BMJ Open

APpropriAteness of percutaneous Coronary interventions in patients with ischemic HEart disease in Italy: The APACHE Pilot study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016909
Article Type:	Research
Date Submitted by the Author:	20-Mar-2017
Complete List of Authors:	Leonardi, Sergio; Fondazione IRCCS Policlinico San Matteo, Marino, Marcello; Aziende Socio Sanitarie Territoriale di Crema Crimi , Gabriel ; Fondazione IRCCS Policlinico San Matteo, Maiorana, Florinda; Fondazione IRCCS Policlinico San Matteo Rizzotti, Diego; Fondazione IRCCS Policlinico San Matteo Lettieri, Corrado; Azienda Socio Sanitaria Territoriale di Mantova Bettari, Luca; Azienda Socio Sanitaria Territoriale di Cremona Zuccari, Marco Sganzerla, Paolo; Agenzia di Tutela della Salute di Bergamo Ovest Tresoldi, Simone ; Azienda Ospedaliera di Desio e Vimercate Adamo, Marianna; Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia Ghiringhelli, Sergio; Ospedale di Circolo e Fondazione Macchi Sponzilli, Carlo; Ospedale San Paolo Pasquetto, Giampaolo; Presidio Ospedaliero di Monselice Pavei, Andrea; Presidio di Conegliano Pedon, Luigi; Presidio Ospedaliero di Cittadella Bassan, Luciano; Azienda ULSS 4 Alto Vicentino Bollati, Mario; IRCCS Policlinico San Donato Camisasca, Paola; Azienda Ospedaliera San Gerardo Trabattoni, Daniela; Centro Cardiologico Monzino Brancati, Marta; Fondazione Poliambulanza Istituto Ospedaliero Poli, Arnaldo; Aziende Socio Sanitarie Territoriale Ovest Milanese Panciroli, Claudio Lettino, Maddalena; Istituto Clinico Humanitas Tarelli, Giuseppe; Istituto Clinico Humanitas Tarantini, Giuseppe; Azienda Ospedaliera di Padova De Luca, Leonardo; Ospedale di Tivoli Varbella, Ferdinando; 1Cardiology Unit, Ospedale degli Infermi, Musumeci, Giuseppe; Azienda Ospedaliera S Croce e Carle Cuneo De Servi, Stefano; IRCCS Sesto San Giovanni
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Health services research
Keywords:	Coronary heart disease < CARDIOLOGY, Percutaneous Coronary Intervention, Multidisciplinary Decision Making

APpropriAteness of percutaneous Coronary interventions in patients with ischemic HEart disease in Italy: The APACHE Pilot study

Sergio Leonardi, MD, MHS, FESC [1] Marcello Marino, MD [2] Gabriele Crimi, MD [1] Florinda Maiorana, MSc, [1] Diego Rizzotti, MSc [1] Corrado Lettieri, MD [3] Luca Bettari, MD [4] Marco Zuccari, MD[5] Paolo Sganzerla, MD [6] Simone Tresoldi, MD [7] Marianna Adamo, MD [8] Sergio Ghiringhelli, MD [9] Carlo Sponzilli, MD [10] Giampaolo Pasquetto, MD [11] Andrea Pavei, MD [12] Luigi Pedon, MD [13] Luciano Bassan, MD [14] Mario Bollati, MD [15] Paola Camisasca, MD [16] Daniela Trabattoni ,MD [17] Marta Brancati, MD [18] Arnaldo Poli, MD [19] Claudio Panciroli, MD [20] Maddalena Lettino, MD [21] Giuseppe Tarelli[21], MD Giuseppe Tarantini, MD [22] Leonardo De Luca, MD [23] Ferdinando Varbella, MD [24], Giuseppe Musumeci, MD [25] *and* Stefano De Servi, MD [26].

1: Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
2: Ospedale Maggiore di Crema, Crema, Italy
3: ASST Mantova – Ospedale Carlo Poma, Mantova, Italy
4: ASST Cremona – Ospedale di Cremona, Cremona, Italy
5: Ospedale Fornaroli di Magenta, Magenta, Italy
6: ASST Bergamo ovest – Ospedale di Treviglio, Italy
7: Azienda Ospedaliera di Desio e Vimercate, Vimercate, Italy
8: Spedali Civili di Brescia, Brescia, Italy
9: Ospedale di Circolo Fondazione Macchi, Varese,Italy
10: Ospedale San Paolo, Milano, Italy
11: Ospedali Riuniti Padova Sud Madre Teresa di Calcutta, Monselice, Italy
12: Presidio Ospedaliero di Conegliano, Conegliano, Italy
13: Presidio Ospedaliero di Cittadella, Cittadella, Italy
14: ULSS 4 Alto Vicentino, Thiene, Italy
15: IRCCS Policlinico San Donato, San Donato Milanese, Italy
16: Ospedale San Gerardo, Monza, Italy
17: Centro Cardiologico Monzino, Milano, Italy
18: Fondazione Poliambulanza, Brescia, Italy
19: ASST Ovest Milanese, Legnano, Italy
20: ASST di Lodi, Lodi, Italy
21: Humanitas Research Hospital, Rozzano (MI), Italy
22: Ospedale di Padova, Padova, Italy
23: Ospedale San Giovanni Evangelista, Tivoli (Rome), Italy
24: Ospedale degli Infermi, Rivoli, Italy
25: ASST – Papa Giovanni XXIII- Bergamo, Italy
26: IRCCS MultiMedica, Milano, Italy

Word Count: 4093

Address for correspondence
Sergio Leonardi, MD, MHS, FESC
Fondazione IRCCS Policlinico S. Matteo
Viale Golgi 19
27100
Pavia, Italy
S.Leonardi@smatteo.pv.it

Abstract *Word count: 305*

Objectives: To first explore in Italy appropriateness of indication, adherence to guideline recommendations, and mode of selection for coronary revascularization.

Design: Retrospective, pilot study.

Setting: Twenty-two percutaneous coronary intervention (PCI)-performing hospitals (20 patients/site), 13 (59%) with on-site cardiac surgery.

Participants: 440 patients who received PCI for stable coronary artery disease (CAD) or non-ST elevation acute coronary syndrome were independently selected in a 4:1 ratio with half diabetics.

Primary and Secondary Outcome Measures: Proportion of patients who received appropriate PCI using validated appropriate use scores (ie AUS ≥ 7). Also, in patients with stable CAD, we examined adherence to the following ESC recommendations: a) % of patients with complex coronary anatomy treated after heart-team discussion; b) % of fractional flow reserve-guided PCI for borderline stenoses in patients without documented ischemia; c) % of patients receiving guideline-directed medical therapy at the time of PCI as well as use of provocative test of ischemia according to pre-test probability (PTP) of CAD.

Results: Of the 401 mappable PCIs (91%), 38.7% were classified as appropriate, 47.6% as uncertain, and 13.7% as inappropriate. Median PTP in stable CAD patients without known coronary anatomy was 69% (78% intermediate PTP, 22% high PTP). Their use was similar (p=0.71) in patients with intermediate (*n*=140, 63%) and with high PTP (*n*=40, 66%). In patients with stable CAD (n=352) guideline adherence to the 3 recommendations explored was: a) 11%; b) 25%; c) 23%. AUS was higher in patients evaluated by the heart team as compared to patients who were not [7 (6,8) vs 5 (4,7); P=0.001].

Conclusions: Use of heart-teams approaches and adherence to guideline recommendations on coronary revascularization in a real world setting is limited. This pilot study documents the feasibility of measuring appropriateness and guideline adherence in clinical practice and identifies substantial opportunities for quality improvement.

Study Registration: NCT02748603.

Strengths and Limitations of this study

- APACHE is a first-in-class study in Italy designed to measure the degree of appropriateness of indication, multi-disciplinary decision-making processes, and implementation of key guideline recommendations in patients undergoing PCI.
- This study, with patients with stable CAD and diabetes, was intentionally designed to focus on high-risk patients for inappropriate PCI. Also, it examined the appropriateness of PCI indication, not of coronary angiography. Therefore we have no data to inform appropriateness of surgical revascularization, nor indication to invasive angiography.
- Rather than an epidemiological study, APACHE intention was to serve as first initiative sponsored by a national medical society to measure care process and improve quality. By quality we intend the degree of match between health care services and the needs they are intended to meet. [20] APACHE was designed to first quantify this match, inform the design of future investigations on this topic, and promote a continuous review of practice that may, in turn, inform a more effective, efficient, and equitable resources allocation, and ultimately, better outcomes for patients.

Introduction

Percutaneous coronary intervention (PCI) has dramatically improved the prognosis of patients with coronary artery disease (CAD). Yet, many patients receive PCI whose clinical indication appears uncertain or inappropriate, especially in the non-acute setting. [1,2] The development of appropriate use criteria by cardiovascular societies has provided the basis for a standardized approach to systematically assess the clinical appropriateness of PCI [3] and has produced a reduction of the volume of non-acute PCI as well as an increase in the proportion of procedures classified as appropriate [4] but these studies have been mostly performed in the US.

In Europe, data on appropriateness of indication and mode of selection for coronary revascularization strategies as well as the degree of implementation of guideline recommendations are lacking. European Society of Cardiology (ESC) guidelines [5,6] urge the implementation of a multidisciplinary decision-making approach – the heart team – to select the optimal mode of revascularization but data on the implementation of this process in patients with complex coronary artery disease (CAD), including those with stable CAD and diabetes, are scarce. Specifically the ESC [5,6] recommend that 1) complex pathologies in stable patients, including lesions of the left main or proximal left anterior descending artery (LAD) and three-vessel disease, should in general not be treated *ad hoc*, but discussed by the heart team; 2) pressure derived fractional flow reserve (FFR) should be used to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available; and 3) patients with stable CAD must receive guideline-recommended medical treatment prior to revascularization.

We designed the APpropriAteness of percutaneous Coronary interventions in patients with ischemic HEart disease – APACHE Pilot study to first explore the degree of appropriateness of indication of PCI, multi-disciplinary decision-making

processes, and implementation of key guideline recommendations in patients undergoing PCI in Italy.

Methods

Study Design and Patient Selection

APACHE was designed as a pilot initiative to assess appropriateness of PCI indication and adherence to key guideline recommendations on coronary revascularization in patients with predominantly stable CAD and diabetes, considered to be at high risk for inappropriate indication and mode for coronary revascularization (ie PCI treatment in patients with an indication for CABG). All PCI performing hospitals of the Lombardia and Veneto region in Italy, serving a population of ≈ 15.000.000 people, were invited to participate in the study. Twenty-two sites agreed to participate, obtained regulatory approval, and were eventually included.

At each participating hospital, 20 patients were independently selected on-site by the study team (see online appendix) among consecutive patients who were admitted in the previous year for an elective procedure to treat stable CAD or urgently for an episode of non-ST elevation acute coronary syndrome in a 4:1 ratio and without site personnel involvement in the selection of the cases identified to minimize selection bias. The study population was also selected to preserve an overall 1:1 ratio on diabetes status. If the number of patients selected was insufficient older cases were evaluated for possible inclusion. Due to the low likelihood of receiving a *redo* procedure as well as the inability to measure a SYNTAX score, patients with a history of bypass surgery were excluded.

Data Collection, Core Angiographic Assessment, and Central Heart Team

Variables of interest were collected by the study team during dedicated visits at participating hospitals via clinical chart abstraction. Sites were requested to provide

the complete clinical chart, including the coronary angiogram of the index PCI. Source documentation was reviewed in full to abstract symptoms status (angina class); cardiovascular risk factors and comorbidities; medical therapy at time of PCI; site-reported indication for PCI; presence, results, and timing of any noninvasive functional test, fractional flow reserve (FFR) or intracoronary imaging, if performed; coronary anatomy and reported significance of angiographic stenosis for treated lesion(s) on the catheterization report; and evidence for heart-team discussion involving a cardiac surgeon. Finally, pretest probability (PTP) of significant coronary artery disease was calculated in patients with stable CAD according to guideline recommendations [6].

The Angiographic Core Laboratory (ACL) was composed by two independent physicians with experience in interventional cardiology (MM, GC) who centrally and independently reviewed coronary angiography for each patient to define 1) baseline SYNTAX score 2) category of coronary anatomy (eg. one, two or three-vessel CAD with or without proximal LAD involvement) [3] and 3) presence of "borderline" angiographic stenosis (50% to 60%). For the SYNTAX score a disagreement was arbitrarily considered to be present if there was a between score difference ≥ 10 or both scores were not in the same tertile (0-22, 23-32, >32). In case of agreement an average SYNTAX score was calculated. In case of disagreement between reviewers the case was first resolved by consensus. If a consensus could not be reached (or if the case was deemed particularly challenging) the conflict was resolved by the central heart team. Anatomical category and presence of borderline coronary stenoses were analyzed by a single reviewer (GC or MM).

The central heart team was represented by four members – two interventional cardiologists (LDL, FV), one cardiac surgeon (GT), and one clinical cardiologist

(ML) – nominated by the Italian Society of Interventional Cardiology (SICI-GISE) among recognized experts in their respective specialty. The role of the central heart team was to review cases with unresolved conflicts by the ACL, cases considered complex or challenging by the study team or cases with incomplete or conflicting documentation. Assessments of the central heart team were performed by consensus.

Evaluation of Appropriateness of Indications for Coronary Revascularization

The comprehensive documentation of indications for PCI was formally examined based on the 2013 ACC/AHA/SCAI/AMA-PCPI/NCQA Percutaneous Coronary Intervention Measurement Set. [7] This diagnostic measure was defined as the proportion of patients whose clinical documentation includes, at a minimum, the following elements:

1. Priority (acute coronary syndrome, elective, urgent, emergency/salvage); 2. Presence and severity of angina symptoms (eg, Canadian Cardiovascular Society classification system); 3. Use of antianginal medical therapies within 2 weeks before the procedure, if any; 4. Presence, results, and timing of noninvasive stress test, FFR, or intravascular ultrasound, if performed; and 5. Significance of angiographic stenosis on coronary angiography for treated lesion.

Appropriateness of indication of coronary revascularization was examined by assigning to each procedure an appropriate use score (AUS), with a score of 1 indicating a completely inappropriate procedure to a score of 9 indicating a completely appropriate one. [3] Scores of 7 to 9 indicate that revascularization is considered generally appropriate and likely to improve patients' symptoms or survival. Scores of 1 to 3 considered generally inappropriate while scores of 4 to 6 indicate a clinical scenario for which the likelihood that coronary revascularization will improve health outcomes or symptoms is uncertain. This score was defined by

considering clinical presentation; severity of angina; extent of ischemia on noninvasive testing; presence of other prognostic factors, such as congestive heart failure or depressed left ventricular function; extent of medical therapy at the time of PCI; and extent of anatomic coronary disease. If the scenario was not considered by the consensus document, [3] the procedure was considered non mappable.

To limit site operator-related bias, the study team calculated two scores for each procedure:

1. AUS_{SITE}, based on site-reported extent of anatomic coronary disease;
2. AUS_{CORE}, based on ACL reported extent of anatomic coronary disease.

Evaluation of adherence to ESC Guidelines and Heart Team Processes

In patients with stable CAD we assessed adherence to three class I recommendations according to ESC guidelines [5,6]:

Recommendation 1: Proportion of patients with stable CAD and complex anatomy (including lesions of the left main, proximal left anterior descending (LAD) and/or three-vessel CAD) who were treated after local heart team discussion. This recommendation was explored using both site-reported and ACL-reported coronary anatomy. We also explored adherence to this recommendation by calculating the proportion of patients with complex anatomy who received *ad hoc* PCI without documented heart team discussion. To better define optimal mode of coronary revascularization, the SYNTAX II score [8] as well as the Society of Thoracic Surgeons (STS) [9], and EuroScore II [10] were calculated.

Recommendation 2: Proportion of patients with stable CAD, no evidence of ischemia, and borderline lesions according to the ACL in whom FFR was used to identify haemodynamically relevant coronary lesion(s).

Specifically, this recommendation was explored as follows:

a) Proportion of patients with no functional test (ie test negative or not performed) and at least one borderline stenosis according to ACL in whom pressure-derived FFR was used;

b) Proportion of patients with no functional test or asymptomatic and at least one borderline stenosis according to ACL in whom pressure derived FFR was used;

c) Proportion of patients with no functional test or asymptomatic and site-reported multivessel CAD in whom pressure derived FFR was used. [11]

Recommendation 3: Proportion of patients with stable CAD who received guideline-directed medical therapy prior to revascularization. [6]

Specifically:

a) Proportion of patients without known allergy or documented intolerance taking low dose aspirin (75-150 mg daily) or clopidogrel;

b) Proportion of patients without known allergy or documented intolerance receiving a statin;

c) Proportion of patients with heart failure, hypertension or diabetes treated with an ACE-inhibitor or angiotensin receptor blocker;

d) Proportion of patients on optimal medical therapy defined as drugs for event prevention (aspirin and/or clopidogrel; a statin; an ACE-I/ARB if heart failure, hypertension or diabetes) plus at least one drug for angina relief if symptomatic, such as beta-blockers, calcium channel blockers, long acting nitrates, ivabradine, or ranolazine.

In patients with NSTEACS, we examined the proportion of PCI procedures performed within 24 hours of admission in patients with a Global Registry of Acute Coronary Events (GRACE) score > 140.

Finally we assessed, by structured investigators surveys, the presence of written institutional protocols developed locally by the Heart Team in accordance with current guidelines including specific anatomical criteria and clinical subsets that may be (or should not be) treated *ad hoc* as well as the modalities and timing for convocation of heart team meetings.

Statistical Analysis and Sample Size Considerations

Categorical data are presented as counts and proportion and continuous data as median (25^{th}, 75^{th} percentile) and were analyzed, as appropriate, using Pearson's X^2 (or Fisher's exact) and Wilcoxon rank-sum test. Given the lack of prior studies to estimate appropriateness of coronary revascularization in Italy, sample size estimation was challenging. The study was powered on the primary subgroup of interest, patients with stable CAD, assuming an appropriateness of 35% in this patient population based on prior reports. [4] Using a normal approximation to the binomial distribution for this proportion a population of 350 stable CAD patients was needed to obtain a 95% confidence interval between 30% and 40% for appropriateness. [12] The study obtained institutional review board approval by all participating hospitals and is registered on ClinicalTrial.Gov ID: NCT02748603.

Sponsor and Funding

The APACHE study was designed by the chair and principal investigator and approved by the institutional review board at each participating center. The study was sponsored by the Italian Society of Invasive Cardiology (SICI-GISE), a nonprofit organization, and received unrestricted grant support from the Abbott Vascular and Daiichi-Sankyo. The sponsor and funders had no role in the design of the study, the collection, monitoring, analysis, and interpretation of the data, or the writing of the

report. The first draft of the manuscript was written by the first author. All the authors vouch for the accuracy and completeness of the data and all analyses.

Results

Of the 22 hospitals included, 13 (59%) have onsite cardiac surgery and 4 (18%) are private hospitals. Overall, PCI procedures of 440 patients (performed between January 2014 and May 2016) were included: 352 for patients with stable CAD and 88 with NSTEACS [12 with unstable angina and 76 with non-ST elevation myocardial infarction; median GRACE score 109 (89.5, 125.5), median Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) score 24 (16,40)]. A SYNTAX score could be calculated in 422 patients (96%) with 87 disagreements (21%) between ACL reviewers. Of these, 55 were resolved by consensus and 32 by the central heart team. Clinical profile of the selected patients stratified by clinical indication is showed in **Table 1**. By design, ≈ half of the patients had diabetes (n=216, 49.1%) with a high proportion of patients with dyslipidemia (54%), prior PCI (40%) and history of angina (69%). **Table 2** presents data on indication and test selection in patients with stable CAD. Median PTP of CAD in stable CAD patients without known coronary anatomy was 69% (78% intermediate PTP, 22% high PTP, no patient with low PTP). The use of provocative tests of ischemia was similar (p=0.71) in patients with intermediate (*n*=140, 63%) and with high PTP (*n*=40, 66%). Of the 88 patients with NSTEACS, a GRACE score > 140 was present in 11 (12%) patients. Of these, 5 patients had PCI within 24 hours.

