriateness category and the nearest match recommendation from conventional broad guidelines.

Patients

Using a computer algorithm, we matched the ARIA indications and their associated ratings to 9356 consecutive patients attending rapid-access chest pain clinics in 6 urban centers in the United Kingdom (Oldchurch, Newham, Kingston, Manchester, Blackburn, and Burnley) between 1996 and 2002. The sample size was determined by the availability of baseline data in these clinics that were systematically collected by using the same electronic record system. Physicians made decisions about investigation on these patients independent of the ARIA appropriateness ratings. These ambulatory care clinics are run by cardiology teams and accept same-day referrals from family physicians of patients with recent-onset chest pain in whom stable angina pectoris is suspected. Patients who had previously undergone angiography or received a diagnosis of coronary disease and those in whom acute or unstable coronary syndromes were suspected were not eligible for referral to these clinics. Using a common database, each center recorded patient age, sex, and ethnicity (South Asian, white, black, or other); whether chest pain was typical, atypical, or nonspecific; smoking, hypertension, hypercholesterolemia, and diabetes status; whether the resting ECG was abnormal; the exercise ECG result; and medical therapy at discharge. Angina symptom severity was not recorded; we assumed that angina was mild when matching patients to indications and performed sensitivity analyses on this assumption. Ethical approval was obtained from a multicenter research ethics committee.

Follow-up and Clinical Outcomes

More than 99% of patients were successfully matched at the Office for National Statistics and the National Health Service (NHS)–wide clearing system. The Office for National Statistics informed us of the date and cause of death or date of hospital discharge. Causes of death and hospitalization were coded according to the International Classification of Diseases, 10th revision. Median follow-up for the cohort was 3 years, until the end of 2003. Use of coronary angiography was obtained from the NHS-wide clearing system. Our a priori primary end point, used in all reports from this data set (13–15), was death from coronary heart disease (codes I20 to I25) and hospitalizations due to acute myocardial infarction (codes I21 to I23) and unstable angina (codes I20.0 to I20.9, I24.0, I24.8, and I24.9). The primary discharge diagnosis after hospital admission was used to define nonfatal events in these analyses. To define a group of patients without major comorbid conditions, we identified those with no hospital admission for noncoronary reasons within 1 year of the clinic visit.

Statistical Analysis

To assess reliability, we analyzed the appropriateness scores by using the 3-level a priori categories (inappropri-

ate, uncertain, or appropriate), and we used each individual score (1 to 9) to investigate threshold effects (5). Agreement between panels beyond chance was assessed by using the κ statistic; values of 0.40 to 0.60 indicated moderate agreement, and values greater than 0.60 to 0.80 indicated good agreement (16). In a post hoc analysis, we compared agreement between panels among patient subsets defined by age, sex, typicality of symptoms, exercise ECG findings, and prevalence of indications. We present results based on panel A scores and use panel B as an independent replication. To assess validity, we used Cox proportional hazards models to calculate hazard ratios with 95% CIs for the association between appropriateness score and receipt of first coronary angiography after the clinic visit. Using Cox models, we compared the coronary event rates among patients who did not have angiography with rates among those who did. Coronary events occurring after the clinic visit but before angiography were attributed to the group that did not have angiography, because angiography (and subsequent treatment) had had no opportunity to improve outcomes and an intercurrent event changes the appropriateness of subsequent angiography.

For a sensitivity analysis, we excluded patients who had an event and subsequently underwent angiography within 30 days. In the models, we adjusted for clinic as a fixed effect. To address the possibility of confounding by indication—patients who did not undergo coronary angiography might have had too high a coronary risk—we adjusted for age, sex, ethnicity, secondary prevention medication, and exercise ECG result. We developed a propensity score (the probability of exposure to angiography) in a multivariable logistic regression model that included age, sex, ethnicity, smoking status, hypertension, hypercholesterolemia, diabetes, symptom typicality and duration of chest pain, and exercise ECG result. The median propensity score was 0.32 (interquartile range, 0.17 to 0.60) for patients who received angiography and 0.04 (interquartile range, 0.02 to 0.09) for those who did not. The propensity score was included as a linear term in the adjusted Cox regression models (17). To address the possibility that patients who are sicker for noncoronary reasons may be denied angiography, we repeated the analyses among patients with no noncoronary admissions within 1 year of the clinic visit.

We used Stata, version 8 (Stata, College Station, Texas), for all analyses.

Role of the Funding Source

The United Kingdom Department of Health's Policy Research Programme and the NHS Research and Development Service Delivery and Organisation Programme had no role in study design, data collection, data analysis or interpretation, manuscript preparation, or the decision to submit the paper for publication.

Table 2. Baseline Characteristics of 9356 Patients with Recent-Onset Chest Pain, by Angiography Appropriateness Rating*

Characteristic†	Patients, n (%)					
	Angiography Appropriateness Rating: Panel A			Angiography Appropriateness Rating: Panel B		
	Inappropriate	Uncertain	Appropriate	Inappropriate	Uncertain	Appropriate
All patients	7665 (82)	929 (10)	762 (8)	5286 (57)	2686 (29)	1384 (15)
Chest pain						
Typical	712 (9)	803 (87)	585 (77)	152 (2)	811 (31)	1164 (84)
Atypical	5090 (67)	119 (13)	171 (23)	3507 (67)	1655 (62)	218 (16)
Nonspecific	1767 (23)	2 (0.2)	2 (0.3)	1584 (30)	187 (7)	0 (0.0)
Duration						
<1 mo	2493 (33)	184 (20)	131 (17)	1829 (35)	723 (27)	256 (19)
<6 mo	6628 (87)	790 (86)	668 (88)	4606 (88)	2291 (86)	1189 (86)
Risk factors						
Age >55 y	3070 (40)	689 (74)	536 (70)	1670 (32)	1568 (58)	1057 (76)
Male sex	3977 (52)	411 (44)	513 (67)	3183 (60)	1158 (43)	560 (40)
South Asian ethnicity	2053 (27)	146 (16)	149 (20)	1705 (32)	413 (15)	230 (17)
Current or former smoking	3115 (41)	445 (48)	384 (51)	2239 (42)	1083 (40)	622 (45)
Hypertension	2526 (33)	436 (47)	309 (41)	1587 (30)	1038 (39)	646 (47)
Hypercholesterolemia	1398 (18)	229 (30)	231 (30)	1006 (19)	529 (20)	373 (27)
Diabetes	739 (10)	156 (17)	101 (14)	562 (11)	237 (9)	197 (14)
Previous myocardial infarction	2 (0.03)	1 (0.01)	0 (0)	0 (0)	3 (0.1)	0 (0)
Investigation						
Abnormal resting ECG	966 (13)	426 (46)	213 (28)	350 (7)	661 (25)	594 (43)
Exercise ECG						
Performed	4108 (54)	674 (73)	757 (99)	3000 (57)	1583 (59)	956 (69)
Abnormal in those performed	1 (0.02)	175 (26)	757 (100)	1 (0.03)	276 (18)	656 (70)
Diagnosis of angina	1009 (13)	714 (78)	744 (98)	279 (5)	1003 (39)	1185 (87)
Treatment at baseline						
Nitrates	337 (4)	260 (28)	197 (26)	95 (2)	306 (11)	393 (28)
Secondary prevention agents						
Aspirin	1482 (19)	665 (72)	671 (88)	659 (12)	1076 (40)	1083 (78)
β-Blocker	933 (12)	420 (45)	530 (70)	469 (9)	636 (24)	778 (56)
Statin	667 (9)	224 (24)	261 (34)	410 (8)	367 (14)	375 (27)

ECG = electrocardiogram.

* A score of 1 to 3 defined “inappropriate,” 4 to 6 defined “uncertain,” and 7 to 9 defined “appropriate.”