Comprehensive Documentation and Appropriateness of Indications for Coronary Revascularization

A comprehensive documentation of PCI indication was present in 427 (97%) patients. Most common reasons for unfulfilling this diagnostic measure were the lack of documentation in the clinical chart of any non-invasive testing, both functional and imaging (n=5) or missing information on therapy at admission (n=8).

An AUS_{SITE} could be calculated in 405 (92%) of patients while the remaining 35 patients did not have comprehensive documentation of indications for PCI or the scenario was not applicable (ie non mappable AUC). The median AUS_{SITE} was 6 (5,7) corresponding to 153 (37.8%) of PCI classified as appropriate, 193 (47.7%) as uncertain, and 59 (14.6%) as inappropriate AUC, similar in patients with a and without diabetes (**Figure 1**). AUS_{SITE} was higher in patients evaluated by the local heart team as compared to patients who were not [7 (5,8) vs 5 (4,7); p=0.003].

An AUS_{CORE} could be calculated in 401 patients (91%). Of these, 23 (6%) required a review by the central heart team. Median AUS_{CORE} was 6 (5,7) with 155 (38.7%) of PCI classified as appropriate, 191 (47.6%) as uncertain, and 55 (13.7%) as inappropriate AUC. AUS_{CORE} results in key subgroups are reported in the **Supplementary Figure**. AUS_{CORE} was higher in patients with NSTEACS as compared to patients with stable CAD with no significant difference according to diabetic status or type of hospitals. AUS_{CORE} was higher in patients evaluated by the local heart team as compared to patients who were not [7 (6,8) vs 5 (4,7); p=0.001] (**Figure 2**).

Recommendation 1: Proportion of stable CAD patients with complex pathologies who were treated after heart team discussion

Of the 352 patients with stable CAD, 148 (42%) had a complex site-reported coronary anatomy including significant lesions of the left main (n=16), proximal LAD (n=73) and three-vessel disease (n=59). Of these, 17 (11%) underwent local heart

team discussion. Median operative mortality was low-to-intermediate as estimated by both the Euroscore II [1.15 % (0.64, 2.05)] and the STS score [0.92% (0.45,1.81)]. Also, 118 of the 148 patients with complex site-reported coronary anatomy (80%) received *ad hoc* PCI without evidence of discussion with the local heart team in the clinical chart, with no difference in patients treated at hospitals with or without on-site cardiac surgery (p=0.74). The proportion of patients with complex coronary lesions according to the ACL was 46% (n=164). Of these, 20 (12%) underwent local heart team discussion and 124 (75%) were treated *ad hoc* without evidence of heart team discussion.

The median SYNTAX score in patients with stable CAD was 12 (8-20), with 83% of patients with a score < 23, 13% between 23 and 32, and 4% above 32.

A SYNTAX II score could be calculated in 337 cases (96%). Of these, CABG was the recommended option for 40 patients (12%), PCI the recommended option for 14 (4%), and either mode of revascularization was recommended in the remaining 283 cases (84%). Of the 40 patients where SYNTAX II score recommended CABG a local heart team discussion was performed in 3 cases (7%). Finally, a total of 75 stable CAD patients (21%) with diabetes and multi-vessel CAD underwent *ad hoc* PCI without local heart discussion documented in the patient's chart.

Recommendation 2: Proportion of stable CAD patients with no evidence of ischemia where pressure derived fractional flow reserve (FFR) was used to identify haemodynamically relevant coronary lesion(s).

Of the 352 patients with stable CAD, 151 (43%) had no objective evidence of ischemia (135 patients had no provocative test of ischemia, 8 had negative testing and 8 inconclusive testing), 36 (10%) were asymptomatic and 82 (23%) had multi-vessel CAD according to the site. A pressure-derived FFR to guide PCI was used for 29

patients (8.2%) with stable CAD while intravascular ultrasound for 12 patients (3%). No PCI were guided by coronary optical coherence tomography.

Of the 151 patients with no evidence of ischemia, the ACL identified 28 patients (18%) with at least one borderline coronary lesion treated with PCI with FFR performed in 7 of these 28 cases (25%).

Of the 175 (50%) patients who had no objective evidence of ischemia or were asymptomatic, 33 borderline lesions were identified by the ACL with FFR performed in 10 cases. In the subgroup of 91 patients who also had site-reported multi-vessel CAD, 13 borderline lesions were identified by the ACL, with FFR performed in 4 cases.

Recommendation 3: Use of guideline-directed medical therapy at the time of PCI in patients with stable CAD

Of the 352 patients with stable CAD, 299 (85%) were treated with single antiplatelet therapy at the time of angiography (292 low-dose aspirin and 7 with clopidogrel) and 20 (6%) received dual antiplatelet therapy with aspirin and clopidogrel (only 1 reported case of aspirin intolerance who successfully underwent aspirin desensitization); 266 (76%) were on a statin (no reported case of statin intolerance); 202 (57%) received an ACE-I or an angiotensin receptor blocker (no reported case of allergy or intolerance). Among the subgroup of stable CAD patients with hypertension, heart failure (or asymptomatic left ventricular ejection fraction of 40% or less), or diabetes (N=265; 75% of the overall stable CAD population), a treatment with ACE-I or ARB was given to 176 patients (66%). Finally, a therapy with an anti-anginal agent (beta-blocker, calcium channel blocker, nitrates, ivabradine, or ranolazine) was administered to 237 patients overall and to 169 patients

of the 248 with symptoms of angina (68%). Overall a total of 100 patients (23%) received guideline-directed medical therapy at time of PCI.

Adoption of institutional heart-team protocols

Investigators from all participating centers (n=22) were interviewed and all responded. A written institutional heart-team protocol was available in 5 (23%) centers (1 with on-site cardiac surgery, 4 without on-site cardiac surgery) while in other 5 centers (3 with on-site cardiac surgery) heart team meetings were being scheduled on a regular basis (usually weekly). All other hospitals (n=12) did not have either a heart team institutional protocol or regularly planned heart team meetings.

Discussion

In this pilot investigation we assessed appropriateness of indication of coronary revascularization and adherence to key guideline recommendations in a real world population with a high prevalence of stable CAD and diabetes as well as multidisciplinary decision-making processes. We identified important gaps in implementations of guideline recommendations and opportunities to improve the care patients undergoing PCI.

Considerations on Appropriateness of Indication for Coronary Revascularization

The proportion of appropriate indication for coronary revascularization was 39% in the overall population and 32% in patients with stable CAD with similar rates observed using local vs ACL anatomical category. These proportions are similar to what was observed in the US when AUC were first released in 2009. [4,13] As expected, appropriateness was higher in patients with NSTEACS as compared to patients with stable CAD but similar according to diabetes status as well as in hospitals with and without on-site cardiac surgery. Importantly both AUS_{SITE} and AUS_{CORE} were

significantly higher in patients who were evaluated by a heart team suggesting multi-disciplinary decision-making is a surrogate of optimal revascularization choice.

In patients with stable CAD a functional testing strategy (used in 62% of patients) was far more common than an anatomical-testing strategy with coronary CTA (used only for 8% of patients), in agreement with the neutral findings of the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial. [14] Notably, the use of functional testing was similar in patients with intermediate and with high PTP of significant CAD suggesting that the determination of PTP, considered the first major step in clinical decision making in this patient population, [6] has limited influence in the real world to define a diagnostic strategy. Also, 33% of stable CAD patients with unknown coronary anatomy had neither functional nor anatomical testing before PCI and only 38% had maximal anti-ischemic medical therapy before PCI, proportions that have contributed to the observed suboptimal appropriateness and call for implementation of quality improvements initiatives. Indeed, it has been observed that most (55.5%) of Medicare patients with stable CAD do not have documentation of ischemia by noninvasive testing prior to elective PCI and that pre-PCI stress testing was associated with lower mortality in patients undergoing elective PCI. [15,16] Overall these findings suggest a need to focus on PTP assessment in decision-making, appropriate classification of risk by non-invasive tests, and optimization of medical therapy before PCI.

Adherence to and Implementation of ESC Guidelines

To explore potential "specialty bias" – ie PCI treatment in patients with an indication for CABG – we examined the proportion of patients with complex coronary lesions, including significant disease of the left main, proximal LAD, and/or three-vessel disease, who were treated *ad hoc* without evidence of heart team

discussion in the medical charts. We observed that only ≈ one of ten eligible patients underwent heart discussion and 75 to 80% of patients with complex coronary anatomy were treated *ad hoc*, with no significant differences in sites with and without on-site cardiac surgery. To further explore this, we surveyed investigators to better understand local decision-making processes. We observed that most sites did not have a written institutional protocol and decision of heart team convocation was left at the discretion of the interventional cardiologist on call. The high proportion of *ad hoc* PCI in patients with complex disease together with the lack of structured local heart teams identify a substantial opportunity to improve multidisciplinary decision making processes and indicate the need for standardized institutional protocols, that 1) should avoid the need for the systematic case-by-case review of all diagnostic angiograms but guide the management of complex cases 2) define standards for heart team composition and roles, and 3) generate consensus on practical ways to implement them.

The SYNTAX score is also considered by the guidelines to inform choice on optimal type of revascularization. This score, which relies on subjective assessment of lesions using coronary angiography, is well known to have limited reproducibility. [17] The highest kappa value observed in a study of the SYNTAX investigators to assess intra-observer variability was 0.54, and only 0.36 for bifurcations [17] and inter-observer reproducibility was even lower. [18] We therefore decided to adopt a conservative approach to define a disagreement between reviewers (arbitrarily defined as a difference of at least 10 points or change of tertile) but still observed a disagreement in 21% of patients. This variability suggests that for clinical decision-making SYNTAX score should not be used in isolation but rather integrated with clinical data. The SYNTAX II score was developed to address this need. By

implementing this score in the APACHE population, we observed that in the vast majority of patients (84%) either modality of revascularization was recommended. However in the 40 patients (12%) where CABG was modality of choice, a heart team discussion was performed only in 3 cases.

Fractional flow reserve, the current gold standard for the functional assessment of lesion severity [19], is recommended (class I, level of evidence A) to identify haemodynamically relevant coronary lesions in stable patients when evidence of ischaemia is not available or to assess the functional consequences of moderate coronary stenoses.[5] According to the ACL, the proportion of patients without documented ischemia or borderline coronary stenoses who had a FFR guided PCI was 25% although the absolute numbers were small (7 FFR in 28 patients). While recent data suggest that FFR use is increasing, these data indicate another gap in use of a well-established technique to define physiological consequences of a coronary stenosis thus optimizing appropriate indication for revascularization.

Finally, we observed that prescription of guideline-directed medical therapy before PCI was suboptimal with just 23% of patients on "optimal medical therapy" and a high prescription only for antiplatelet therapy before PCI (>90%). This gap may have multiple reasons including resource availability, patient's compliance, and physician preference but should be an important, and easily modifiable target, for any quality improvement initiative.

Conclusions

Use of heart teams approaches and adherence to guideline recommendation on coronary revascularization in a real world setting is limited. The APACHE study identifies substantial opportunities to improve the care of patients undergoing PCI.

Acknowledgments

We thank all investigators and patients who participated in this study to pioneer advancements in clinical care.

References

1. Chan PS, Rao SV, Bhatt DL, Rumsfeld JS, Gurm HS, Nallamothu BK, Cavender MA, Kennedy KF, Spertus JA. Patient and hospital characteristics associated with inappropriate percutaneous coronary interventions. J Am Coll Cardiol 2013;62(24):2274-81.
2. Baig SS, Altman DG, Taggart DP. Major geographical variations in elective coronary revascularization by stents or surgery in England. Eur J Cardiothorac Surg 2014.
3. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/ SCCT 2012 Appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2012;59(9): 857-81.
4. Desai NR, Bradley SM, Parzynski CS, Nallamothu BK, Chan PS, Spertus JA, Patel MR, Ader J, Soufer A, Krumholz HM, Curtis JP. Appropriate Use Criteria for Coronary Revascularization and Trends in Utilization, Patient Selection, and Appropriateness of Percutaneous Coronary Intervention. JAMA 2015;314(19):2045-53.
5. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35(37):2541-619.
6. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ; ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ,

Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013 Oct;34(38):2949-3003.

7. Nallamothu BK, Tommaso CL, Anderson HV, Anderson JL, Cleveland JC Jr, Dudley RA, Duffy PL, Faxon DP, Gurm HS, Hamilton LA, Jensen NC, Josephson RA, Malenka DJ, Maniu CV, McCabe KW, Mortimer JD, Patel MR, Persell SD, Rumsfeld JS, Shunk KA, Smith SC Jr, Stanko SJ, Watts B. ACC/AHA/SCAI/AMA-Convened PCPI/NCQA 2013 performance measures for adults undergoing percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures, the Society for Cardiovascular Angiography and Interventions, the American Medical Association-Convened Physician Consortium for Performance Improvement, and the National Committee for Quality Assurance. J Am Coll Cardiol 2014;63(7):722-45.
8. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Ståhle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381(9867):639-50.
9. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP; Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1--coronary artery bypass grafting surgery. Ann Thorac Surg 2009;88(1 Suppl):S2-22.
10. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. Eur J Cardiothorac Surg 2012;41(4):734-44; discussion 744-5.
11. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009 Jan 15;360(3):213-24.
12. Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB. Designing clinical research : an epidemiologic approach. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. Appendix 6E, page 81.
13. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA; American College of Cardiology Foundation Appropriateness Criteria Task Force.; Society for Cardiovascular Angiography and Interventions.; Society of

Thoracic Surgeons.; American Association for Thoracic Surgery.; American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography.; Heart Failure Society of America.; Society of Cardiovascular Computed Tomography. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol. 2009 Feb 10;53(6):530-53

14. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015 Apr 2;372(14):1291-300.
15. Lin GA, Dudley RA, Lucas FL, Malenka DJ, Vittinghoff E, Redberg RF. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. JAMA 2008;300(15):1765-73.
16. Lin GA, Lucas FL, Malenka DJ, Skinner J, Redberg RF. Mortality in Medicare patients undergoing elective percutaneous coronary intervention with or without antecedent stress testing. Circ Cardiovasc Qual Outcomes. 2013 May 1;6(3):309-14.
17. Garg S, Girasis C, Sarno G, Goedhart D, Morel MA, Garcia-Garcia HM, Bressers M, van Es GA, Serruys PW; SYNTAX trial investigators. The SYNTAX score revisited: a reassessment of the SYNTAX score reproducibility. Catheter Cardiovasc Interv. 2010 May 1;75(6):946-52.
18. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the syntax study. *EuroIntervention*. 2009;5(1):50-56.
19. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334(26):1703–1708.
20. Berwick DM. Avoiding overuse-the next quality frontier. Lancet 2017; S0140-6736(16)32570-3.

Text Tables

Table 1. Baseline characteristics, cardiovascular risk factors, and history stratified by clinical indication.

	Stable CAD (n=352)	NSTEACS (n=88)	Overall (n=440)
Age (years)	69.3 (62.9-75.1)	71 (63.4-77.4)	69.6 (63-75.8)
Females *n* (%)	71 (20)	27 (31)	98 (22)
BMI (kg/m^2)	26.2 (24.2-28.9)	27 (24.6-30)	26.3 (24.2-29.3)
Creatinine (mg/dl)	0.9 (0.79,1.08)	0.97 (0.85, 1.18)	0.91 (0.8, 1.10)
SYNTAX score	12 (8-20)	15 (8-20)	13 (8-20)
CV Risk Factors			
Diabetes *n* (%)	173 (49)	43 (49)	216 (49)
Hypertension *n* (%)	262 (75)	71 (78)	333 (75)
Dyslipidemia *n* (%)	190 (54)	48 (55)	238 (54)
Active smoker *n* (%)	53 (15)	16 (18)	69 (16)
Prior Smoker *n* (%)	85 (24)	13 (15)	98 (22)
History of premature CAD *n*(%)	99 (28)	19 (22)	118 (27)
History			
Prior Angina *n* (%)	250 (71)	52 (59)	302 (69)
Prior MI *n* (%)	95 (27)	20 (23)	115 (26)
Prior PCI *n* (%)	148 (42)	28 (32)	176 (40)
Renal Insufficiency *n* (%)	38 (11)	20 (23)	58 (13)
Heart Failure *n* (%)	14 (4)	2 (2)	16 (4)
LVSD *n* (%)	23 (7)	8 (9)	31 (7)
COPD *n* (%)	26 (7)	8 (9)	34 (8)
Stroke *n* (%)	18 (5)	5 (6)	23 (5)
PAD *n* (%)	55 (16)	10 (11)	65 (15)

Legend. BMI, Body mass index; SYNTAX: synergy between percutaneous coronary intervention with TAXUS and cardiac surgery; SCAD: coronary artery disease; NSTEACS: non-ST elevation acute coronary syndrome; MI: myocardial infarction; PCI: percutaneous coronary intervention; LVSD: left ventricular systolic dysfunction defined as ejection fraction of 0.40 or less; COPD: Chronic obstructive pulmonary disease; PAD: peripheral artery disease.

Table 2. Characterization of the indication for PCI in patients with stable CAD (n=352).

Parameter	Value
Pre-Test Probability of CAD (%) #	69 (54-84)
Low (<15%) *n* (%)	0 (0)
Intermediate (15-85%) *n* (%)	222 (78)
High (>85%) *n* (%)	61 (22)
Ad hoc PCI *n (%)*	307 (87)
Any functional test of ischemia performed *n (%)**	217 (62)
Exercise electrocardiography *n*	153
SPECT *n*	46
Stress echocardiography *n*	31
Stress cardiac magnetic resonance imaging *n*	3
Coronary computed tomographic angiography *n (%)*	27 (8)
No functional or anatomical testing *n (%)*	125 (35%)
AUC_{CORE} mappable	318 (90)
Appropriate *n* (%)	102 (32)
Uncertain *n* (%)	163 (51)
Inappropriate *n* (%)	52 (16)
AUC_{SITE} mappable	320 (91)
Appropriate *n* (%)	100 (31)
Uncertain *n* (%)	163 (51)
Inappropriate *n* (%)	57 (18)

#: Calculated according to (5) only in patients with unknown coronary anatomy (n=285): defined as a history of invasive coronary angiography or coronary computed tomography angiography in the year preceding the index PCI. *: Some patients (n=15) underwent more than 1 functional test before PCI 1 patient received 3 tests; SPECT: Single-Photon Emission Computed Tomography.