† For each patient characteristic, *P* values for heterogeneity among the 3 appropriateness categories within each panel value are <0.001, except for duration of symptoms.

RESULTS

Sample Characteristics

Patients with chest pain encompassed 338 indications, and no single indication accounted for more than 3.6% of the sample. Patients with scores of 7 to 9 were considered a priori as to have had appropriate procedures, although no patient had a score of 9.

The 2 panels used different factors in reaching their decisions (Table 2). For example, all the patients whom panel A rated as having had appropriate angiography had an abnormal ECG result, whereas this was not the case for panel B. Very few patients had a history of definite coronary disease, and more than 85% of angiographic procedures were done within 6 months of clinic visit.

Agreement between Panels

Agreement between panels A and B across the 3 appropriateness categories was moderate ($\kappa = 0.58$) (Table 3). All 285 patients in whom angiography was rated inappropriate by panel A but appropriate by panel B had no

exercise ECG result. We explored whether disagreements might reflect the calibration of panels. When we defined “appropriate” as a score of 6 or more in panel A and compared this with “appropriate” as defined as a score of 7 or more in panel B, the agreement on appropriateness be-

Table 3. Interpanel Agreement in Rating the Appropriateness of Coronary Angiography*

Panel A	Panel B			Total
	Inappropriate	Uncertain	Appropriate	
Inappropriate	5241 (56.0)	2139 (22.9)	285 (3.0)	7665 (81.9)
Uncertain	45 (0.5)	414 (4.4)	470 (5.0)	929 (9.9)
Appropriate	0 (0.0)	133 (1.4)	629 (6.7)	762 (8.1)
Total	5286 (56.5)	2686 (28.7)	1384 (14.8)	9356 (100)

* Values are the number (percentage) of patients, calculated by row. A score of 1 to 3 defined “inappropriate,” 4 to 6 defined “uncertain,” and 7 to 9 defined “appropriate.” Uncalibrated agreement between the panels was 67.2% (weighted $\kappa = 0.58$ [95% CI, 0.56 to 0.60]; *P* < 0.001).

Table 4. Factors That Influence Interpanel Agreement

Factor	Patients, n	Crude Agreement, %	Weighted κ Value
Age			
<50 y	3552	88.1	0.64
50–64 y	3591	55.6	0.53
≥65 y	2213	52.4	0.50
Sex			
Female	4455	57.2	0.45
Male	4901	76.2	0.73
Symptoms			
Typical	2100	44.9	0.39
Atypical	5380	68.4	0.30
Nonspecific	1771	89.6	0.05*
Exercise ECG result			
Normal	4102	73.4	0.44
Abnormal	933	82.3	0.53
Not done/indeterminate	4321	58.0	0.24
Indication prevalence			
Low (n = 212)	3237	80.2	0.58
Medium (n = 80)	3092	73.2	0.65
High (n = 41)	3027	47.0	0.45

ECG = electrocardiogram.

* This κ value is not interpretable because 5 of the 9 cells contained zeroes.

tween panels was 94% (weighted $\kappa = 0.76$; $P < 0.001$). Agreement was higher among subsets of indications defined by young age, male sex, nonspecific chest pain, and abnormal exercise ECG result. For example, the crude agreement was 76.2% ($\kappa = 0.73$) in men versus 57.2% ($\kappa = 0.45$) in women (Table 4). Agreement was poor among patients in whom exercise ECG was not done or results were indeterminate.

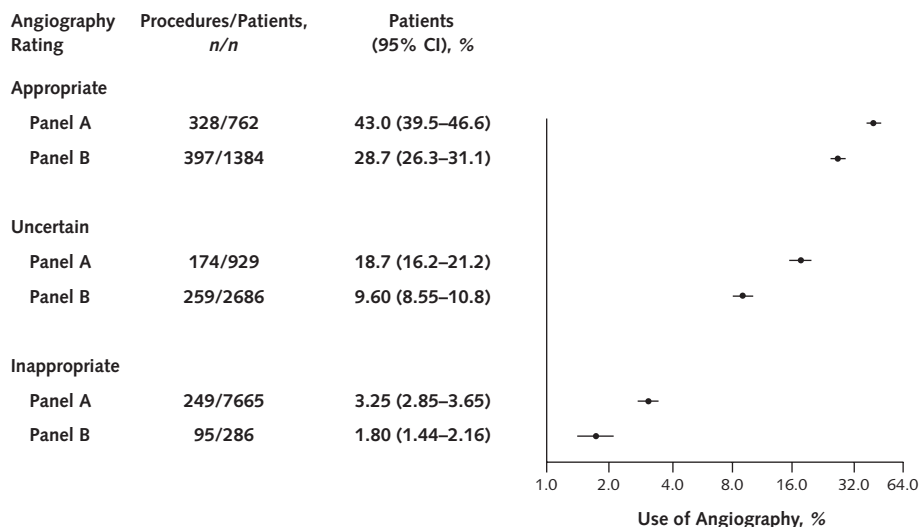
Angiography Rates across Appropriateness Categories

Most patients in our undifferentiated, test-naïve cohort were judged to be inappropriate candidates for angiography to a greater extent by panel A than by panel B (7665 of 9356 patients [81.9%] vs. 5286 of 9356 patients [56.5%], respectively) (Figure 2). In absolute terms, the use of angiography increased in a linear, dose–response manner across the 3 appropriateness categories: Rates for panel A were 3.25% for patients classified as inappropriate, 18.7% for those classified as indeterminate, and 43% for those classified as appropriate, and the respective values for panel B were 1.8%, 9.6%, and 28.7%. Thus, angiography was not performed in half of the patients rated appropriate for the procedure. Within appropriateness categories, and among patients with definite angina, the appropriateness score predicted the use of angiography. For example, among patients scoring 5, 6, 7, or 8 according to panel A, the hazard ratios for angiography (compared with patients scoring 1) were 2.21, 2.78, 4.16, and 4.13, respectively.

Coronary Events among Appropriate Candidates for Angiography

Not undergoing coronary angiography was associated with higher coronary event rates among patients who were judged to be appropriate candidates (Table 5 and Appendix Figure, available at www.annals.org). The hazard ratio after adjustment for age, sex, exercise ECG result, and secondary prevention medication was similar according to panel A (2.78 [95% CI, 1.77 to 4.37]) and panel B (2.47 [CI, 1.72 to 3.55]). This effect was consistent among those with no admissions for comorbid conditions. It did not change substantially in a further adjustment for the propensity score or when alternate assumptions about the severity of anginal symptoms were made (data available on

Figure 2. Use of angiography, by appropriateness ratings by panel A and panel B.



request). Of the 98 patients who had an acute coronary syndrome event among those who did not receive angiography (appropriate according to panel A), 35 patients had angiography within the next 30 days after the event. Removal of these patients from the analysis gave a fully adjusted hazard ratio of 1.61 (CI, 1.03 to 2.51). For panel B, 50 of 190 patients were removed, giving a hazard ratio of 1.68 (CI, 1.15 to 2.45). Overall, coronary event rates were lowest among patients in whom angiography was judged inappropriate. A small proportion of these patients had angiography nonetheless (249 of 7665 patients [3.3%] judged inappropriate by panel A and 95 of 5191 patients [1.8%] judged inappropriate by panel B). Among these patients, the coronary event rate was lower among those who did not undergo the procedure; the revascularization rate was 78 of 249 patients (31.3%) for panel A and 23 of 95 patients (24.2%) for panel B.