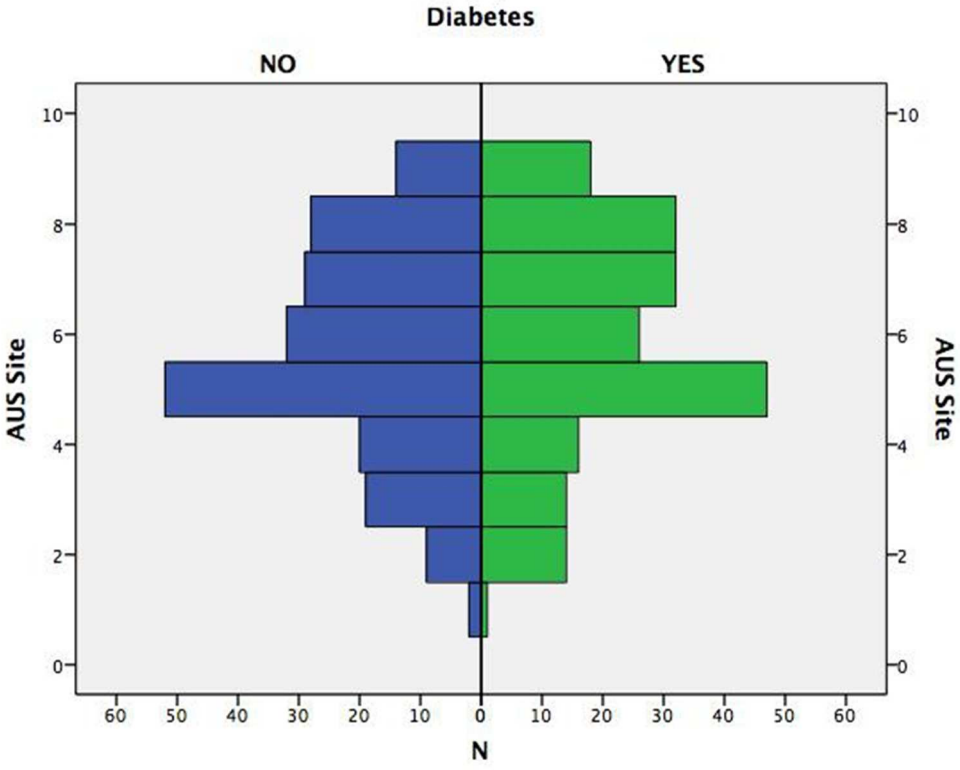
Author contributions:
Sergio Leonardi and Stefano De Servi: Study design, manuscript drafting, statistical analysis and critical revision.
Marcello Marino and Gabriele Crimi: angiographic core lab analysis, critical revision.
Florinda Maiorana, Diego Rizzotti: Data management, statistical analysis and critical revision
Corrado Lettieri, Luca Bettari, Marco Zuccari, Paolo Sganzerla, Simone Tresoldi, Marianna Adamo, Sergio Ghiringhelli, Carlo Sponzilli, Giampaolo Pasquetto, Andrea Pavei, Luigi Pedon, Luciano Bassan, Mario Bollati, Paola Camisasca, Daniela Trabattoni, Marta Brancati, Arnaldo Poli, Claudio Panciroli: critical Revision
Maddalena Lettino, Giuseppe Tarelli, Giuseppe Tarantini, Leonardo de Luca, Ferdinando Varbella: Central Heart Team and critical revision
Giuseppe Musumeci: Study design and critical revision

Competing interests
ICJME forms are available for all authors.
Dr Leonardi reports honoraria for advisory boards from AstraZeneca, Daiichi Sankyo, and The Medicines Company during the conduct of the study outside the submitted work; Dr. De Luca reports personal fees from Astra Zeneca, personal fees from Bayer , personal fees from Boehringer-Ingelheim, personal fees from

Eli Lilly and Daiichi Sankyo, personal fees from Menarini , personal fees from The Medicines Company, outside the submitted work. Dr. De Servi reports personal fees from Pfizer, personal fees from AstraZeneca, personal fees from Daichi-sankyo, personal fees from Correvio, outside the submitted work. The other authors report nothing to disclose. All authors have read and understood BMJ policy on declaration of interests and have no other relevant interests to declare in addition to these.

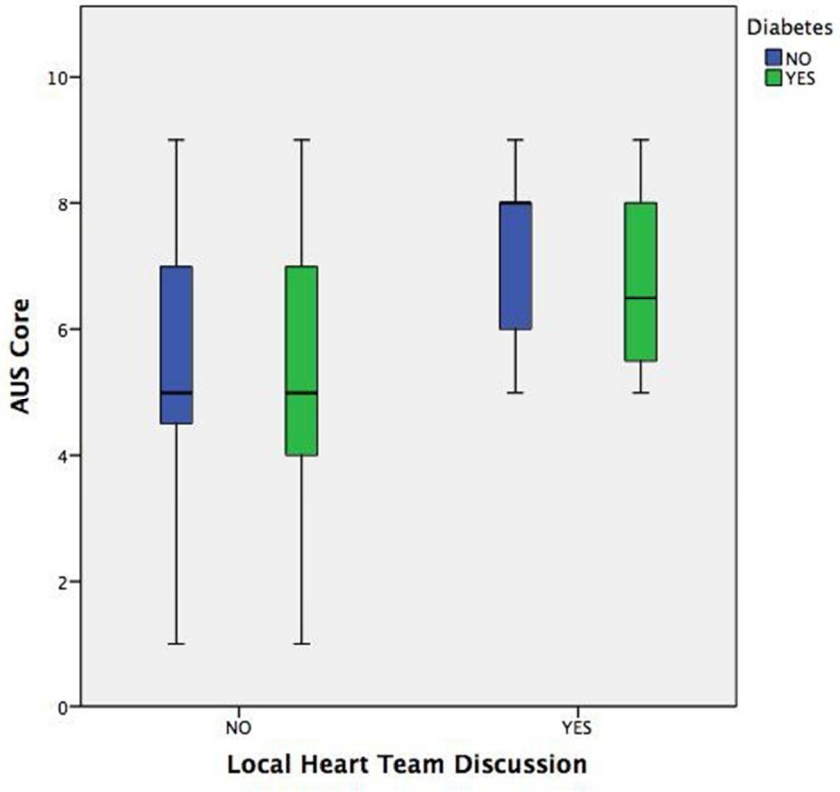
Data Sharing Statement

No additional unpublished data for this study will be available.



Histogram of Appropriate Use Score according to site-reported coronary anatomy (AUSSITE) in patients with and without diabetes.

220x176mm (72 x 72 DPI)



Boxplot of Appropriate Use Score according to ACL (AUSCORE) in patients who underwent and who did not underwent local heart team discussion, stratified by diabetes status.

220x176mm (72 x 72 DPI)

APPENDIX

Executive Committee and Medical Leadership

Stefano De Servi (study chair), Sergio Leonardi (principal investigator), Giuseppe Musumeci (GISE Lombardia President), Giuseppe Tarantini (GISE Veneto President).

Data management

Florinda Maiorana, Diego Rizzotti, Arianna Elia.

Central Heart Team

Maddalena Lettino, Giuseppe Tarelli, Ferdinando Varbella, Leonardo De Luca.

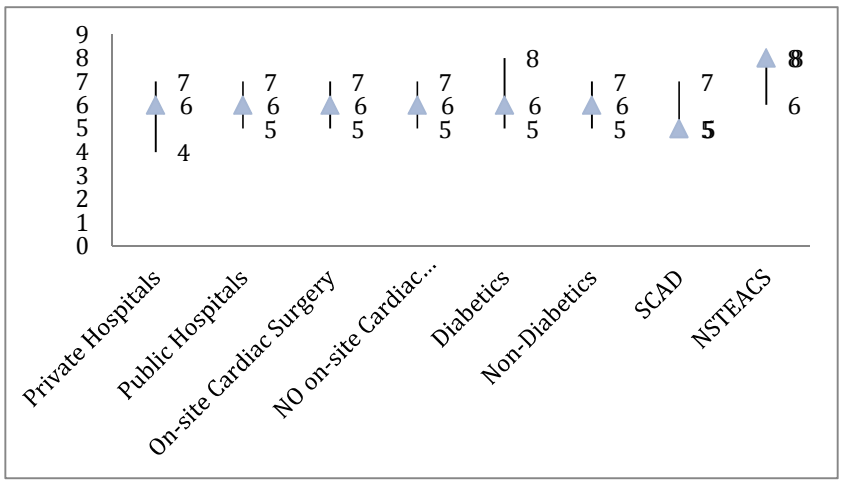
Angiographic Core Laboratory

Marcello Marino, Gabriele Crimi

Investigators

Maurizio Ferrario, *Fondazione IRCCS Policlinico San Matteo, Pavia, Italy;* Corrado Lettieri, *ASST Mantova – Ospedale Carlo Poma, Mantova, Italy;* Maurizio D'urbano, Marco Zuccari *Ospedale Fornaroli di Magenta, Magenta, Italy*; Enrico Passamonti, Luca Bettari, Sergio Signore, *Ospedale di Cremona, Cremona, Italy*; Paolo Sganzerla, Mauro Rondi, *Ospedale di Treviglio e Caravaggio, Treviglio, Italy*; Planca Enrico, Simone Tresoldi, *Azienda Ospedaliera di Desio e Vimercate, Vimercate, Italy*; Federica Ettori, Marianna Adamo, *Spedali Civili di Brescia, Brescia, Italy*; Sergio Ghiringhelli, *Ospedale di Circolo Fondazione Macchi, Varese, Italy*; Carlo Sponzilli, *Ospedale San Paolo, Milano, Italy*; Giuseppe Musumeci, Federica Piazzoni, *ASST – Papa Giovanni XXIII- Bergamo, Italy*; Giampaolo Pasquetto, Michela Facchin, *Ospedali Riuniti Padova Sud Madre Teresa di Calcutta, Monselice, Italy*; Andrea Pavei, Gerlando Preti, *Presidio Ospedaliero di Conegliano, Conegliano, Italy*; Luigi Pedon, *Presidio Ospedaliero di Cittadella, Cittadella, Italy*; Luciano Bassan, *ULSS 4 Alto Vicentino, Thiene, Italy*; Francesco Bedogni, Mario Bollati, Luca Testa, Giovanni Bianchi, *IRCCS Policlinico San Donato, San Donato Milanese, Italy*; Paola Camisasca, *Ospedale San Gerardo, Monza, Italy*; Daniela Trabattoni, *Centro Cardiologico Monzino, Milano, Italy*; Ornella Leonzi, Marta Brancati, *Fondazione Poliambulanza, Brescia, Italy*; Arnaldo Poli, Katia Stefanin, *ASST Ovest Milanese, Legnano, Italy*; Claudio Panciroli, Emanuele Prina, *ASST di Lodi, Lodi, Italy*; Paolo Pagnotta, Daniela Cattani, *IRCCS Humanitas, Rozzano (MI),Italy*; Giuseppe Tarantini, Ervis Hiso, *Ospedale Di Padova, Padova,Italy*.

Supplementary Figure



STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract (**Title Page**)
		(a)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (**Abstract Page 2**)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (**Introduction, page 4**)
Objectives	3	State specific objectives, including any prespecified hypotheses (**Objective, abstract**)
Methods		
Study design	4	Present key elements of study design early in the paper (**Study Design, page 5**)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (**Methods, page 5 and Results, page 11**)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants (**Methods, page 5, Patient Selection Section**)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (**Methods, page 5**)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (**Methods, page 5 Data Collection Section**)
Bias	9	Describe any efforts to address potential sources of bias (**Methods, page 5**)
Study size	10	Explain how the study size was arrived at (**Sample Size Consideration, page 10**)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (**Statistical Section for all below, page 10**)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (**Results, page 11**)
		(b) Give reasons for non-participation at each stage (**NA**)
		(c) Consider use of a flow diagram (**NA**)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (**Results, page 11**)
		(b) Indicate number of participants with missing data for each variable of interest (**Results, page 11**)
Outcome data	15*	Report numbers of outcome events or summary measures (**Results, page 11**)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included (**Results, page 11**)
		(*b*) Report category boundaries when continuous variables were categorized (**Results, page 11**)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (**Results, page 11**)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (**Results, page 11**)
Discussion		
Key results	18	Summarise key results with reference to study objectives (**Discussion, page 15**)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (**Discussion, page 15**)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (**Discussion, page 15**)
Generalisability	21	Discuss the generalisability (external validity) of the study results (**Discussion, page 15**)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (**Funding Statement, page 10**)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

APpropriAteness of percutaneous Coronary interventions in patients with ischemic HEart disease in Italy: The APACHE Pilot study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016909.R1
Article Type:	Research
Date Submitted by the Author:	19-Jun-2017
Complete List of Authors:	Leonardi, Sergio; Fondazione IRCCS Policlinico San Matteo, Marino, Marcello; Aziende Socio Sanitarie Territoriale di Crema Crimi , Gabriel ; Fondazione IRCCS Policlinico San Matteo, Maiorana, Florinda; Fondazione IRCCS Policlinico San Matteo Rizzotti, Diego; Fondazione IRCCS Policlinico San Matteo Lettieri, Corrado; Azienda Socio Sanitaria Territoriale di Mantova Bettari, Luca; Azienda Socio Sanitaria Territoriale di Cremona Zuccari, Marco Sganzerla, Paolo; Agenzia di Tutela della Salute di Bergamo Ovest Tresoldi, Simone ; Azienda Ospedaliera di Desio e Vimercate Adamo, Marianna; Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia Ghiringhelli, Sergio; Ospedale di Circolo e Fondazione Macchi Sponzilli, Carlo; Ospedale San Paolo Pasquetto, Giampaolo; Presidio Ospedaliero di Monselice Pavei, Andrea; Presidio di Conegliano Pedon, Luigi; Presidio Ospedaliero di Cittadella Bassan, Luciano; Azienda ULSS 4 Alto Vicentino Bollati, Mario; IRCCS Policlinico San Donato Camisasca, Paola; Azienda Ospedaliera San Gerardo Trabattoni, Daniela; Centro Cardiologico Monzino Brancati, Marta; Fondazione Poliambulanza Istituto Ospedaliero Poli, Arnaldo; Aziende Socio Sanitarie Territoriale Ovest Milanese Panciroli, Claudio Lettino, Maddalena; Istituto Clinico Humanitas Tarelli, Giuseppe; Istituto Clinico Humanitas Tarantini, Giuseppe; Azienda Ospedaliera di Padova De Luca, Leonardo; Ospedale di Tivoli Varbella, Ferdinando; 1Cardiology Unit, Ospedale degli Infermi, Musumeci, Giuseppe; Azienda Ospedaliera S Croce e Carle Cuneo De Servi, Stefano; IRCCS Sesto San Giovanni
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Health services research
Keywords:	Coronary heart disease < CARDIOLOGY, Percutaneous Coronary Intervention, Multidisciplinary Decision Making

APpropriAteness of percutaneous Coronary interventions in patients with ischemic HEart disease in Italy: The APACHE Pilot study

Sergio Leonardi, MD, MHS, FESC [1] Marcello Marino, MD [2] Gabriele Crimi, MD [1] Florinda Maiorana, MSc, [1] Diego Rizzotti, MSc [1] Corrado Lettieri, MD [3] Luca Bettari, MD [4] Marco Zuccari, MD[5] Paolo Sganzerla, MD [6] Simone Tresoldi, MD [7] Marianna Adamo, MD [8] Sergio Ghiringhelli, MD [9] Carlo Sponzilli, MD [10] Giampaolo Pasquetto, MD [11] Andrea Pavei, MD [12] Luigi Pedon, MD [13] Luciano Bassan, MD [14] Mario Bollati, MD [15] Paola Camisasca, MD [16] Daniela Trabattoni ,MD [17] Marta Brancati, MD [18] Arnaldo Poli, MD [19] Claudio Panciroli, MD [20] Maddalena Lettino, MD [21] Giuseppe Tarelli[21], MD Giuseppe Tarantini, MD [22] Leonardo De Luca, MD [23] Ferdinando Varbella, MD [24], Giuseppe Musumeci, MD [25] *and* Stefano De Servi, MD, FESC [26].

1: Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
2: Ospedale Maggiore di Crema, Crema, Italy
3: ASST Mantova – Ospedale Carlo Poma, Mantova, Italy
4: ASST Cremona – Ospedale di Cremona, Cremona, Italy
5: Ospedale Fornaroli di Magenta, Magenta, Italy
6: ASST Bergamo ovest – Ospedale di Treviglio, Italy
7: Azienda Ospedaliera di Desio e Vimercate, Vimercate, Italy
8: Spedali Civili di Brescia, Brescia, Italy
9: Ospedale di Circolo Fondazione Macchi, Varese,Italy
10: Ospedale San Paolo, Milano, Italy
11: Ospedali Riuniti Padova Sud Madre Teresa di Calcutta, Monselice, Italy
12: Presidio Ospedaliero di Conegliano, Conegliano, Italy
13: Presidio Ospedaliero di Cittadella, Cittadella, Italy
14: ULSS 4 Alto Vicentino, Thiene, Italy
15: IRCCS Policlinico San Donato, San Donato Milanese, Italy
16: Ospedale San Gerardo, Monza, Italy
17: Centro Cardiologico Monzino, Milano, Italy
18: Fondazione Poliambulanza, Brescia, Italy
19: ASST Ovest Milanese, Legnano, Italy
20: ASST di Lodi, Lodi, Italy
21: Humanitas Research Hospital, Rozzano (MI), Italy
22: Ospedale di Padova, Padova, Italy
23: Ospedale San Giovanni Evangelista, Tivoli (Rome), Italy
24: Ospedale degli Infermi, Rivoli, Italy
25: ASST – Papa Giovanni XXIII- Bergamo, Italy
26: IRCCS MultiMedica, Milano, Italy

Word Count: 4093

Address for correspondence
Sergio Leonardi, MD, MHS, FESC
Fondazione IRCCS Policlinico S. Matteo
Viale Golgi 19
27100
Pavia, Italy
S.Leonardi@smatteo.pv.it

Abstract *Word count: 305*

Objectives: To first explore in Italy appropriateness of indication, adherence to guideline recommendations, and mode of selection for coronary revascularization.

Design: Retrospective, pilot study.

Setting: Twenty-two percutaneous coronary intervention (PCI)-performing hospitals (20 patients/site), 13 (59%) with on-site cardiac surgery.

Participants: 440 patients who received PCI for stable coronary artery disease (CAD) or non-ST elevation acute coronary syndrome were independently selected in a 4:1 ratio with half diabetics.

Primary and Secondary Outcome Measures: Proportion of patients who received appropriate PCI using validated appropriate use scores (ie AUS ≥ 7). Also, in patients with stable CAD, we examined adherence to the following ESC recommendations: a) % of patients with complex coronary anatomy treated after heart-team discussion; b) % of fractional flow reserve-guided PCI for borderline stenoses in patients without documented ischemia; c) % of patients receiving guideline-directed medical therapy at the time of PCI as well as use of provocative test of ischemia according to pre-test probability (PTP) of CAD.

Results: Of the 401 mappable PCIs (91%), 38.7% (95%CI: 33.9-43.6) were classified as appropriate, 47.6% (95%CI: 42.7-52.6) as uncertain, and 13.7% (95%CI: 10.5-17.5%) as inappropriate. Median PTP in stable CAD patients without known coronary anatomy was 69% (78% intermediate PTP, 22% high PTP). Ischemia testing use was similar (p=0.71) in patients with intermediate (*n*=140, 63%) and with high PTP (*n*=40, 66%). In patients with stable CAD (n=352) guideline adherence to the 3 recommendations explored was: a) 11%; b) 25%; c) 23%. AUS was higher in patients

evaluated by the heart team as compared to patients who were not [7 (6,8) vs 5 (4,7); P=0.001].

Conclusions: Use of heart-teams approaches and adherence to guideline recommendations on coronary revascularization in a real world setting is limited. This pilot study documents the feasibility of measuring appropriateness and guideline adherence in clinical practice and identifies substantial opportunities for quality improvement.

Study Registration: NCT02748603.

Strengths and limitations of this study

- APACHE is a first-in-class study in Italy designed to measure the degree of appropriateness of indication, multi-disciplinary decision-making processes, and implementation of key guideline recommendations in patients undergoing PCI.
- This study, that enrolled patients with stable CAD and diabetes, was intentionally designed to focus on high-risk patients for inappropriate PCI. Therefore true appropriateness of PCI may be underestimated. However, rather than an epidemiological study, APACHE intention was to serve as first initiative sponsored by a national medical society to measure care process and improve quality.
- APACHE examined the appropriateness of PCI indication, not of coronary angiography. Therefore we acknowledge as a limitation that we have no data to inform appropriateness of surgical revascularization, nor indication to invasive angiography.

Introduction

Percutaneous coronary intervention (PCI) has dramatically improved the prognosis of patients with coronary artery disease (CAD). Yet, many patients receive PCI whose clinical indication appears uncertain or inappropriate, especially in the non-acute setting. [1,2] The development of appropriate use criteria by cardiovascular societies has provided the basis for a standardized approach to systematically assess the clinical appropriateness of PCI [3] and has produced a reduction of the volume of non-acute PCI as well as an increase in the proportion of procedures classified as appropriate [4] but these studies have been mostly performed in the US.

In Europe, data on appropriateness of indication and mode of selection for coronary revascularization strategies as well as the degree of implementation of guideline recommendations are limited. [5] European Society of Cardiology (ESC) guidelines [6,7] urge the implementation of a multidisciplinary decision-making approach – the heart team – to select the optimal mode of revascularization but data on the implementation of this process in patients with complex coronary artery disease (CAD), including those with stable CAD and diabetes, are scarce. [8] Specifically the ESC [6,7] recommend that 1) complex pathologies in stable patients, including lesions of the left main or proximal left anterior descending artery (LAD) and three-vessel disease, should in general not be treated *ad hoc*, but discussed by the heart team; 2) pressure derived fractional flow reserve (FFR) should be used to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available; and 3) patients with stable CAD must receive guideline-recommended medical treatment prior to revascularization.

We designed the APpropriAteness of percutaneous Coronary interventions in patients with ischemic HEart disease – APACHE Pilot study to first explore the degree of appropriateness of indication of PCI, multi-disciplinary decision-making

processes, and implementation of key guideline recommendations in patients undergoing PCI in Italy.

Methods

Study Design and Patient Selection

APACHE was designed as a pilot initiative to assess appropriateness of PCI indication and adherence to key guideline recommendations on coronary revascularization in patients with predominantly stable CAD and diabetes, considered to be at high risk for inappropriate indication and mode for coronary revascularization (ie PCI treatment in patients with an indication for CABG). All PCI performing hospitals of the Lombardia and Veneto region in Italy, serving a population of ≈ 15.000.000 people, were invited to participate in the study. Twenty-two sites agreed to participate, obtained regulatory approval, and were eventually included.

At each participating hospital, 20 patients were independently selected on-site by the study team (see online appendix) among consecutive patients who were admitted in the previous year for an elective procedure to treat stable CAD or urgently for an episode of non-ST elevation acute coronary syndrome in a 4:1 ratio without site personnel involvement in the selection of the cases identified to minimize selection bias. The study population was also selected to preserve an overall 1:1 ratio on diabetes status. If the number of patients selected was insufficient older cases were evaluated for possible inclusion. Due to the low likelihood of receiving a *redo* procedure as well as the inability to measure a SYNTAX score, patients with a history of bypass surgery were excluded.

Data Collection, Core Angiographic Assessment, and Central Heart Team

Variables of interest were collected by the study team during dedicated visits at participating hospitals via clinical chart abstraction. Sites were requested to provide

the complete clinical chart, including the coronary angiogram of the index PCI. Source documentation was reviewed in full to abstract symptoms status (angina class); cardiovascular risk factors and comorbidities; medical therapy at time of PCI; site-reported indication for PCI; presence, results, and timing of any noninvasive functional test, fractional flow reserve (FFR) or intracoronary imaging, if performed; coronary anatomy and reported significance of angiographic stenoses for treated lesion(s) on the catheterization report; and evidence for heart-team discussion involving a cardiac surgeon. Finally, pretest probability (PTP) of significant coronary artery disease was calculated in patients with stable CAD according to guideline recommendations [7].

The Angiographic Core Laboratory (ACL) was composed by two independent physicians with experience in interventional cardiology (MM, GC) who centrally and independently reviewed coronary angiography for each patient to define 1) baseline SYNTAX score 2) category of coronary anatomy (eg. one, two or three-vessel CAD with or without proximal LAD involvement) [3] and 3) presence of "borderline" angiographic stenoses (50% to 60%). For the SYNTAX score a disagreement was arbitrarily considered to be present if there was a between score difference ≥ 10 or both scores were not in the same tertile (0-22, 23-32, >32). In case of agreement an average SYNTAX score was calculated. In case of disagreement between reviewers the case was first resolved by consensus. If a consensus could not be reached (or if the case was deemed particularly challenging) the conflict was resolved by the central heart team. Anatomical category and presence of borderline coronary stenoses were analyzed by a single reviewer (GC or MM).

The central heart team was represented by four members – two interventional cardiologists (LDL, FV), one cardiac surgeon (GT), and one clinical cardiologist

(ML) – nominated by the Italian Society of Interventional Cardiology (SICI-GISE) among recognized experts in their respective specialty. The role of the central heart team was to review cases with unresolved conflicts by the ACL, cases considered complex or challenging by the study team or cases with incomplete or conflicting documentation. Assessments of the central heart team were performed by consensus.

Evaluation of Appropriateness of Indications for Coronary Revascularization

The comprehensive documentation of indications for PCI was formally examined based on the 2013 ACC/AHA/SCAI/AMA-PCPI/NCQA Percutaneous Coronary Intervention Measurement Set. [9] This diagnostic measure was defined as the proportion of patients whose clinical documentation includes, at a minimum, the following elements:

1. Priority (acute coronary syndrome, elective, urgent, emergency/salvage); 2. Presence and severity of angina symptoms (eg, Canadian Cardiovascular Society classification system); 3. Use of antianginal medical therapies within 2 weeks before the procedure, if any; 4. Presence, results, and timing of noninvasive stress test, FFR, or intravascular ultrasound, if performed; and 5. Significance of angiographic stenosis on coronary angiography for treated lesion.

Appropriateness of indication of coronary revascularization was examined by assigning to each procedure an appropriate use score (AUS), with a score of 1 indicating a completely inappropriate procedure to a score of 9 indicating a completely appropriate one. [3] Scores of 7 to 9 indicate that revascularization is considered generally appropriate and likely to improve patients' symptoms or survival. Scores of 1 to 3 considered generally inappropriate while scores of 4 to 6 indicate a clinical scenario for which the likelihood that coronary revascularization will improve health outcomes or symptoms is uncertain. This score was defined by

considering clinical presentation; severity of angina; extent of ischemia on noninvasive testing; presence of other prognostic factors, such as congestive heart failure or depressed left ventricular function; extent of medical therapy at the time of PCI; and extent of anatomic coronary disease. If the scenario was not considered by the consensus document, [3] the procedure was considered non mappable.

To limit site operator-related bias, the study team calculated two scores for each procedure:

1. AUS_{SITE}, based on site-reported extent of anatomic coronary disease;
2. AUS_{CORE}, based on ACL reported extent of anatomic coronary disease.

Evaluation of adherence to ESC Guidelines and Heart Team Processes

In patients with stable CAD we assessed adherence to three class I recommendations according to ESC guidelines [6,7]:

Recommendation 1: Proportion of patients with stable CAD and complex anatomy [including lesions of the left main, proximal left anterior descending (LAD) and/or three-vessel CAD] who were treated after local heart team discussion. This recommendation was explored using both site-reported and ACL-reported coronary anatomy. We also explored adherence to this recommendation by calculating the proportion of patients with complex anatomy who received *ad hoc* PCI without documented heart team discussion. To better define optimal mode of coronary revascularization, the SYNTAX II score [10] as well as the Society of Thoracic Surgeons (STS) [11], and EuroScore II [12] were calculated.

Recommendation 2: Proportion of patients with stable CAD, no evidence of ischemia, and borderline lesions according to the ACL in whom FFR was used to identify haemodynamically relevant coronary lesion(s).

Specifically, this recommendation was explored as follows:

a) Proportion of patients with no functional test (ie test negative or not performed) and at least one borderline stenosis according to ACL in whom pressure-derived FFR was used;

b) Proportion of patients with no functional test or asymptomatic and at least one borderline stenosis according to ACL in whom pressure derived FFR was used;

c) Proportion of patients with no functional test or asymptomatic and site-reported multivessel CAD in whom pressure derived FFR was used. [13]

Recommendation 3: Proportion of patients with stable CAD who received guideline-directed medical therapy prior to revascularization. [7]

Specifically:

a) Proportion of patients without known allergy or documented intolerance taking low dose aspirin (75-150 mg daily) or clopidogrel;

b) Proportion of patients without known allergy or documented intolerance receiving a statin;

c) Proportion of patients with heart failure, hypertension or diabetes treated with an ACE-inhibitor or angiotensin receptor blocker;

d) Proportion of patients on optimal medical therapy defined as drugs for event prevention (aspirin and/or clopidogrel; a statin; an ACE-I/ARB if heart failure, hypertension or diabetes) plus at least one drug for angina relief if symptomatic, such as beta-blockers, calcium channel blockers, long acting nitrates, ivabradine, or ranolazine.

In patients with NSTEACS, we examined the proportion of PCI procedures performed within 24 hours of admission in patients with a Global Registry of Acute Coronary Events (GRACE) score > 140.

Finally we assessed, by structured investigators surveys, the presence of written institutional protocols developed locally by the Heart Team in accordance with current guidelines including specific anatomical criteria and clinical subsets that may be (or should not be) treated *ad hoc* as well as the modalities and timing for convocation of heart team meetings.

Statistical Analysis and Sample Size Considerations

Categorical data are presented as counts and proportion and continuous data as median (25^{th}, 75^{th} percentile) and were analyzed, as appropriate, using chi-square (or Fisher's exact) and Wilcoxon rank-sum test. We calculated 95% confidence intervals for the proportion using the normal approximation to the binomial calculation. To control for the effect of participating site as well as the presence of cardiac surgery on-site on the primary outcome (AUS), we used ANOVA generalized linear model procedures including participating site and presence of cardiac surgery on-site as a covariates for the key subgroup (factor) of interest (ie. patients evaluated by the heart team vs not).

Given the lack of prior studies to estimate appropriateness of coronary revascularization in Italy, sample size estimation was challenging. The study was powered on the primary subgroup of interest, patients with stable CAD, assuming an appropriateness of 35% in this patient population based on prior reports. [4] Using a normal approximation to the binomial distribution for this proportion a population of 350 stable CAD patients was needed to obtain a 95% confidence interval between 30% and 40% for appropriateness. [14] The study obtained institutional review board approval by all participating hospitals and is registered on ClinicalTrial.Gov ID: NCT02748603.

Sponsor and Funding

The APACHE study was designed by the chair and principal investigator and approved by the institutional review board at each participating center. The study was sponsored by the Italian Society of Invasive Cardiology (SICI-GISE), a nonprofit organization, and received unrestricted grant support from the Abbott Vascular and Daiichi-Sankyo. The sponsor and funders had no role in the design of the study, the collection, monitoring, analysis, and interpretation of the data, or the writing of the report. The first draft of the manuscript was written by the first author. All the authors vouch for the accuracy and completeness of the data and all analyses.

Results

Of the 22 hospitals included, 13 (59%) have onsite cardiac surgery and 4 (18%) are private hospitals. Overall, PCI procedures of 440 patients (performed between January 2014 and May 2016) were included: 352 for patients with stable CAD and 88 with NSTEACS [12 with unstable angina and 76 with non-ST elevation myocardial infarction; median GRACE score 109 (89.5, 125.5), median Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) score 24 (16,40)]. A SYNTAX score could be calculated in 422 patients (96%) with 87 disagreements (21%) between ACL reviewers. Of these, 55 were resolved by consensus and 32 by the central heart team. Clinical profile of the selected patients stratified by clinical indication is showed in **Table 1**. By design, ≈ half of the patients had diabetes (n=216, 49.1%) with a high proportion of patients with dyslipidemia (54%), prior PCI (40%) and history of angina (69%). **Table 2** presents data on indication and test selection in patients with stable CAD. Median PTP of CAD in stable CAD patients without known coronary anatomy was 69% (78% intermediate PTP, 22% high PTP, no patient with low PTP). The use of provocative tests of ischemia was similar

(p=0.71) in patients with intermediate (*n*=140, 63%) and with high PTP (*n*=40, 66%). Of the 88 patients with NSTEACS, a GRACE score > 140 was present in 11 (12%) patients. Of these, 5 patients had PCI within 24 hours.

Comprehensive Documentation and Appropriateness of Indications for Coronary Revascularization

A comprehensive documentation of PCI indication was present in 427 (97%) patients. Most common reasons for unfulfilling this diagnostic measure were the lack of documentation in the clinical chart of any non-invasive testing, both functional and imaging (n=5) or missing information on therapy at admission (n=8).

An AUS_{SITE} could be calculated in 405 (92%) of patients while the remaining 35 patients did not have comprehensive documentation of indications for PCI or the scenario was not applicable (ie non mappable AUC). The median AUS_{SITE} was 6 (5,7) corresponding to 153 (37.8%, 95%CI: 33.1-43.5) of PCI classified as appropriate, 193 (47.7%, 95%CI: 42.8-52.5) as uncertain, and 59 (14.6%, 95%CI: 11.1-18) as inappropriate AUC, similar in patients with a and without diabetes (**Figure 1 and Figure 2A**). AUS_{SITE} was higher in patients evaluated by the local heart team as compared to patients who were not, both in unadjusted [7 (5,8) vs 5 (4,7); p=0.003] and adjusted analysis (mean AUS_{SITE} 7.0, SD 1.8 vs 5.7 SD 1.9; p=0.001; participating site and cardiac surgery on-site both NS).

An AUS_{CORE} could be calculated in 401 patients (91%). Of these, 23 (6%) required a review by the central heart team. Median AUS_{CORE} was 6 (5,7) with 155 (38.7%, 95%CI:33.9-43.4) of PCI classified as appropriate, 191 (47.6%,95%CI: 42.7-52.5) as uncertain, and 55 (13.7%,95%CI:10.3-17.1) as inappropriate AUC. AUS_{CORE} results by site and in key subgroups are reported in the **Figure 2B** and the **Supplementary Figure respectively**. AUS_{CORE} was higher in patients with

NSTEACS as compared to patients with stable CAD with no significant difference according to diabetic status or type of hospitals. AUS_{CORE} was higher in patients evaluated by the local heart team as compared to patients who were not both in unadjusted [7 (6,8) vs 5 (4,7); p=0.001] and adjusted analysis (mean AUS_{CORE} 7.1, SD 1.5 vs 5.8 SD 1.9; p=0.001; participating site and cardiac surgery on-site both NS). (**Figure 3**).

Recommendation 1: Proportion of stable CAD patients with complex pathologies who were treated after heart team discussion

Of the 352 patients with stable CAD, 148 (42%) had a complex site-reported coronary anatomy including significant lesions of the left main (n=16), proximal LAD (n=73) and three-vessel disease (n=59). Of these, 17 (11%) underwent local heart team discussion. Median operative mortality was low-to-intermediate as estimated by both the Euroscore II [1.15 % (0.64, 2.05)] and the STS score [0.92% (0.45,1.81)]. Also, 118 of the 148 patients with complex site-reported coronary anatomy (80%) received *ad hoc* PCI without evidence of discussion with the local heart team in the clinical chart, with no difference in patients treated at hospitals with or without on-site cardiac surgery (p=0.74). The proportion of patients with complex coronary lesions according to the ACL was 46% (n=164). Of these, 20 (12%) underwent local heart team discussion and 124 (75%) were treated *ad hoc* without evidence of heart team discussion.

The median SYNTAX score in patients with stable CAD was 12 (8-20), with 83% of patients with a score < 23, 13% between 23 and 32, and 4% above 32.

A SYNTAX II score could be calculated in 337 cases (96%). Of these, CABG was the recommended option for 40 patients (12%), PCI the recommended option for 14 (4%), and either mode of revascularization was recommended in the remaining 283 cases (84%). Of the 40 patients where SYNTAX II score recommended CABG a

local heart team discussion was performed in 3 cases (7%). Finally, a total of 75 stable CAD patients (21%) with diabetes and multi-vessel CAD underwent *ad hoc* PCI without local heart team discussion documented in the patient's chart.

Recommendation 2: Proportion of stable CAD patients with no evidence of ischemia where pressure derived fractional flow reserve (FFR) was used to identify haemodynamically relevant coronary lesion(s).

Of the 352 patients with stable CAD, 151 (43%) had no objective evidence of ischemia (135 patients had no provocative test of ischemia, 8 had negative testing and 8 inconclusive testing), 36 (10%) were asymptomatic and 82 (23%) had multi-vessel CAD according to the site. A pressure-derived FFR to guide PCI was used for 29 patients (8.2%) with stable CAD while intravascular ultrasound for 12 patients (3%). No PCI were guided by coronary optical coherence tomography.

Of the 151 patients with no evidence of ischemia, the ACL identified 28 patients (18%) with at least one borderline coronary lesion treated with PCI with FFR performed in 7 of these 28 cases (25%).

Of the 175 (50%) patients who had no objective evidence of ischemia or were asymptomatic, 33 borderline lesions were identified by the ACL with FFR performed in 10 cases. In the subgroup of 91 patients who also had site-reported multi-vessel CAD, 13 borderline lesions were identified by the ACL, with FFR performed in 4 cases.

Recommendation 3: Use of guideline-directed medical therapy at the time of PCI in patients with stable CAD

Of the 352 patients with stable CAD, 299 (85%) were treated with single antiplatelet therapy at the time of angiography (292 low-dose aspirin and 7 with clopidogrel) and 20 (6%) received dual antiplatelet therapy with aspirin and clopidogrel (only 1 reported case of aspirin intolerance who successfully underwent

aspirin desensitization); 266 (76%) were on a statin (no reported case of statin intolerance); 202 (57%) received an ACE-I or an angiotensin receptor blocker (no reported case of allergy or intolerance). Among the subgroup of stable CAD patients with hypertension, heart failure (or asymptomatic left ventricular ejection fraction of 40% or less), or diabetes (N=265; 75% of the overall stable CAD population), a treatment with ACE-I or ARB was given to 176 patients (66%). Finally, a therapy with an anti-anginal agent (beta-blocker, calcium channel blocker, nitrates, ivabradine, or ranolazine) was administered to 237 patients overall and to 169 patients of the 248 with symptoms of angina (68%). Overall a total of 100 patients (23%) received guideline-directed medical therapy at time of PCI.

Adoption of institutional heart-team protocols

Investigators from all participating centers (n=22) were interviewed and all responded. A written institutional heart-team protocol was available in 5 (23%) centers (1 with on-site cardiac surgery, 4 without on-site cardiac surgery) while in other 5 centers (3 with on-site cardiac surgery) heart team meetings were being scheduled on a regular basis (usually weekly). All other hospitals (n=12) did not have either a heart team institutional protocol or regularly planned heart team meetings.

Discussion

In this pilot investigation we assessed appropriateness of indication of coronary revascularization and adherence to key guideline recommendations in a real world population with a high prevalence of stable CAD and diabetes as well as multidisciplinary decision-making processes. We identified important gaps in implementations of guideline recommendations and opportunities to improve the care patients undergoing PCI.

Considerations on Appropriateness of Indication for Coronary Revascularization

The proportion of appropriate indication for coronary revascularization was 39% in the overall population and 32% in patients with stable CAD with similar rates observed using local vs ACL anatomical category. These proportions are similar to what was observed in the US when AUC were first released in 2009. [4,15] As expected, appropriateness was higher in patients with NSTEACS as compared to patients with stable CAD but similar according to diabetes status as well as in hospitals with and without on-site cardiac surgery. Importantly both AUS_{SITE} and AUS_{CORE} were significantly higher in patients who were evaluated by a heart team suggesting multi-disciplinary decision-making is a surrogate of optimal revascularization choice.

In patients with stable CAD a functional testing strategy (used in 62% of patients) was far more common than an anatomical-testing strategy with coronary CTA (used only for 8% of patients), in agreement with the neutral findings of the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial. [16] Notably, the use of functional testing was similar in patients with intermediate and with high PTP of significant CAD suggesting that the determination of PTP, considered the first major step in clinical decision making in this patient population, [7] has limited influence in the real world to define a diagnostic strategy. Also, 33% of stable CAD patients with unknown coronary anatomy had neither functional nor anatomical testing before PCI and only 38% had maximal anti-ischemic medical therapy before PCI, proportions that have contributed to the observed suboptimal appropriateness and call for implementation of quality improvements initiatives. Indeed, it has been observed that most (55.5%) of Medicare patients with stable CAD do not have documentation of ischemia by noninvasive testing prior to elective PCI and that pre-PCI stress testing was associated with lower mortality in patients

undergoing elective PCI. [17,18] Overall these findings suggest a need to focus on PTP assessment in decision-making, appropriate classification of risk by non-invasive tests, and optimization of medical therapy before PCI.