DISCUSSION

We developed and rated new scores for the appropriateness of coronary angiography for suspected angina and found that agreement between 2 independent panels was moderate. Among more than 9000 consecutive ambulatory patients with chest pain presenting for initial cardiologic assessment, each panel's scores strongly predicted receipt of subsequent angiography. Among patients in whom angiography was deemed appropriate by either panel, those who did not undergo coronary angiography had higher coronary event rates. In the ongoing absence of randomized clinical outcome trials of different investigation strategies among patients with suspected angina pectoris, the appropriateness method is an important tool for decision support in individual patients and for assessing quality of care in groups of patients.

In an English-language MEDLINE search to April 2008, we found no studies that compared the reliability of 2 independent panels judging the appropriateness of investigation procedures, nor did we find any studies in which ratings of appropriateness were applied to patients with the spectrum of chest pain at initial referral to a cardiologist's clinic or office. Previous studies have been limited by recruitment of patients at the time of investigation, and thus lack of a comparison group of patients in whom investigation is not performed (3, 18, 19); inclusion of patients with definite coronary disease (history of myocardial infarction or revascularization) (20, 21); and cross-sectional design (3, 18, 19). The characteristics of patients with incident angina about whom we report were similar to those of patients in a recent study from the United States (22). Sekhri and colleagues recently reported (13) that, among patients classified by either panel as appropriate for angiography, not receiving angiography was associated with worse outcomes in older people, women, South Asian persons, and people from socially deprived areas.

The moderate agreement between the 2 panels

($\kappa = 0.58$) should be taken in context. First, little is known about the reliability of any form of guidance for investigation. The reliability of the current American College of Cardiology/American Heart Association recommendations for investigation (23) has not been assessed. The absence of structured indications in conventional guidelines (Table 1) is a barrier to quantitative assessment of whether independent guideline development groups would make the same recommendations. Previous intergroup comparisons of guidance for investigation have involved different countries (24, 25) or different periods (26) and therefore do not assess reliability. We found some evidence that disagreement between panels may represent miscalibration, because a score of 6 on panel A was related to a score of 7 on panel B. Second, higher levels of agreement are reported for appropriateness ratings for revascularization, which may reflect the effect of randomized trial evidence in reducing panel uncertainty (27). Finally, all measurements made in clinical medicine that are based on judgment are subject to error, and the imperfect agreement between the ARIA panels is similar to that between independent readings of coronary angiograms ($\kappa = 0.53$ to 0.63) (28, 29), thallium scanning ($\kappa = 0.45$ to 0.46) (20, 30), screening mammography ($\kappa = 0.47$) (31), and cervical smear grading ($\kappa = 0.50$) (32, 33).

Our appropriateness study is unique in that we tested the extent to which relations to procedure use and clinical outcomes were robust to independent replication across both panels. We found a strong monotonic relation between appropriateness category and use of subsequent angiography in both panels. Angiography was not performed in more than one half of patients in whom angiography was deemed appropriate. Underuse of procedures is a ubiquitous phenomenon (9, 34), and such levels of underuse are consistent with previous estimates from U.S. studies. For example, among patients in whom angiography was deemed appropriate, the proportion who did not receive it was 71% in patients with chronic renal disease after myocardial infarction (34), 26% among acute patients presenting to the emergency department (9), 57% in patients with an abnormal exercise ECG (19), and 54% among fee-for-service and 63% among managed care patients with acute myocardial infarction (20). This allows the "natural experiment" of comparing outcomes among those who do and do not receive an appropriate procedure. Not undergoing angiography reflects in part the uncertainty in management of unselected patients in a community setting at initial presentation to a cardiologist. The reasons for underuse, which we did not assess, are likely to be complex and may include physician judgment factors, supply factors, and patient preference.