Adherence to and Implementation of ESC Guidelines

To explore potential "specialty bias" – ie PCI treatment in patients with an indication for CABG – we examined the proportion of patients with complex coronary lesions, including significant disease of the left main, proximal LAD, and/or three-vessel disease, who were treated *ad hoc* without evidence of heart team discussion in the medical charts. We observed that only ≈ one of ten eligible patients underwent heart team discussion and 75 to 80% of patients with complex coronary anatomy were treated *ad hoc*, with no significant differences in sites with and without on-site cardiac surgery. To further explore this, we surveyed investigators to better understand local decision-making processes. We observed that most sites did not have a written institutional protocol and decision of heart team convocation was left at the discretion of the interventional cardiologist on call. The high proportion of *ad hoc* PCI in patients with complex disease together with the lack of structured local heart teams identify a substantial opportunity to improve multidisciplinary decision making processes and indicate the need for standardized institutional protocols, that 1) should avoid the need for the systematic case-by-case review of all diagnostic angiograms but guide the management of complex cases 2) define standards for heart team composition and roles, and 3) generate consensus on practical ways to implement them.

The SYNTAX score is also considered by the guidelines to inform choice on optimal type of revascularization. This score, which relies on subjective assessment of lesions using coronary angiography, is well known to have limited reproducibility. [19]

The highest kappa value observed in a study of the SYNTAX investigators to assess intra-observer variability was 0.54, and only 0.36 for bifurcations [19] and inter-observer reproducibility was even lower. [20] We therefore decided to adopt a conservative approach to define a disagreement between reviewers (arbitrarily defined as a difference of at least 10 points or change of tertile) but still observed a disagreement in 21% of patients. This variability suggests that for clinical decision-making SYNTAX score should not be used in isolation but rather integrated with clinical data. The SYNTAX II score was developed to address this need. By implementing this score in the APACHE population, we observed that in the vast majority of patients (84%) either modality of revascularization was recommended. However in the 40 patients (12%) where CABG was modality of choice, a heart team discussion was performed only in 3 cases.

Fractional flow reserve, the current gold standard for the functional assessment of lesion severity [21], is recommended (class I, level of evidence A) to identify haemodynamically relevant coronary lesions in stable patients when evidence of ischaemia is not available or to assess the functional consequences of moderate coronary stenoses.[6] According to the ACL, the proportion of patients without documented ischemia or borderline coronary stenoses who had a FFR guided PCI was 25% although the absolute numbers were small (7 FFR in 28 patients). While recent data suggest that FFR use is increasing, these data indicate another gap in use of a well-established technique to define physiological consequences of a coronary stenosis thus optimizing appropriate indication for revascularization.

Finally, we observed that prescription of guideline-directed medical therapy before PCI was suboptimal with just 23% of patients on “optimal medical therapy” and a high prescription only for antiplatelet therapy before PCI (>90%). This gap may

have multiple reasons including resource availability, patient's compliance, and physician preference but should be an important, and easily modifiable target, for any quality improvement initiative. By quality we intend the degree of match between health care services and the needs they are intended to meet. [22] APACHE was designed to first quantify this match, inform the design of future investigations on this topic (including a planned larger initiative in Italy extended to the whole country designed to develop, implement, and adhere to shared heart team protocols), and promote a continuous review of practice that may, in turn, inform a more effective, efficient, and equitable resources allocation, and ultimately, better outcomes for patients.

Conclusions

Use of heart teams approaches and adherence to guideline recommendation on coronary revascularization in a real world setting is limited. The APACHE study identifies substantial opportunities to improve the care of patients undergoing PCI.

Acknowledgments

We thank all investigators and patients who participated in this study to pioneer advancements in clinical care.

References

1. Chan PS, Rao SV, Bhatt DL, Rumsfeld JS, Gurm HS, Nallamothu BK, Cavender MA, Kennedy KF, Spertus JA. Patient and hospital characteristics associated with inappropriate percutaneous coronary interventions. J Am Coll Cardiol 2013;62(24):2274-81.
2. Baig SS, Altman DG, Taggart DP. Major geographical variations in elective coronary revascularization by stents or surgery in England. Eur J Cardiothorac Surg 2014.
3. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/ SCCT 2012 Appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2012;59(9): 857-81.
4. Desai NR, Bradley SM, Parzynski CS, Nallamothu BK, Chan PS, Spertus JA, Patel MR, Ader J, Soufer A, Krumholz HM, Curtis JP. Appropriate Use Criteria for Coronary Revascularization and Trends in Utilization, Patient Selection, and Appropriateness of Percutaneous Coronary Intervention. JAMA 2015;314(19):2045-53.
5. Maier W, Enderlin MF, Bonzel T, Danchin N, Heyndrickx G, Mühlberger V, Neuhaus KL, Piscione F, Reifart N, Antoni J, Ogurol Y, Wischnewsky MB, Meier B. Audit and quality control in angioplasty in Europe: procedural results of the AQUA Study 1997: assessment of 250 randomly selected coronary interventions performed in 25 centres of five European countries. AQUA Study Group, Nucleus Clinical Issues, Working Group Coronary Circulation, of the European Society of Cardiology. Eur Heart J 1999;20(17):1261-70.
6. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35(37):2541-619.
7. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ; ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C,

Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013 Oct;34(38):2949-3003.

8. Bonzel T, Schächinger V2, Dörge H3.Description of a Heart Team approach to coronary revascularization and its beneficial long-term effect on clinical events after PCI. Clin Res Cardiol. 2016;105(5):388-400.
9. Nallamothu BK, Tommaso CL, Anderson HV, Anderson JL, Cleveland JC Jr, Dudley RA, Duffy PL, Faxon DP, Gurm HS, Hamilton LA, Jensen NC, Josephson RA, Malenka DJ, Maniu CV, McCabe KW, Mortimer JD, Patel MR, Persell SD, Rumsfeld JS, Shunk KA, Smith SC Jr, Stanko SJ, Watts B. ACC/AHA/SCAI/AMA-Convened PCPI/NCQA 2013 performance measures for adults undergoing percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures, the Society for Cardiovascular Angiography and Interventions, the American Medical Association-Convened Physician Consortium for Performance Improvement, and the National Committee for Quality Assurance. J Am Coll Cardiol 2014;63(7):722-45.
10. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Ståhle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381(9867):639-50.
11. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP; Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1--coronary artery bypass grafting surgery. Ann Thorac Surg 2009;88(1 Suppl):S2-22.
12. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. Eur J Cardiothorac Surg 2012;41(4):734-44; discussion 744-5.
13. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009 Jan 15;360(3):213-24.
14. Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB. Designing clinical research : an epidemiologic approach. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. Appendix 6E, page 81.
15. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA; American College of Cardiology Foundation Appropriateness Criteria Task Force.; Society for Cardiovascular Angiography and Interventions.; Society of Thoracic Surgeons.; American Association for Thoracic Surgery.; American Heart Association, and the American Society of Nuclear Cardiology Endorsed

by the American Society of Echocardiography.; Heart Failure Society of America.; Society of Cardiovascular Computed Tomography. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol. 2009 Feb 10;53(6):530-53

16. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015 Apr 2;372(14):1291-300.
17. Lin GA, Dudley RA, Lucas FL, Malenka DJ, Vittinghoff E, Redberg RF. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. JAMA 2008;300(15):1765-73.
18. Lin GA, Lucas FL, Malenka DJ, Skinner J, Redberg RF. Mortality in Medicare patients undergoing elective percutaneous coronary intervention with or without antecedent stress testing. Circ Cardiovasc Qual Outcomes. 2013 May 1;6(3):309-14.
19. Garg S, Girasis C, Sarno G, Goedhart D, Morel MA, Garcia-Garcia HM, Bressers M, van Es GA, Serruys PW; SYNTAX trial investigators. The SYNTAX score revisited: a reassessment of the SYNTAX score reproducibility. Catheter Cardiovasc Interv. 2010 May 1;75(6):946-52.
20. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the syntax study. *EuroIntervention*. 2009;5(1):50-56.
21. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334(26):1703–1708.
22. Berwick DM. Avoiding overuse-the next quality frontier. Lancet 2017; S0140-6736(16)32570-3.

Text Tables

Table 1. Baseline characteristics, cardiovascular risk factors, and history stratified by clinical indication.

	Stable CAD (n=352)	NSTEACS (n=88)	Overall (n=440)
Age (years)	69.3 (62.9-75.1)	71 (63.4-77.4)	69.6 (63-75.8)
Females *n* (%)	71 (20)	27 (31)	98 (22)
BMI (kg/m^2)	26.2 (24.2-28.9)	27 (24.6-30)	26.3 (24.2-29.3)
Creatinine (mg/dl)	0.9 (0.79,1.08)	0.97 (0.85, 1.18)	0.91 (0.8, 1.10)
SYNTAX score	12 (8-20)	15 (8-20)	13 (8-20)
CV Risk Factors			
Diabetes *n* (%)	173 (49)	43 (49)	216 (49)
Hypertension *n* (%)	262 (75)	71 (78)	333 (75)
Dyslipidemia *n* (%)	190 (54)	48 (55)	238 (54)
Active smoker *n* (%)	53 (15)	16 (18)	69 (16)
Prior Smoker *n* (%)	85 (24)	13 (15)	98 (22)
History of premature CAD *n*(%)	99 (28)	19 (22)	118 (27)
History			
Prior Angina *n* (%)	250 (71)	52 (59)	302 (69)
Prior MI *n* (%)	95 (27)	20 (23)	115 (26)
Prior PCI *n* (%)	148 (42)	28 (32)	176 (40)
Renal Insufficiency *n* (%)	38 (11)	20 (23)	58 (13)
Heart Failure *n* (%)	14 (4)	2 (2)	16 (4)
LVSD *n* (%)	23 (7)	8 (9)	31 (7)
COPD *n* (%)	26 (7)	8 (9)	34 (8)
Stroke *n* (%)	18 (5)	5 (6)	23 (5)
PAD *n* (%)	55 (16)	10 (11)	65 (15)

Legend. BMI, Body mass index; SYNTAX: synergy between percutaneous coronary intervention with TAXUS and cardiac surgery; SCAD: coronary artery disease; NSTEACS: non-ST elevation acute coronary syndrome; MI: myocardial infarction; PCI: percutaneous coronary intervention; LVSD: left ventricular systolic dysfunction defined as ejection fraction of 0.40 or less; COPD: Chronic obstructive pulmonary disease; PAD: peripheral artery disease.

Table 2. Characterization of the indication for PCI in patients with stable CAD (n=352).

Parameter	Value
Pre-Test Probability of CAD (%) #	69 (54-84)
Low (<15%) *n* (%)	0 (0)
Intermediate (15-85%) *n* (%)	222 (78)
High (>85%) *n* (%)	61 (22)
Ad hoc PCI *n (%)*	307 (87)
Any functional test of ischemia performed *n (%)**	217 (62)
Exercise electrocardiography *n*	153
SPECT *n*	46
Stress echocardiography *n*	31
Stress cardiac magnetic resonance imaging *n*	3
Coronary computed tomographic angiography *n (%)*	27 (8)
No functional or anatomical testing *n (%)*	125 (35%)
AUC_{CORE} mappable	318 (90)
Appropriate *n* (%)	102 (32)
Uncertain *n* (%)	163 (51)
Inappropriate *n* (%)	52 (16)
AUC_{SITE} mappable	320 (91)
Appropriate *n* (%)	100 (31)
Uncertain *n* (%)	163 (51)
Inappropriate *n* (%)	57 (18)

#: Calculated according to (5) only in patients with unknown coronary anatomy (n=285): defined as a history of invasive coronary angiography or coronary computed tomography angiography in the year preceding the index PCI. *: Some patients (n=15) underwent more than 1 functional test before PCI 1 patient received 3 tests; SPECT: Single-Photon Emission Computed Tomography.

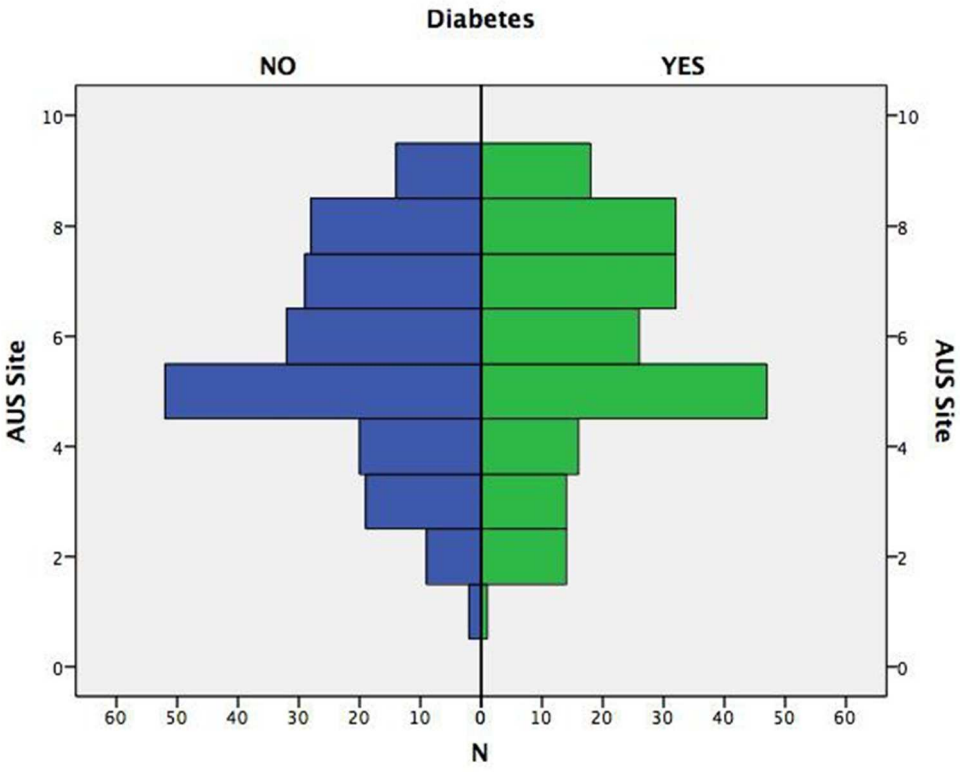
Author contributions:
Sergio Leonardi and Stefano De Servi: Study design, manuscript drafting, statistical analysis and critical revision.
Marcello Marino and Gabriele Crimi: angiographic core lab analysis, critical revision.
Florinda Maiorana, Diego Rizzotti: Data management, statistical analysis and critical revision
Corrado Lettieri, Luca Bettari, Marco Zuccari, Paolo Sganzerla, Simone Tresoldi, Marianna Adamo, Sergio Ghiringhelli, Carlo Sponzilli, Giampaolo Pasquetto, Andrea Pavei, Luigi Pedon, Luciano Bassan, Mario Bollati, Paola Camisasca, Daniela Trabattoni, Marta Brancati, Arnaldo Poli, Claudio Panciroli: critical Revision
Maddalena Lettino, Giuseppe Tarelli, Giuseppe Tarantini, Leonardo de Luca, Ferdinando Varbella: Central Heart Team and critical revision
Giuseppe Musumeci: Study design and critical revision

Competing interests
ICJME forms are available for all authors.
Dr Leonardi reports honoraria for advisory boards from AstraZeneca, Daiichi Sankyo, and The Medicines Company during the conduct of the study outside the submitted work; Dr. De Luca reports personal fees from Astra Zeneca, personal fees from Bayer , personal fees from Boehringer-Ingelheim, personal fees from

Eli Lilly and Daiichi Sankyo, personal fees from Menarini , personal fees from The Medicines Company, outside the submitted work. Dr. De Servi reports personal fees from Pfizer, personal fees from AstraZeneca, personal fees from Daichi-sankyo, personal fees from Correvio, outside the submitted work. The other authors report nothing to disclose. All authors have read and understood BMJ policy on declaration of interests and have no other relevant interests to declare in addition to these.

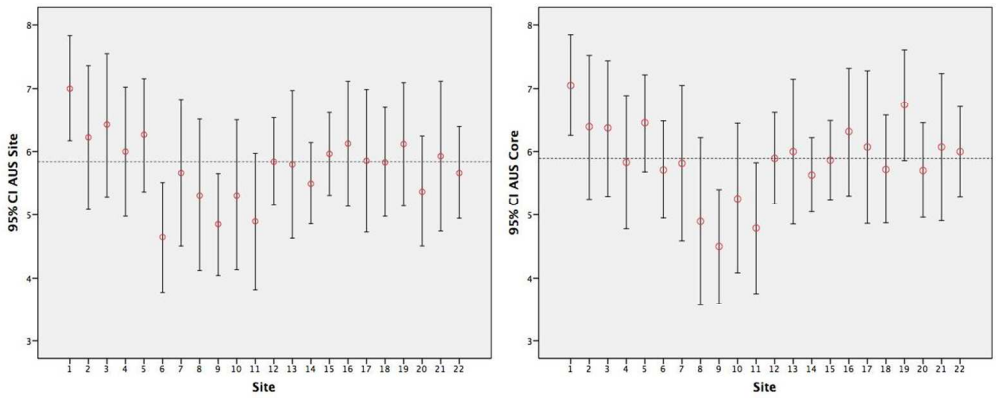
Data Sharing Statement

No additional unpublished data for this study will be available.



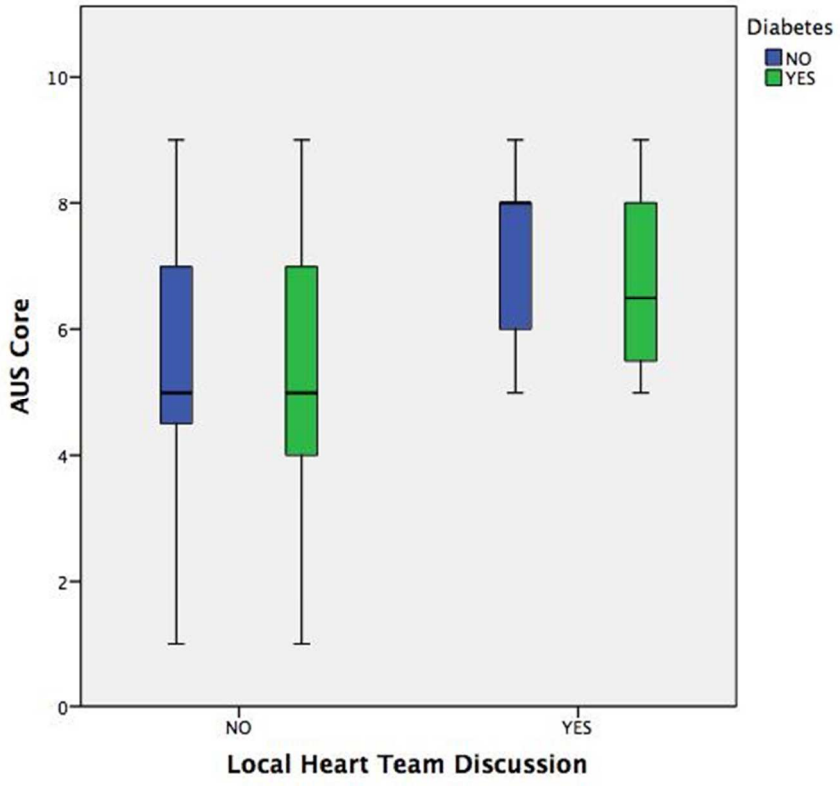
Histogram of Appropriate Use Score according to site-reported coronary anatomy (AUSSITE) in patients with and without diabetes.

53x42mm (300 x 300 DPI)



Error bars of AUSsite (left) and AUScore (right) by participating site. The dotted line indicates the median AUS site level (5.8).

106x42mm (300 x 300 DPI)



Boxplot of AUScore in patients who underwent and who did not undergo local heart team discussion, stratified by diabetes status.

53x42mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract (**Title Page**)
		(a)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (**Abstract Page 2**)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (**Introduction, page 4**)
Objectives	3	State specific objectives, including any prespecified hypotheses (**Objective, abstract**)
Methods		
Study design	4	Present key elements of study design early in the paper (**Study Design, page 5**)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (**Methods, page 5 and Results, page 11**)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants (**Methods, page 5, Patient Selection Section**)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (**Methods, page 5**)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (**Methods, page 5 Data Collection Section**)
Bias	9	Describe any efforts to address potential sources of bias (**Methods, page 5**)
Study size	10	Explain how the study size was arrived at (**Sample Size Consideration, page 10**)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (**Statistical Section for all below, page 10**)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (**Results, page 11**)
		(b) Give reasons for non-participation at each stage (**NA**)
		(c) Consider use of a flow diagram (**NA**)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (**Results, page 11**)
		(b) Indicate number of participants with missing data for each variable of interest (**Results, page 11**)
Outcome data	15*	Report numbers of outcome events or summary measures (**Results, page 11**)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included (**Results, page 11**)
		(*b*) Report category boundaries when continuous variables were categorized (**Results, page 11**)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (**Results, page 11**)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (**Results, page 11**)
Discussion		
Key results	18	Summarise key results with reference to study objectives (**Discussion, page 15**)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (**Discussion, page 15**)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (**Discussion, page 15**)
Generalisability	21	Discuss the generalisability (external validity) of the study results (**Discussion, page 15**)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (**Funding Statement, page 10**)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

APpropriAteness of percutaneous Coronary interventions in patients with ischemic HEart disease in Italy: The APACHE Pilot study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016909.R2
Article Type:	Research
Date Submitted by the Author:	26-Jul-2017
Complete List of Authors:	Leonardi, Sergio; Fondazione IRCCS Policlinico San Matteo, Marino, Marcello; Aziende Socio Sanitarie Territoriale di Crema Crimi , Gabriel ; Fondazione IRCCS Policlinico San Matteo, Maiorana, Florinda; Fondazione IRCCS Policlinico San Matteo Rizzotti, Diego; Fondazione IRCCS Policlinico San Matteo Lettieri, Corrado; Azienda Socio Sanitaria Territoriale di Mantova Bettari, Luca; Azienda Socio Sanitaria Territoriale di Cremona Zuccari, Marco Sganzerla, Paolo; Agenzia di Tutela della Salute di Bergamo Ovest Tresoldi, Simone ; Azienda Ospedaliera di Desio e Vimercate Adamo, Marianna; Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia Ghiringhelli, Sergio; Ospedale di Circolo e Fondazione Macchi Sponzilli, Carlo; Ospedale San Paolo Pasquetto, Giampaolo; Presidio Ospedaliero di Monselice Pavei, Andrea; Presidio di Conegliano Pedon, Luigi; Presidio Ospedaliero di Cittadella Bassan, Luciano; Azienda ULSS 4 Alto Vicentino Bollati, Mario; IRCCS Policlinico San Donato Camisasca, Paola; Azienda Ospedaliera San Gerardo Trabattoni, Daniela; Centro Cardiologico Monzino Brancati, Marta; Fondazione Poliambulanza Istituto Ospedaliero Poli, Arnaldo; Aziende Socio Sanitarie Territoriale Ovest Milanese Panciroli, Claudio Lettino, Maddalena; Istituto Clinico Humanitas Tarelli, Giuseppe; Istituto Clinico Humanitas Tarantini, Giuseppe; Azienda Ospedaliera di Padova De Luca, Leonardo; Ospedale di Tivoli Varbella, Ferdinando; 1Cardiology Unit, Ospedale degli Infermi, Musumeci, Giuseppe; Azienda Ospedaliera S Croce e Carle Cuneo De Servi, Stefano; IRCCS Sesto San Giovanni
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Health services research
Keywords:	Coronary heart disease < CARDIOLOGY, Percutaneous Coronary Intervention, Multidisciplinary Decision Making

APpropriAteness of percutaneous Coronary interventions in patients with ischemic HEart disease in Italy: The APACHE Pilot study

Sergio Leonardi, MD, MHS, FESC [1] Marcello Marino, MD [2] Gabriele Crimi, MD [1] Florinda Maiorana, MSc, [1] Diego Rizzotti, MSc [1] Corrado Lettieri, MD [3] Luca Bettari, MD [4] Marco Zuccari, MD[5] Paolo Sganzerla, MD [6] Simone Tresoldi, MD [7] Marianna Adamo, MD [8] Sergio Ghiringhelli, MD [9] Carlo Sponzilli, MD [10] Giampaolo Pasquetto, MD [11] Andrea Pavei, MD [12] Luigi Pedon, MD [13] Luciano Bassan, MD [14] Mario Bollati, MD [15] Paola Camisasca, MD [16] Daniela Trabattoni ,MD [17] Marta Brancati, MD [18] Arnaldo Poli, MD [19] Claudio Panciroli, MD [20] Maddalena Lettino, MD [21] Giuseppe Tarelli[21], MD Giuseppe Tarantini, MD [22] Leonardo De Luca, MD [23] Ferdinando Varbella, MD [24], Giuseppe Musumeci, MD [25] *and* Stefano De Servi, MD, FESC [26].

1: Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
2: Ospedale Maggiore di Crema, Crema, Italy
3: ASST Mantova – Ospedale Carlo Poma, Mantova, Italy
4: ASST Cremona – Ospedale di Cremona, Cremona, Italy
5: Ospedale Fornaroli di Magenta, Magenta, Italy
6: ASST Bergamo ovest – Ospedale di Treviglio, Italy
7: Azienda Ospedaliera di Desio e Vimercate, Vimercate, Italy
8: Spedali Civili di Brescia, Brescia, Italy
9: Ospedale di Circolo Fondazione Macchi, Varese,Italy
10: Ospedale San Paolo, Milano, Italy
11: Ospedali Riuniti Padova Sud Madre Teresa di Calcutta, Monselice, Italy
12: Presidio Ospedaliero di Conegliano, Conegliano, Italy
13: Presidio Ospedaliero di Cittadella, Cittadella, Italy
14: ULSS 4 Alto Vicentino, Thiene, Italy
15: IRCCS Policlinico San Donato, San Donato Milanese, Italy
16: Ospedale San Gerardo, Monza, Italy
17: Centro Cardiologico Monzino, Milano, Italy
18: Fondazione Poliambulanza, Brescia, Italy
19: ASST Ovest Milanese, Legnano, Italy
20: ASST di Lodi, Lodi, Italy
21: Humanitas Research Hospital, Rozzano (MI), Italy
22: Ospedale di Padova, Padova, Italy
23: Ospedale San Giovanni Evangelista, Tivoli (Rome), Italy
24: Ospedale degli Infermi, Rivoli, Italy
25: ASST – Papa Giovanni XXIII- Bergamo, Italy
26: IRCCS MultiMedica, Milano, Italy

Word Count: 4456

Address for correspondence
Sergio Leonardi, MD, MHS, FESC
Fondazione IRCCS Policlinico S. Matteo
Viale Golgi 19
27100
Pavia, Italy
S.Leonardi@smatteo.pv.it

Abstract *Word count: 305*

Objectives: To first explore in Italy appropriateness of indication, adherence to guideline recommendations, and mode of selection for coronary revascularization.

Design: Retrospective, pilot study.

Setting: Twenty-two percutaneous coronary intervention (PCI)-performing hospitals (20 patients/site), 13 (59%) with on-site cardiac surgery.

Participants: 440 patients who received PCI for stable coronary artery disease (CAD) or non-ST elevation acute coronary syndrome were independently selected in a 4:1 ratio with half diabetics.

Primary and Secondary Outcome Measures: Proportion of patients who received appropriate PCI using validated appropriate use scores (ie AUS ≥ 7). Also, in patients with stable CAD, we examined adherence to the following ESC recommendations: a) % of patients with complex coronary anatomy treated after heart-team discussion; b) % of fractional flow reserve-guided PCI for borderline stenoses in patients without documented ischemia; c) % of patients receiving guideline-directed medical therapy at the time of PCI as well as use of provocative test of ischemia according to pre-test probability (PTP) of CAD.

Results: Of the 401 mappable PCIs (91%), 38.7% (95%CI: 33.9-43.6) were classified as appropriate, 47.6% (95%CI: 42.7-52.6) as uncertain, and 13.7% (95%CI: 10.5-17.5%) as inappropriate. Median PTP in stable CAD patients without known coronary anatomy was 69% (78% intermediate PTP, 22% high PTP). Ischemia testing use was similar (p=0.71) in patients with intermediate (*n*=140, 63%) and with high PTP (*n*=40, 66%). In patients with stable CAD (n=352) guideline adherence to the 3 recommendations explored was: a) 11%; b) 25%; c) 23%. AUS was higher in patients

evaluated by the heart team as compared to patients who were not [7 (6,8) vs 5 (4,7); P=0.001].

Conclusions: Use of heart-teams approaches and adherence to guideline recommendations on coronary revascularization in a real world setting is limited. This pilot study documents the feasibility of measuring appropriateness and guideline adherence in clinical practice and identifies substantial opportunities for quality improvement.

Study Registration: NCT02748603.

Strengths and limitations of this study

- APACHE is a first-in-class study in Italy designed to measure the degree of appropriateness of indication, multi-disciplinary decision-making processes, and implementation of key guideline recommendations in patients undergoing PCI.
- This study, that enrolled patients with stable CAD and diabetes, was intentionally designed to focus on high-risk patients for inappropriate PCI. Therefore true appropriateness of PCI may be underestimated. However, rather than an epidemiological study, APACHE intention was to serve as first initiative sponsored by a national medical society to measure care process and improve quality.
- APACHE examined the appropriateness of PCI indication, not of coronary angiography. Therefore we acknowledge as a limitation that we have no data to inform appropriateness of surgical revascularization, nor indication to invasive angiography.

Introduction

Percutaneous coronary intervention (PCI) has dramatically improved the prognosis of patients with coronary artery disease (CAD). Yet, many patients receive PCI whose clinical indication appears uncertain or inappropriate, especially in the non-acute setting. [1,2] The development of appropriate use criteria by cardiovascular societies has provided the basis for a standardized approach to systematically assess the clinical appropriateness of PCI [3] and has produced a reduction of the volume of non-acute PCI as well as an increase in the proportion of procedures classified as appropriate [4] but these studies have been mostly performed in the US.

In Europe, data on appropriateness of indication and mode of selection for coronary revascularization strategies as well as the degree of implementation of guideline recommendations are limited. [5] European Society of Cardiology (ESC) guidelines [6,7] urge the implementation of a multidisciplinary decision-making approach – the heart team – to select the optimal mode of revascularization but data on the implementation of this process in patients with complex coronary artery disease (CAD), including those with stable CAD and diabetes, are scarce. [8] Specifically the ESC [6,7] recommend that 1) complex pathologies in stable patients, including lesions of the left main or proximal left anterior descending artery (LAD) and three-vessel disease, should in general not be treated *ad hoc*, but discussed by the heart team; 2) pressure derived fractional flow reserve (FFR) should be used to identify haemodynamically relevant coronary lesion(s) in stable patients when evidence of ischaemia is not available; and 3) patients with stable CAD must receive guideline-recommended medical treatment prior to revascularization.

We designed the APpropriAteness of percutaneous Coronary interventions in patients with ischemic HEart disease – APACHE Pilot study to first explore the degree of appropriateness of indication of PCI, multi-disciplinary decision-making

processes, and implementation of key guideline recommendations in patients undergoing PCI in Italy.

Methods

Study Design and Patient Selection

APACHE was designed as a pilot initiative to assess appropriateness of PCI indication and adherence to key guideline recommendations on coronary revascularization in patients with predominantly stable CAD and diabetes, considered to be at high risk for inappropriate indication and mode for coronary revascularization (ie PCI treatment in patients with an indication for CABG). All PCI performing hospitals of the Lombardia and Veneto region in Italy, serving a population of ≈ 15.000.000 people, were invited to participate in the study. Twenty-two sites agreed to participate, obtained regulatory approval, and were eventually included.

At each participating hospital, 20 patients were independently selected on-site by the study team (see online appendix) among consecutive patients who were admitted in the previous year for an elective procedure to treat stable CAD or urgently for an episode of non-ST elevation acute coronary syndrome in a 4:1 ratio without site personnel involvement in the selection of the cases identified to minimize selection bias. The study population was also selected to preserve an overall 1:1 ratio on diabetes status. If the number of patients selected was insufficient older cases were evaluated for possible inclusion. Due to the low likelihood of receiving a *redo* procedure as well as the inability to measure a SYNTAX score, patients with a history of bypass surgery were excluded.

Data Collection, Core Angiographic Assessment, and Central Heart Team

Variables of interest were collected by the study team during dedicated visits at participating hospitals via clinical chart abstraction. Sites were requested to provide

the complete clinical chart, including the coronary angiogram of the index PCI. Source documentation was reviewed in full to abstract symptoms status (angina class); cardiovascular risk factors and comorbidities; medical therapy at time of PCI; site-reported indication for PCI; presence, results, and timing of any noninvasive functional test, fractional flow reserve (FFR) or intracoronary imaging, if performed; coronary anatomy and reported significance of angiographic stenoses for treated lesion(s) on the catheterization report; and evidence for heart-team discussion involving a cardiac surgeon. Finally, pretest probability (PTP) of significant coronary artery disease was calculated in patients with stable CAD according to guideline recommendations [7].

The Angiographic Core Laboratory (ACL) was composed by two independent physicians with experience in interventional cardiology (MM, GC) who centrally and independently reviewed coronary angiography for each patient to define 1) baseline SYNTAX score 2) category of coronary anatomy (eg. one, two or three-vessel CAD with or without proximal LAD involvement) [3] and 3) presence of "borderline" angiographic stenoses (50% to 60%). For the SYNTAX score a disagreement was arbitrarily considered to be present if there was a between score difference ≥ 10 or both scores were not in the same tertile (0-22, 23-32, >32). In case of agreement an average SYNTAX score was calculated. In case of disagreement between reviewers the case was first resolved by consensus. If a consensus could not be reached (or if the case was deemed particularly challenging) the conflict was resolved by the central heart team. Anatomical category and presence of borderline coronary stenoses were analyzed by a single reviewer (GC or MM).

The central heart team was represented by four members – two interventional cardiologists (LDL, FV), one cardiac surgeon (GT), and one clinical cardiologist

(ML) – nominated by the Italian Society of Interventional Cardiology (SICI-GISE) among recognized experts in their respective specialty. The role of the central heart team was to review cases with unresolved conflicts by the ACL, cases considered complex or challenging by the study team or cases with incomplete or conflicting documentation. Assessments of the central heart team were performed by consensus.

Evaluation of Appropriateness of Indications for Coronary Revascularization

The comprehensive documentation of indications for PCI was formally examined based on the 2013 ACC/AHA/SCAI/AMA-PCPI/NCQA Percutaneous Coronary Intervention Measurement Set. [9] This diagnostic measure was defined as the proportion of patients whose clinical documentation includes, at a minimum, the following elements:

1. Priority (acute coronary syndrome, elective, urgent, emergency/salvage); 2. Presence and severity of angina symptoms (eg, Canadian Cardiovascular Society classification system); 3. Use of antianginal medical therapies within 2 weeks before the procedure, if any; 4. Presence, results, and timing of noninvasive stress test, FFR, or intravascular ultrasound, if performed; and 5. Significance of angiographic stenosis on coronary angiography for treated lesion.

Appropriateness of indication of coronary revascularization was examined by assigning to each procedure an appropriate use score (AUS), with a score of 1 indicating a completely inappropriate procedure to a score of 9 indicating a completely appropriate one. [3] Scores of 7 to 9 indicate that revascularization is considered generally appropriate and likely to improve patients' symptoms or survival. Scores of 1 to 3 considered generally inappropriate while scores of 4 to 6 indicate a clinical scenario for which the likelihood that coronary revascularization will improve health outcomes or symptoms is uncertain. This score was defined by

considering clinical presentation; severity of angina; extent of ischemia on noninvasive testing; presence of other prognostic factors, such as congestive heart failure or depressed left ventricular function; extent of medical therapy at the time of PCI; and extent of anatomic coronary disease. If the scenario was not considered by the consensus document, [3] the procedure was considered non mappable.

To limit site operator-related bias, the study team calculated two scores for each procedure:

1. AUS_{SITE}, based on site-reported extent of anatomic coronary disease;
2. AUS_{CORE}, based on ACL reported extent of anatomic coronary disease.

Evaluation of adherence to ESC Guidelines and Heart Team Processes

In patients with stable CAD we assessed adherence to three class I recommendations according to ESC guidelines [6,7]:

Recommendation 1: Proportion of patients with stable CAD and complex anatomy [including lesions of the left main, proximal left anterior descending (LAD) and/or three-vessel CAD] who were treated after local heart team discussion. This recommendation was explored using both site-reported and ACL-reported coronary anatomy. We also explored adherence to this recommendation by calculating the proportion of patients with complex anatomy who received *ad hoc* PCI without documented heart team discussion. To better define optimal mode of coronary revascularization, the SYNTAX II score [10] as well as the Society of Thoracic Surgeons (STS) [11], and EuroScore II [12] were calculated.

Recommendation 2: Proportion of patients with stable CAD, no evidence of ischemia, and borderline lesions according to the ACL in whom FFR was used to identify haemodynamically relevant coronary lesion(s).

Specifically, this recommendation was explored as follows:

a) Proportion of patients with no functional test (ie test negative or not performed) and at least one borderline stenosis according to ACL in whom pressure-derived FFR was used;

b) Proportion of patients with no functional test or asymptomatic and at least one borderline stenosis according to ACL in whom pressure derived FFR was used;

c) Proportion of patients with no functional test or asymptomatic and site-reported multivessel CAD in whom pressure derived FFR was used. [13]

Recommendation 3: Proportion of patients with stable CAD who received guideline-directed medical therapy prior to revascularization. [7]

Specifically:

a) Proportion of patients without known allergy or documented intolerance taking low dose aspirin (75-150 mg daily) or clopidogrel;

b) Proportion of patients without known allergy or documented intolerance receiving a statin;

c) Proportion of patients with heart failure, hypertension or diabetes treated with an ACE-inhibitor or angiotensin receptor blocker;

d) Proportion of patients on optimal medical therapy defined as drugs for event prevention (aspirin and/or clopidogrel; a statin; an ACE-I/ARB if heart failure, hypertension or diabetes) plus at least one drug for angina relief if symptomatic, such as beta-blockers, calcium channel blockers, long acting nitrates, ivabradine, or ranolazine.

In patients with NSTEACS, we examined the proportion of PCI procedures performed within 24 hours of admission in patients with a Global Registry of Acute Coronary Events (GRACE) score > 140.

Finally we assessed, by structured investigators surveys, the presence of written institutional protocols developed locally by the Heart Team in accordance with current guidelines including specific anatomical criteria and clinical subsets that may be (or should not be) treated *ad hoc* as well as the modalities and timing for convocation of heart team meetings.

Statistical Analysis and Sample Size Considerations

Categorical data are presented as counts and proportion and continuous data as median (25^{th}, 75^{th} percentile) and were analyzed, as appropriate, using chi-square (or Fisher's exact) and Wilcoxon rank-sum test. We calculated 95% confidence intervals for the proportion using the normal approximation to the binomial calculation. To control for the effect of participating site as well as the presence of cardiac surgery on-site on the primary outcome (AUS), we used ANOVA provided in the generalized linear model procedure of SPSS version 20 including participating site and presence of cardiac surgery on-site as co-factors for the key subgroup (factor) of interest (i.e. patients evaluated by the heart team vs not)".