Underuse of coronary angiography was associated with adverse prognosis: Patients who were appropriate for investigation and who received it had lower rates of coronary end points than did patients who were appropriate for investigation but did not receive it. This finding supports the

Table 5. Primary End Point Event Rates, by Coronary Angiography Status and Appropriateness Rating*

Appropriateness Rating	Panel A					
	Events in All Patients		Events/Patients, by Angiography Status, n/n (%)		Adjusted Hazard Ratio If Angiography Is Not Performed (95% CI)†	
	Events/Patients, n/n	Absolute Risk for Events, %‡	Angiography Not Performed	Angiography Performed	All Patients	Patients without Comorbid Conditions§
Inappropriate	386/7665	4.2	354/7416 (4.8)	32/249 (12.9)	0.69 (0.48–1.01)	0.80 (0.50–1.28)
Uncertain	140/929	13.1	121/755 (16.0)	19/174 (10.9)	1.98 (1.17–3.36)	1.68 (0.91–3.08)
Appropriate	134/762	19.4	98/434 (22.6)	36/328 (11.0)	2.67 (1.77–4.01)	2.78 (1.77–4.37)

* The primary end point was a combination of coronary death and nonfatal acute coronary syndromes.
 † Hazard ratios compare coronary event rates in patients not undergoing coronary angiography with those of patients undergoing coronary angiography, adjusted for age, sex, ethnicity, abnormal exercise electrocardiogram, secondary prevention (aspirin, β -blocker, or statin), and clinic.
 ‡ Standardized for age (≤ 44 , 45–54, 55–64, or ≥ 65 years) and sex.
 § Patients with no admissions for comorbid conditions within 1 year after the first visit. Panel A classified 6330, 732, and 630 of these patients as inappropriate, uncertain, and appropriate for angiography, respectively; the respective values for panel B were 4435, 2156, and 1101 patients.

prognostic validity (5) of the ARIA ratings and is consistent with findings in other clinical settings in the United States (4, 10, 34). The conventional threshold of 7 for classifying an indication as “appropriate” led to a 2-fold difference in the number of procedures considered appropriate. This may represent thresholds of judgment, because evidence indicated that prognostically relevant underuse of angiography extended into the group of patients who scored 6 (uncertain) (hazard ratio, 4.55 [CI, 1.55 to 13.40]). A similar finding has been demonstrated for revascularization (5). If this information is used to recalibrate the scores, defining appropriate as 6 or greater for panel A and 7 or greater for panel B, similar proportions of patients are classified as appropriate and with similar relative hazards on end points. For these reasons, panel B may have more accurately classified angiography appropriateness. Additional research is needed to determine whether the arbitrary cut-point of 7 proposed in the original appropriateness method requires modification.

Our study has limitations. We cannot exclude the possibility of confounding, which is inherent in all observational research—that is, patients who were selected for angiography were at lower coronary risk and were destined to do better than those patients who were not selected for angiography. Several lines of evidence reduce the likelihood of such an effect. First, patients have already been selected by their family physician for cardiologic assessment, removing some in whom co-existing conditions might preclude further assessment. Furthermore, there is selective pressure in the opposite direction: Patients undergo angiography precisely because they are considered to be at high coronary risk. Second, the appropriateness method “matches” patients in terms of risk factors. Third, we adjusted for measured covariates at baseline and the propensity score, and these had little effect on the estimates. Fourth, our findings were robust among patients without comorbid conditions resulting in hospital admission. We did not collect data on the clinicians’ intentions

to perform angiography and therefore cannot assess whether clinicians decided not to do angiography or whether waiting list (35), patient preference, or other reasons meant that it did not occur before an event. This distinction between appropriateness and urgency of investigation in chronic conditions is important in policy terms. Finally, the patient sample was too small to assess effects on more specific coronary end points, such as coronary death (36).

Several mechanisms may be involved in conferring benefit on those undergoing angiography. Not only is the demonstration of angiographic disease a prerequisite for subsequent revascularization, but securing a more definitive diagnosis may also motivate better secondary preventive interventions (medication and lifestyle) in terms of uptake and adherence compared with similar patients in whom the coronary arteries have not been visualized. These multiple points of action may explain why the effects that we observe are reasonably strong compared with those observed from the randomized trials of angiography after myocardial infarction, in whom everyone is at high risk and has a definitive diagnosis (37). Not adhering to guidance for diagnostic practices has been associated with adverse outcome in other conditions, including suspected pulmonary embolism (38) and depression (39).

We studied unselected, consecutive, test-naïve patients with undifferentiated chest pain and no history of myocardial infarction. As anticipated, angiography was judged inappropriate in most patients. However, angiography was performed in a small proportion (<5%) of patients in whom it was judged inappropriate. We suspect that this represents misclassification by the panels for 2 reasons. First, in patients classified as inappropriate for angiography, coronary event rates were higher among those who did have angiography, as would be expected if these patients had been correctly selected as being at higher risk than those in whom angiography was not performed. In

Table 5—Continued

Events in All Patients		Events/Patients, by Angiography Status, n/n (%)		Adjusted Hazard Ratio If Angiography Is Not Performed (95% CI) [†]	
Events/ Patients, n/n	Absolute Risk for Events, % [‡]	Angiography Not Performed	Angiography Performed	All Patients	Patients without Comorbid Conditions [§]
197/5286	3.2	188/5191 (3.6)	9/95 (9.5)	0.52 (0.26–1.03)	0.57 (0.26–1.25)
232/2686	7.7	195/2427 (8.0)	37/259 (14.3)	1.16 (0.79–1.72)	1.38 (0.85–2.23)
231/1384	22.9	190/987 (19.3)	41/397 (10.3)	2.47 (1.72–3.55)	2.29 (1.53–3.42)

addition, about 30% of these patients subsequently underwent revascularization.

The ARIA study provides a framework for evaluating the rapidly expanding development of appropriateness criteria to guide investigation procedures, which includes nuclear imaging (4), cardiac computed tomography (41), echocardiography (42), and stress echocardiography (43). Our findings pinpoint clinical groups in which the reliability of the appropriateness ratings are most in need of improvement. By focusing on the subset of indications that give rise to disagreements, further panel iterations may resolve some uncertainty, but better empirical research is required in other areas. For example, indications for investigation in different scenarios among women (44), for whom agreement between panels was worse than among men, remain uncertain despite the similar population prevalence of typical angina symptoms in women and men (45). Randomized trials are required to test whether interventions based on appropriateness ratings can improve clinical outcomes in cardiovascular and noncardiovascular conditions, and if so, whether this is cost-effective (46). The importance of such research in angina is underscored by the continued high incidence and prognostic burden (47) of angina; direct costs in the United States estimated at up to \$75 billion; and the potential for new imaging techniques, such as computed tomography and magnetic resonance angiography (48), to exacerbate practice variations.

Although there is an ongoing need for refinement, our findings support the use of ARIA appropriateness ratings as a decision-support tool in the electronic patient record. Unlike broad conventional guidelines (22), the recommendations are tailored to specific patient scenarios and are prognostically validated. A simple computer algorithm returns an appropriateness rating in each patient, unlike the complex situation for less comprehensive criteria (18). Furthermore, the ratings change physician behavior. We randomly assigned 292 physicians in the ARIA randomized trial to appropriateness ratings or conventional guidelines and found that only the former group changed their test-ordering intentions on patient vignettes (49). This is consistent with a meta-analysis of randomized trials of decision-support tools that found that features associated with

appropriateness ratings, such as patient-specific guidance and ease of computerized delivery at the point of patient contact, influence clinical practice (50).

Appropriateness scores offer prognostically valid criteria for judging the potential harms of not performing coronary angiography among patients with suspected stable angina pectoris. In the ARIA trial, appropriateness scores were effective in changing physician testing intentions (49). Taken together, these findings suggest that appropriateness scores offer a promising intervention in improving the quality of care of patients with suspected stable angina pectoris.

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Appendix Figure. Cumulative probability of coronary heart disease (CHD) death or acute coronary syndrome (ACS) events according to receipt of coronary angiography among candidates judged appropriate by panel A and panel B.