Given the lack of prior studies to estimate appropriateness of coronary revascularization in Italy, sample size estimation was challenging. The study was powered on the primary subgroup of interest, patients with stable CAD, assuming an appropriateness of 35% in this patient population based on prior reports. [4] Using a normal approximation to the binomial distribution for this proportion a population of 350 stable CAD patients was needed to obtain a 95% confidence interval between 30% and 40% for appropriateness. [14] Analyses were performed using SPSS v 20 and sample size was estimated using http://www.sample-size.net/. The study obtained

institutional review board approval by all participating hospitals and is registered on ClinicalTrial.Gov ID: NCT02748603.

Sponsor and Funding

The APACHE study was designed by the chair and principal investigator and approved by the institutional review board at each participating center. The study was sponsored by the Italian Society of Invasive Cardiology (SICI-GISE), a nonprofit organization, and received unrestricted grant support from the Abbott Vascular and Daiichi-Sankyo. The sponsor and funders had no role in the design of the study, the collection, monitoring, analysis, and interpretation of the data, or the writing of the report. The first draft of the manuscript was written by the first author. All the authors vouch for the accuracy and completeness of the data and all analyses.

Results

Of the 22 hospitals included, 13 (59%) have onsite cardiac surgery and 4 (18%) are private hospitals. Overall, PCI procedures of 440 patients (performed between January 2014 and May 2016) were included: 352 for patients with stable CAD and 88 with NSTEACS [12 with unstable angina and 76 with non-ST elevation myocardial infarction; median GRACE score 109 (89.5, 125.5), median Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) score 24 (16,40)]. A SYNTAX score could be calculated in 422 patients (96%) with 87 disagreements (21%) between ACL reviewers. Of these, 55 were resolved by consensus and 32 by the central heart team. Clinical profile of the selected patients stratified by clinical indication is showed in **Table 1**. By design, ≈ half of the patients had diabetes (n=216, 49.1%) with a high proportion of patients with dyslipidemia (54%), prior PCI (40%) and history of angina (69%). **Table 2** presents data on indication and test

selection in patients with stable CAD. Median PTP of CAD in stable CAD patients without known coronary anatomy was 69% (78% intermediate PTP, 22% high PTP, no patient with low PTP). The use of provocative tests of ischemia was similar (p=0.71) in patients with intermediate (*n*=140, 63%) and with high PTP (*n*=40, 66%). Of the 88 patients with NSTEACS, a GRACE score > 140 was present in 11 (12%) patients. Of these, 5 patients had PCI within 24 hours.

Two of the secondary outcomes listed on *ClinicalTrials.gov* ie 1) proportion of patients receiving incomplete revascularization (i.e. residual SYNTAX > 8) and 2) proportion of patients with nSTEACS who are stabilized (no recurrent ischemic symptoms) who have multivessel disease and a high SYNTAX score (>22), without documentation of Heart Team discussion in the medical records for nSTE-ACS were not considered due to the limited reproducibility observed for the SYNTAX score and the small number of subjects (n=3), respectively.

Comprehensive Documentation and Appropriateness of Indications for Coronary Revascularization

A comprehensive documentation of PCI indication was present in 427 (97%) patients. Most common reasons for unfulfilling this diagnostic measure were the lack of documentation in the clinical chart of any non-invasive testing, both functional and imaging (n=5) or missing information on therapy at admission (n=8).

An AUS_{SITE} could be calculated in 405 (92%) of patients while the remaining 35 patients did not have comprehensive documentation of indications for PCI or the scenario was not applicable (ie non mappable AUC). The median AUS_{SITE} was 6 (5,7) corresponding to 153 (37.8%, 95%CI: 33.1-43.5) of PCI classified as appropriate, 193 (47.7%, 95%CI: 42.8-52.5) as uncertain, and 59 (14.6%, 95%CI: 11.1-18) as inappropriate AUC, similar in patients with a and without diabetes (**Figure 1 and**

Figure 2A). AUS_{SITE} was higher in patients evaluated by the local heart team as compared to patients who were not, both in unadjusted [7 (5,8) vs 5 (4,7); p=0.003] and adjusted analysis (mean AUS_{SITE} 7.0, SD 1.8 vs 5.7 SD 1.9; p=0.001; participating site and cardiac surgery on-site both non significant).

An AUS_{CORE} could be calculated in 401 patients (91%). Of these, 23 (6%) required a review by the central heart team. Median AUS_{CORE} was 6 (5,7) with 155 (38.7%, 95%CI:33.9-43.4) of PCI classified as appropriate, 191 (47.6%,95%CI: 42.7-52.5) as uncertain, and 55 (13.7%,95%CI:10.3-17.1) as inappropriate AUC. AUS_{CORE} results by site and in key subgroups are reported in the **Figure 2B** and the **Supplementary Figure respectively**. AUS_{CORE} was higher in patients with NSTEACS as compared to patients with stable CAD with no significant difference according to diabetic status or type of hospitals. AUS_{CORE} was higher in patients evaluated by the local heart team as compared to patients who were not both in unadjusted [7 (6,8) vs 5 (4,7); p=0.001] and adjusted analysis (mean AUS_{CORE} 7.1, SD 1.5 vs 5.8 SD 1.9; p=0.001; participating site and cardiac surgery on-site both non significant). (**Figure 3**).

Recommendation 1: Proportion of stable CAD patients with complex pathologies who were treated after heart team discussion

Of the 352 patients with stable CAD, 148 (42%) had a complex site-reported coronary anatomy including significant lesions of the left main (n=16), proximal LAD (n=73) and three-vessel disease (n=59). Of these, 17 (11%) underwent local heart team discussion. Median operative mortality was low-to-intermediate as estimated by both the Euroscore II [1.15 % (0.64, 2.05)] and the STS score [0.92% (0.45,1.81)]. Also, 118 of the 148 patients with complex site-reported coronary anatomy (80%) received *ad hoc* PCI without evidence of discussion with the local heart team in the clinical chart, with no difference in patients treated at hospitals with or without on-site

cardiac surgery (p=0.74). The proportion of patients with complex coronary lesions according to the ACL was 46% (n=164). Of these, 20 (12%) underwent local heart team discussion and 124 (75%) were treated *ad hoc* without evidence of heart team discussion.

The median SYNTAX score in patients with stable CAD was 12 (8-20), with 83% of patients with a score < 23, 13% between 23 and 32, and 4% above 32.

A SYNTAX II score could be calculated in 337 cases (96%). Of these, CABG was the recommended option for 40 patients (12%), PCI the recommended option for 14 (4%), and either mode of revascularization was recommended in the remaining 283 cases (84%). Of the 40 patients where SYNTAX II score recommended CABG a local heart team discussion was performed in 3 cases (7%). Finally, a total of 75 stable CAD patients (21%) with diabetes and multi-vessel CAD underwent *ad hoc* PCI without local heart team discussion documented in the patient's chart.

Recommendation 2: Proportion of stable CAD patients with no evidence of ischemia where pressure derived fractional flow reserve (FFR) was used to identify haemodynamically relevant coronary lesion(s).

Of the 352 patients with stable CAD, 151 (43%) had no objective evidence of ischemia (135 patients had no provocative test of ischemia, 8 had negative testing and 8 inconclusive testing), 36 (10%) were asymptomatic and 82 (23%) had multi-vessel CAD according to the site. A pressure-derived FFR to guide PCI was used for 29 patients (8.2%) with stable CAD while intravascular ultrasound for 12 patients (3%). No PCI were guided by coronary optical coherence tomography.

Of the 151 patients with no evidence of ischemia, the ACL identified 28 patients (18%) with at least one borderline coronary lesion treated with PCI with FFR performed in 7 of these 28 cases (25%).

Of the 175 (50%) patients who had no objective evidence of ischemia or were asymptomatic, 33 borderline lesions were identified by the ACL with FFR performed in 10 cases. In the subgroup of 91 patients who also had site-reported multi-vessel CAD, 13 borderline lesions were identified by the ACL, with FFR performed in 4 cases.

Recommendation 3: Use of guideline-directed medical therapy at the time of PCI in patients with stable CAD

Of the 352 patients with stable CAD, 299 (85%) were treated with single antiplatelet therapy at the time of angiography (292 low-dose aspirin and 7 with clopidogrel) and 20 (6%) received dual antiplatelet therapy with aspirin and clopidogrel (only 1 reported case of aspirin intolerance who successfully underwent aspirin desensitization); 266 (76%) were on a statin (no reported case of statin intolerance); 202 (57%) received an ACE-I or an angiotensin receptor blocker (no reported case of allergy or intolerance). Among the subgroup of stable CAD patients with hypertension, heart failure (or asymptomatic left ventricular ejection fraction of 40% or less), or diabetes (N=265; 75% of the overall stable CAD population), a treatment with ACE-I or ARB was given to 176 patients (66%). Finally, a therapy with an anti-anginal agent (beta-blocker, calcium channel blocker, nitrates, ivabradine, or ranolazine) was administered to 237 patients overall and to 169 patients of the 248 with symptoms of angina (68%). Overall a total of 100 patients (23%) received guideline-directed medical therapy at time of PCI.

Adoption of institutional heart-team protocols

Investigators from all participating centers (n=22) were interviewed and all responded. A written institutional heart-team protocol was available in 5 (23%) centers (1 with on-site cardiac surgery, 4 without on-site cardiac surgery) while in

other 5 centers (3 with on-site cardiac surgery) heart team meetings were being scheduled on a regular basis (usually weekly). All other hospitals (n=12) did not have either a heart team institutional protocol or regularly planned heart team meetings.

Discussion

In this pilot investigation we assessed appropriateness of indication of coronary revascularization and adherence to key guideline recommendations in a real world population with a high prevalence of stable CAD and diabetes as well as multidisciplinary decision-making processes. We identified important gaps in implementations of guideline recommendations and opportunities to improve the care patients undergoing PCI.

Considerations on Appropriateness of Indication for Coronary Revascularization

The proportion of appropriate indication for coronary revascularization was 39% in the overall population and 32% in patients with stable CAD with similar rates observed using local vs ACL anatomical category. These proportions are similar to what was observed in the US when AUC were first released in 2009. [4,15] As expected, appropriateness was higher in patients with NSTEACS as compared to patients with stable CAD but similar according to diabetes status as well as in hospitals with and without on-site cardiac surgery. Importantly both AUS_{SITE} and AUS_{CORE} were significantly higher in patients who were evaluated by a heart team suggesting multi-disciplinary decision-making is a surrogate of optimal revascularization choice.

In patients with stable CAD a functional testing strategy (used in 62% of patients) was far more common than an anatomical-testing strategy with coronary CTA (used only for 8% of patients), in agreement with the neutral findings of the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial. [16] Notably, the use of functional testing was similar in patients with intermediate

and with high PTP of significant CAD suggesting that the determination of PTP, considered the first major step in clinical decision making in this patient population, [7] has limited influence in the real world to define a diagnostic strategy. Also, 33% of stable CAD patients with unknown coronary anatomy had neither functional nor anatomical testing before PCI and only 38% had maximal anti-ischemic medical therapy before PCI, proportions that have contributed to the observed suboptimal appropriateness and call for implementation of quality improvements initiatives. Indeed, it has been observed that most (55.5%) of Medicare patients with stable CAD do not have documentation of ischemia by noninvasive testing prior to elective PCI and that pre-PCI stress testing was associated with lower mortality in patients undergoing elective PCI. [17,18] Overall these findings suggest a need to focus on PTP assessment in decision-making, appropriate classification of risk by non-invasive tests, and optimization of medical therapy before PCI.

Adherence to and Implementation of ESC Guidelines

To explore potential "specialty bias" – ie PCI treatment in patients with an indication for CABG – we examined the proportion of patients with complex coronary lesions, including significant disease of the left main, proximal LAD, and/or three-vessel disease, who were treated *ad hoc* without evidence of heart team discussion in the medical charts. We observed that only ≈ one of ten eligible patients underwent heart team discussion and 75 to 80% of patients with complex coronary anatomy were treated *ad hoc*, with no significant differences in sites with and without on-site cardiac surgery. To further explore this, we surveyed investigators to better understand local decision-making processes. We observed that most sites did not have a written institutional protocol and decision of heart team convocation was left at the discretion of the interventional cardiologist on call. The high proportion of *ad hoc*

PCI in patients with complex disease together with the lack of structured local heart teams identify a substantial opportunity to improve multidisciplinary decision making processes and indicate the need for standardized institutional protocols, that 1) should avoid the need for the systematic case-by-case review of all diagnostic angiograms but guide the management of complex cases 2) define standards for heart team composition and roles, and 3) generate consensus on practical ways to implement them.

The SYNTAX score is also considered by the guidelines to inform choice on optimal type of revascularization. This score, which relies on subjective assessment of lesions using coronary angiography, is well known to have limited reproducibility. [19] The highest kappa value observed in a study of the SYNTAX investigators to assess intra-observer variability was 0.54, and only 0.36 for bifurcations [19] and inter-observer reproducibility was even lower. [20] We therefore decided to adopt a conservative approach to define a disagreement between reviewers (arbitrarily defined as a difference of at least 10 points or change of tertile) but still observed a disagreement in 21% of patients. This variability suggests that for clinical decision-making SYNTAX score should not be used in isolation but rather integrated with clinical data. The SYNTAX II score was developed to address this need. By implementing this score in the APACHE population, we observed that in the vast majority of patients (84%) either modality of revascularization was recommended. However in the 40 patients (12%) where CABG was modality of choice, a heart team discussion was performed only in 3 cases.

Fractional flow reserve, the current gold standard for the functional assessment of lesion severity [21], is recommended (class I, level of evidence A) to identify haemodynamically relevant coronary lesions in stable patients when evidence

of ischaemia is not available or to assess the functional consequences of moderate coronary stenoses.[6] According to the ACL, the proportion of patients without documented ischemia or borderline coronary stenoses who had a FFR guided PCI was 25% although the absolute numbers were small (7 FFR in 28 patients). While recent data suggest that FFR use is increasing, these data indicate another gap in use of a well-established technique to define physiological consequences of a coronary stenosis thus optimizing appropriate indication for revascularization.

Finally, we observed that prescription of guideline-directed medical therapy before PCI was suboptimal with just 23% of patients on "optimal medical therapy" and a high prescription only for antiplatelet therapy before PCI (>90%). This gap may have multiple reasons including resource availability, patient's compliance, and physician preference but should be an important, and easily modifiable target, for any quality improvement initiative. By quality we intend the degree of match between health care services and the needs they are intended to meet. [22] APACHE was designed to first quantify this match, inform the design of future investigations on this topic (including a planned larger initiative in Italy extended to the whole country designed to develop, implement, and adhere to shared heart team protocols), and promote a continuous review of practice that may, in turn, inform a more effective, efficient, and equitable resources allocation, and ultimately, better outcomes for patients.

Conclusions

Use of heart teams approaches and adherence to guideline recommendation on coronary revascularization in a real world setting is limited. The APACHE study identifies substantial opportunities to improve the care of patients undergoing PCI.

Acknowledgments

We thank all investigators and patients who participated in this study to pioneer advancements in clinical care.

References

1. Chan PS, Rao SV, Bhatt DL, Rumsfeld JS, Gurm HS, Nallamothu BK, Cavender MA, Kennedy KF, Spertus JA. Patient and hospital characteristics associated with inappropriate percutaneous coronary interventions. J Am Coll Cardiol 2013;62(24):2274-81.
2. Baig SS, Altman DG, Taggart DP. Major geographical variations in elective coronary revascularization by stents or surgery in England. Eur J Cardiothorac Surg 2014.
3. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/ SCCT 2012 Appropriate use criteria for coronary revascularization focused update: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2012;59(9): 857-81.
4. Desai NR, Bradley SM, Parzynski CS, Nallamothu BK, Chan PS, Spertus JA, Patel MR, Ader J, Soufer A, Krumholz HM, Curtis JP. Appropriate Use Criteria for Coronary Revascularization and Trends in Utilization, Patient Selection, and Appropriateness of Percutaneous Coronary Intervention. JAMA 2015;314(19):2045-53.
5. Maier W, Enderlin MF, Bonzel T, Danchin N, Heyndrickx G, Mühlberger V, Neuhaus KL, Piscione F, Reifart N, Antoni J, Ogurol Y, Wischnewsky MB, Meier B. Audit and quality control in angioplasty in Europe: procedural results of the AQUA Study 1997: assessment of 250 randomly selected coronary interventions performed in 25 centres of five European countries. AQUA Study Group, Nucleus Clinical Issues, Working Group Coronary Circulation, of the European Society of Cardiology. Eur Heart J 1999;20(17):1261-70.
6. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on

Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35(37):2541-619.

7. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ; ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S; Document Reviewers, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013 Oct;34(38):2949-3003.
8. Bonzel T, Schächinger V2, Dörge H3.Description of a Heart Team approach to coronary revascularization and its beneficial long-term effect on clinical events after PCI. Clin Res Cardiol. 2016;105(5):388-400.
9. Nallamothu BK, Tommaso CL, Anderson HV, Anderson JL, Cleveland JC Jr, Dudley RA, Duffy PL, Faxon DP, Gurm HS, Hamilton LA, Jensen NC, Josephson RA, Malenka DJ, Maniu CV, McCabe KW, Mortimer JD, Patel MR, Persell SD, Rumsfeld JS, Shunk KA, Smith SC Jr, Stanko SJ, Watts B. ACC/AHA/SCAI/AMA-Convened PCPI/NCQA 2013 performance measures for adults undergoing percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures, the Society for Cardiovascular Angiography and Interventions, the American Medical Association-Convened Physician Consortium for Performance Improvement, and the National Committee for Quality Assurance. J Am Coll Cardiol 2014;63(7):722-45.
10. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR Jr, Mack M, Feldman T, Morice MC, Ståhle E, Onuma Y, Morel MA, Garcia-Garcia HM, van Es GA, Dawkins KD, Mohr FW, Serruys PW. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381(9867):639-50.
11. Shahian DM, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, Normand SL, DeLong ER, Shewan CM, Dokholyan RS, Peterson ED, Edwards FH, Anderson RP; Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1--coronary artery bypass grafting surgery. Ann Thorac Surg 2009;88(1 Suppl):S2-22.

12. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, Lockowandt U. EuroSCORE II. Eur J Cardiothorac Surg 2012;41(4):734-44; discussion 744-5.
13. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009 Jan 15;360(3):213-24.
14. Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB. Designing clinical research : an epidemiologic approach. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. Appendix 6E, page 81.
15. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA; American College of Cardiology Foundation Appropriateness Criteria Task Force.; Society for Cardiovascular Angiography and Interventions.; Society of Thoracic Surgeons.; American Association for Thoracic Surgery.; American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography.; Heart Failure Society of America.; Society of Cardiovascular Computed Tomography. ACCF/SCAI/STS/AATS/AHA/ASNC 2009 Appropriateness Criteria for Coronary Revascularization: a report by the American College of Cardiology Foundation Appropriateness Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, and the American Society of Nuclear Cardiology Endorsed by the American Society of Echocardiography, the Heart Failure Society of America, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol. 2009 Feb 10;53(6):530-53
16. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015 Apr 2;372(14):1291-300.
17. Lin GA, Dudley RA, Lucas FL, Malenka DJ, Vittinghoff E, Redberg RF. Frequency of stress testing to document ischemia prior to elective percutaneous coronary intervention. JAMA 2008;300(15):1765-73.
18. Lin GA, Lucas FL, Malenka DJ, Skinner J, Redberg RF. Mortality in Medicare patients undergoing elective percutaneous coronary intervention with or without antecedent stress testing. Circ Cardiovasc Qual Outcomes. 2013 May 1;6(3):309-14.
19. Garg S, Girasis C, Sarno G, Goedhart D, Morel MA, Garcia-Garcia HM, Bressers M, van Es GA, Serruys PW; SYNTAX trial investigators. The SYNTAX score revisited: a reassessment of the SYNTAX score reproducibility. Catheter Cardiovasc Interv. 2010 May 1;75(6):946-52.
20. Serruys PW, Onuma Y, Garg S, Sarno G, van den Brand M, Kappetein AP, Van Dyck N, Mack M, Holmes D, Feldman T, Morice MC, Colombo A, Bass E, Leadley K, Dawkins KD, van Es GA, Morel MA, Mohr FW. Assessment of the SYNTAX score in the syntax study. *EuroIntervention*. 2009;5(1):50-56.
21. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJJ, Koolen JJ. Measurement of fractional flow reserve to assess the

functional severity of coronary-artery stenoses. N Engl J Med 1996;334(26):1703–1708.

22. Berwick DM. Avoiding overuse-the next quality frontier. Lancet 2017; S0140-6736(16)32570-3.

Text Tables

Table 1. Baseline characteristics, cardiovascular risk factors, and history stratified by clinical indication.

	Stable CAD (n=352)	NSTEACS (n=88)	Overall (n=440)
Age (years)	69.3 (62.9-75.1)	71 (63.4-77.4)	69.6 (63-75.8)
Females *n* (%)	71 (20)	27 (31)	98 (22)
BMI (kg/m^2)	26.2 (24.2-28.9)	27 (24.6-30)	26.3 (24.2-29.3)
Creatinine (mg/dl)	0.9 (0.79,1.08)	0.97 (0.85, 1.18)	0.91 (0.8, 1.10)
SYNTAX score	12 (8-20)	15 (8-20)	13 (8-20)
CV Risk Factors			
Diabetes *n* (%)	173 (49)	43 (49)	216 (49)
Hypertension *n* (%)	262 (75)	71 (78)	333 (75)
Dyslipidemia *n* (%)	190 (54)	48 (55)	238 (54)
Active smoker *n* (%)	53 (15)	16 (18)	69 (16)
Prior Smoker *n* (%)	85 (24)	13 (15)	98 (22)
History of premature CAD *n*(%)	99 (28)	19 (22)	118 (27)
History			
Prior Angina *n* (%)	250 (71)	52 (59)	302 (69)
Prior MI *n* (%)	95 (27)	20 (23)	115 (26)
Prior PCI *n* (%)	148 (42)	28 (32)	176 (40)
Renal Insufficiency *n* (%)	38 (11)	20 (23)	58 (13)
Heart Failure *n* (%)	14 (4)	2 (2)	16 (4)
LVSD *n* (%)	23 (7)	8 (9)	31 (7)
COPD *n* (%)	26 (7)	8 (9)	34 (8)
Stroke *n* (%)	18 (5)	5 (6)	23 (5)
PAD *n* (%)	55 (16)	10 (11)	65 (15)

Legend. BMI, Body mass index; SYNTAX: synergy between percutaneous coronary intervention with TAXUS and cardiac surgery; SCAD: coronary artery disease; NSTEACS: non-ST elevation acute coronary syndrome; MI: myocardial infarction; PCI: percutaneous coronary intervention; LVSD: left ventricular systolic dysfunction defined as ejection fraction of 0.40 or less; COPD: Chronic obstructive pulmonary disease; PAD: peripheral artery disease.

Table 2. Characterization of the indication for PCI in patients with stable CAD (n=352).

Parameter	Value
Pre-Test Probability of CAD (%) [#]	69 (54-84)
Low (<15%) *n* (%)	0 (0)
Intermediate (15-85%) *n* (%)	222 (78)
High (>85%) *n* (%)	61 (22)
Ad hoc PCI *n (%)*	307 (87)
Any functional test of ischemia performed *n (%)**	217 (62)
Exercise electrocardiography *n*	153
SPECT *n*	46
Stress echocardiography *n*	31
Stress cardiac magnetic resonance imaging *n*	3
Coronary computed tomographic angiography *n (%)*	27 (8)
No functional or anatomical testing *n (%)*	125 (35%)
AUC_{CORE} mappable	318 (90)
Appropriate *n* (%)	102 (32)
Uncertain *n* (%)	163 (51)
Inappropriate *n* (%)	52 (16)
AUC_{SITE} mappable	320 (91)
Appropriate *n* (%)	100 (31)
Uncertain *n* (%)	163 (51)
Inappropriate *n* (%)	57 (18)

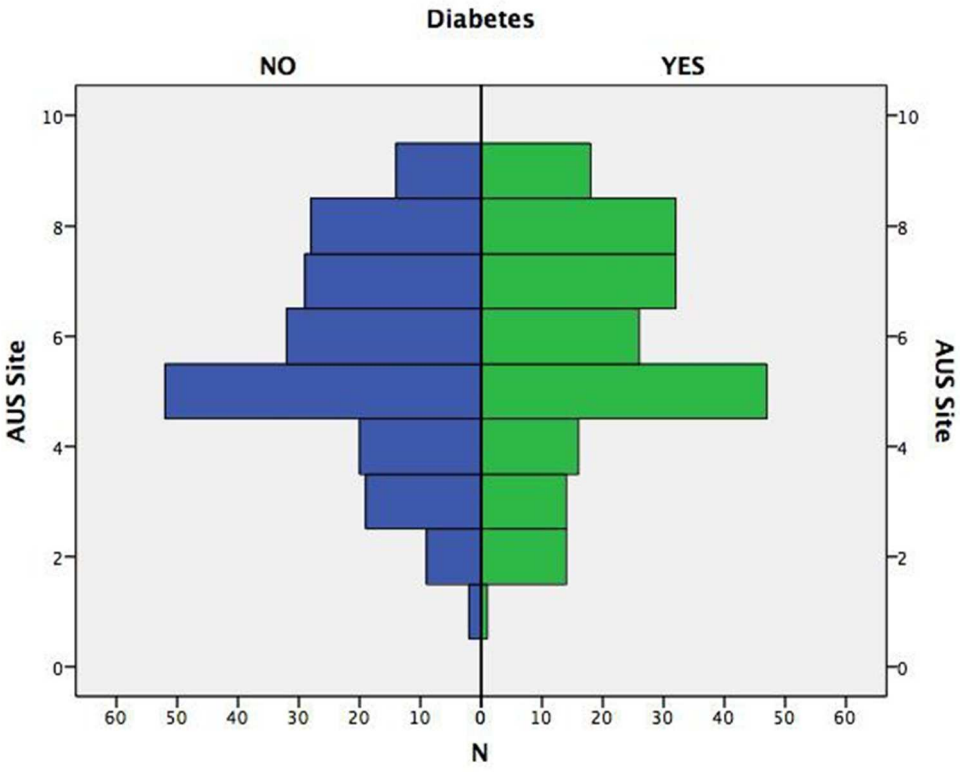
#: Calculated according to (5) only in patients with unknown coronary anatomy (n=285): defined as a history of invasive coronary angiography or coronary computed tomography angiography in the year preceding the index PCI. *: Some patients (n=15) underwent more than 1 functional test before PCI 1 patient received 3 tests; SPECT: Single-Photon Emission Computed Tomography.

Author contributions:
Sergio Leonardi and Stefano De Servi: Study design, manuscript drafting, statistical analysis and critical revision.
Marcello Marino and Gabriele Crimi: angiographic core lab analysis, critical revision.
Florinda Maiorana, Diego Rizzotti: Data management, statistical analysis and critical revision
Corrado Lettieri, Luca Bettari, Marco Zuccari, Paolo Sganzerla, Simone Tresoldi, Marianna Adamo, Sergio Ghiringhelli, Carlo Sponzilli, Giampaolo Pasquetto,

Andrea Pavei, Luigi Pedon, Luciano Bassan, Mario Bollati, Paola Camisasca, Daniela Trabattoni, Marta Brancati, Arnaldo Poli, Claudio Panciroli: critical Revision
Maddalena Lettino, Giuseppe Tarelli, Giuseppe Tarantini, Leonardo de Luca, Ferdinando Varbella: Central Heart Team and critical revision
Giuseppe Musumeci: Study design and critical revision

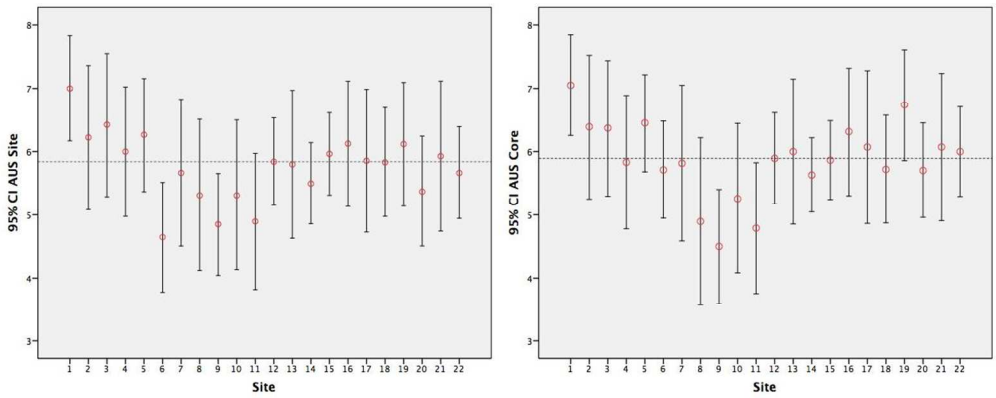
Competing interests
ICJME forms are available for all authors.
Dr Leonardi reports honoraria for advisory boards from AstraZeneca, Daiichi Sankyo, and The Medicines Company during the conduct of the study outside the submitted work; Dr. De Luca reports personal fees from Astra Zeneca, personal fees from Bayer , personal fees from Boehringer-Ingelheim, personal fees from Eli Lilly and Daiichi Sankyo, personal fees from Menarini , personal fees from The Medicines Company, outside the submitted work. Dr. De Servi reports personal fees from Pfizer, personal fees from AstraZeneca, personal fees from Daichi-sankyo, personal fees from Correvio, outside the submitted work. The other authors report nothing to disclose. All authors have read and understood BMJ policy on declaration of interests and have no other relevant interests to declare in addition to these.

Data Sharing Statement
No additional unpublished data for this study will be available.



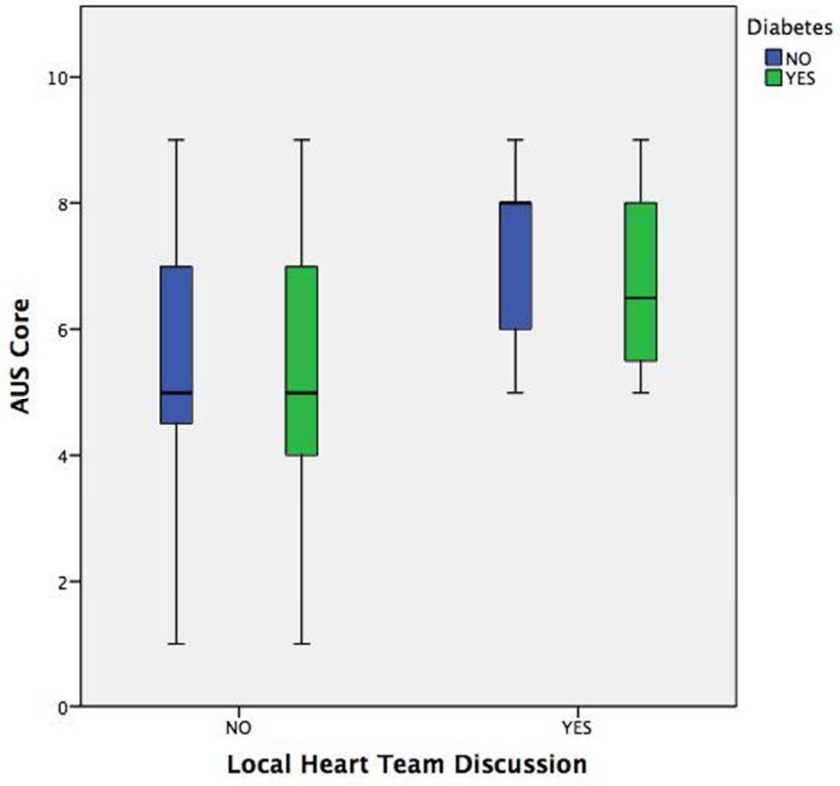
Histogram of Appropriate Use Score according to site-reported coronary anatomy (AUSSITE) in patients with and without diabetes.

53x42mm (300 x 300 DPI)



Error bars of AUSsite (left) and AUScore (right) by participating site. The dotted line indicates the median AUS site level (5.8).

106x42mm (300 x 300 DPI)



Boxplot of AUScore in patients who underwent and who did not undergo local heart team discussion, stratified by diabetes status.

53x42mm (300 x 300 DPI)

APPENDIX

Executive Committee and Medical Leadership

Stefano De Servi (study chair), Sergio Leonardi (principal investigator), Giuseppe Musumeci (GISE Lombardia President), Giuseppe Tarantini (GISE Veneto President).

Data management

Florinda Maiorana, Diego Rizzotti, Arianna Elia.

Central Heart Team

Maddalena Lettino, Giuseppe Tarelli, Ferdinando Varbella, Leonardo De Luca.

Angiographic Core Laboratory

Marcello Marino, Gabriele Crimi

Investigators

Maurizio Ferrario, *Fondazione IRCCS Policlinico San Matteo, Pavia, Italy;* Corrado Lettieri, *ASST Mantova – Ospedale Carlo Poma, Mantova, Italy;* Maurizio D'urbano, Marco Zuccari *Ospedale Fornaroli di Magenta, Magenta, Italy*; Enrico Passamonti, Luca Bettari, Sergio Signore, *Ospedale di Cremona, Cremona, Italy*; Paolo Sganzerla, Mauro Rondi, *Ospedale di Treviglio e Caravaggio, Treviglio, Italy*; Planca Enrico, Simone Tresoldi, *Azienda Ospedaliera di Desio e Vimercate, Vimercate, Italy*; Federica Ettori, Marianna Adamo, *Spedali Civili di Brescia, Brescia, Italy*; Sergio Ghiringhelli, *Ospedale di Circolo Fondazione Macchi, Varese, Italy*; Carlo Sponzilli, *Ospedale San Paolo, Milano, Italy*; Giuseppe Musumeci, Federica Piazzoni, *ASST – Papa Giovanni XXIII- Bergamo, Italy*; Giampaolo Pasquetto, Michela Facchin, *Ospedali Riuniti Padova Sud Madre Teresa di Calcutta, Monselice, Italy*; Andrea Pavei, Gerlando Preti, *Presidio Ospedaliero di Conegliano, Conegliano, Italy*; Luigi Pedon, *Presidio Ospedaliero di Cittadella, Cittadella, Italy*; Luciano Bassan, *ULSS 4 Alto Vicentino, Thiene, Italy*; Francesco Bedogni, Mario Bollati, Luca Testa, Giovanni Bianchi, *IRCCS Policlinico San Donato, San Donato Milanese, Italy*; Paola Camisasca, *Ospedale San Gerardo, Monza, Italy*; Daniela Trabattoni, *Centro Cardiologico Monzino, Milano, Italy*; Ornella Leonzi, Marta Brancati, *Fondazione Poliambulanza, Brescia, Italy*; Arnaldo Poli, Katia Stefanin, *ASST Ovest Milanese, Legnano, Italy*; Claudio Panciroli, Emanuele Prina, *ASST di Lodi, Lodi, Italy*; Paolo Pagnotta, Daniela Cattani, *IRCCS Humanitas, Rozzano (MI),Italy*; Giuseppe Tarantini, Ervis Hiso, *Ospedale Di Padova, Padova,Italy*.

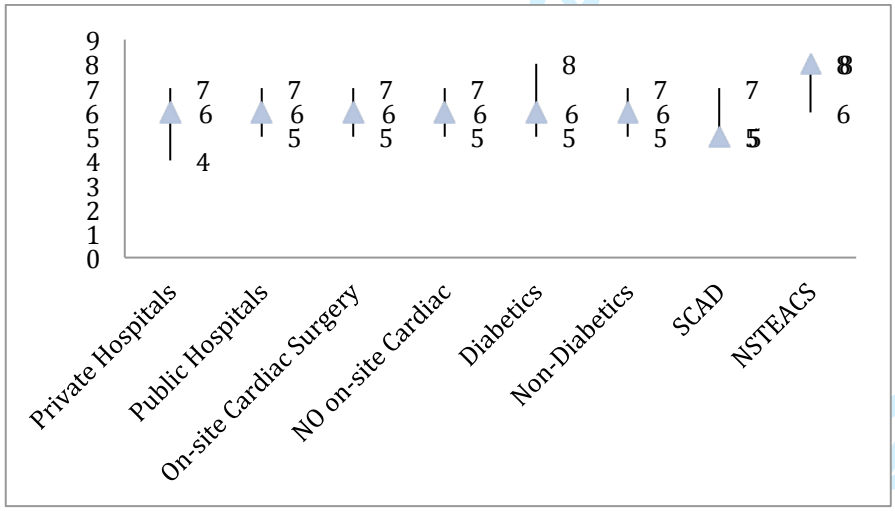
Sites

1. Fondazione IRCCS Policlinico San Matteo, Pavia (Coordinating Site)
2. ASST Mantova – Ospedale Carlo Poma, Mantova
3. Ospedale Fornaroli di Magenta, Magenta
4. Ospedale di Cremona, Cremona
5. Ospedale di Treviglio e Caravaggio, Treviglio
6. Azienda Ospedaliera di Desio e Vimercate, Vimercate
7. Spedali Civili di Brescia, Brescia
8. Ospedale di Circolo Fondazione Macchi, Varese

9. Ospedale San Paolo, Milano
10. ASST – Papa Giovanni XXIII- Bergamo
11. Ospedali Riuniti Padova Sud Madre Teresa di Calcutta, Monselice
12. Presidio Ospedaliero di Conegliano, Conegliano
13. Presidio Ospedaliero di Cittadella, Cittadella
14. ULSS 4 Alto Vicentino, Thiene
15. IRCCS Policlinico San Donato, San Donato Milanese
16. Ospedale San Gerardo, Monza
17. Centro Cardiologico Monzino, Milano
18. Fondazione Poliambulanza, Brescia
19. ASST Ovest Milanese, Legnano
20. ASST di Lodi, Lodi
21. IRCCS Humanitas, Rozzano (MI)
22. Ospedale di Padova, Padova.

Supplementary Figure

Title: AUS$_{CORE}$ for pre-defined study subgroups.



Legend: Appropriate Use Score for pre-defined subgroups including type of hospital (private or public), presence of cardiac surgery on site, diabetic patients, and clinical presentation (stable CAD or NSTEACS).

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract (**Title Page**)
		(a)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (**Abstract Page 2**)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (**Introduction, page 4**)
Objectives	3	State specific objectives, including any prespecified hypotheses (**Objective, abstract**)
Methods		
Study design	4	Present key elements of study design early in the paper (**Study Design, page 5**)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (**Methods, page 5 and Results, page 11**)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants (**Methods, page 5, Patient Selection Section**)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (**Methods, page 5**)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (**Methods, page 5 Data Collection Section**)
Bias	9	Describe any efforts to address potential sources of bias (**Methods, page 5**)
Study size	10	Explain how the study size was arrived at (**Sample Size Consideration, page 10**)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (**Statistical Section for all below, page 10**)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (**Results, page 11**)
		(b) Give reasons for non-participation at each stage (**NA**)
		(c) Consider use of a flow diagram (**NA**)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (**Results, page 11**)
		(b) Indicate number of participants with missing data for each variable of interest (**Results, page 11**)
Outcome data	15*	Report numbers of outcome events or summary measures (**Results, page 11**)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included (**Results, page 11**)
		(*b*) Report category boundaries when continuous variables were categorized (**Results, page 11**)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (**Results, page 11**)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (**Results, page 11**)
Discussion		
Key results	18	Summarise key results with reference to study objectives (**Discussion, page 15**)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (**Discussion, page 15**)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (**Discussion, page 15**)
Generalisability	21	Discuss the generalisability (external validity) of the study results (**Discussion, page 15**)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (**Funding Statement, page 10**)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.