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Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease

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Aims To provide a pooled estimation of contemporary pre-test probabilities (PTPs) of significant coronary artery disease (CAD) across clinical patient categories, re-evaluate the utility of the application of diagnostic techniques according to such estimates, and propose a comprehensive diagnostic technique selection tool for suspected CAD.

Methods and results Estimates of significant CAD prevalence across sex, age, and type of chest pain categories from three large-scale studies were pooled ($n = 15\,815$). The updated PTPs and diagnostic performance profiles of exercise electrocardiogram, invasive coronary angiography, coronary computed tomography angiography (CCTA), positron emission tomography (PET), stress cardiac magnetic resonance (CMR), and SPECT were integrated to define the PTP ranges in which ruling-out CAD is possible with a post-test probability of <10% and <5%. These ranges were then integrated in a new colour-coded tabular *diagnostic technique selection tool*. The Bayesian relationship between PTP and the rate of diagnostic false positives was explored to complement the characterization of their utility. Pooled CAD prevalence was 14.9% (range = 1–52), clearly lower than that used in current clinical guidelines. Ruling-out capabilities of non-invasive imaging were good overall. The greatest ruling-out capacity (i.e. post-test probability <5%) was documented by CCTA, PET, and stress CMR. With decreasing PTP, the fraction of false positive findings rapidly increased, although a lower CAD prevalence partially cancels out such effect.

Conclusion The contemporary PTP of significant CAD across symptomatic patient categories is substantially lower than currently assumed. With a low prevalence of the disease, non-invasive testing can rarely rule-in the disease and focus should shift to ruling-out obstructive CAD. The large proportion of false positive findings must be taken into account when patients with low PTP are investigated.

Keywords prevalence • pre-test probability • coronary artery disease • angina

Introduction

The optimal use of cardiovascular (CV) diagnostic techniques depends on their intrinsic imaging potential, availability, physician expertise, and costs, but also on the prevalence of the disease, i.e. the pre-test probability (PTP) of coronary artery disease (CAD) in the studied population. Bayesian statistics[1] utilize two fundamental elements to estimate the probability of disease and allow, in turn, to gauge the benefit of utilizing a particular diagnostic test to rule-out or rule-in CAD. The two elements are (i) the assumed PTP of the disease (i.e. the prevalence), which represents *a priori* information and (ii) the diagnostic performance profile of the considered technique expressed in likelihood ratios. Once the likelihood ratios are applied to the PTP, the *post-test probability* of the disease is obtained using the Fagan nomogram.[2]

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Current estimations of PTP of significant CAD across clinically distinguishable patient groups (based on sex, age, and type of chest pain) have been stated in the European Society of Cardiology[3] and American College of Cardiology/American Heart Association[4] guidelines on the management of stable CAD. These guidelines consider that patients with an 'intermediate' probability of CAD (i.e. when the PTP ranges from 15 to 85%) should undergo further non-invasive evaluation,[5,6] while subjects below or above these thresholds can be either reassured or assumed to suffer from obstructive CAD. These probability margins have been set at arbitrary values, and therefore, are not definitive.

Several large-scale studies have recently documented lower PTP values in the general population than previously considered.[7–9] Furthermore, in a recent systematic review and meta-analysis, we have characterized the performance profiles of the available techniques [exercise electrocardiogram (ECG), invasive coronary angiography (ICA), coronary computed tomography angiography (CCTA), positron emission tomography (PET), stress cardiac magnetic resonance (CMR), and single photon emission computed tomography (SPECT)] for diagnosing anatomically and functionally significant CAD.[10] Such performance overview also suggested a tabular tool to guide the application of diagnostic techniques for each PTP patient category.

It is likely that the suggested decrease in PTP values will have a major impact on the applicability of diagnostic tests for CAD. For instance, with lower PTPs, there will be more focus on the ruling-out capacity of a given test. Moreover, as an increasing number of patients will belong to the category of *low* PTP at an overall lower base rate, re-evaluation of the current PTP threshold of 15% of PTP to discourage further testing is warranted. Currently, there are no published analyses of the impact of lower thresholds for defining an *intermediate* PTP of CAD on the utility of application of the aforementioned diagnostic tests.

Hence, the present study had two main goals: firstly, to provide a pooled estimation of contemporary PTPs of significant CAD across traditionally considered clinical patient categories, and secondly, to re-evaluate the utility of application of exercise ECG, ICA, CCTA, PET, stress CMR, and SPECT according to such contemporary PTPs, while exploring novel progressive ruling-out thresholds. This will allow suggesting an updated comprehensive diagnostic technique selection tool for clinical work in the contemporary population suspected with CAD.

Methods

A search for studies that reported on CAD prevalence since the last operational estimations by Genders *et al.*,[8] was performed and screened through cross-referencing. Furthermore, we contacted the authors of recent major large population studies to acknowledge the potential *in-press* reports including the above described information. Studies were considered for inclusion when they: (i) demonstrated consistency of methods for identification of significant CAD and (ii) stratified their PTP estimates according to sex, age, and type of chest pain as established in current guidelines.[3]

Data extraction and pooling of PTP estimates

Continuous baseline variables from the included reports were extracted and pooled using their mean, standard deviation, and sample size in order to obtain single overall means and standard deviations.

CAD prevalence data were extracted focusing on the absolute number of identified CAD cases across the clinical patient categories established in the CAD ESC 2013 Guidelines' PTP table [considering sex, age (at 10-year intervals), and type of chest complaints (typical angina, atypical angina, and non-anginal pain)]. Thereon, the number of cases across studies was summed to obtain an overall pool to estimate the updated values of PTP of significant CAD expressed as percentages across all patient categories. Whenever a specific patient category in the table was not present across all three studies, its case count was merged with the nearest neighbouring category that was consistent across the reports. Resulting contemporary PTP estimates were then summarized in the same table format of the current guidelines.[3] A supplementary pooling of patients with 'predominantly' or 'only' dyspnoea as their symptomatic profile was performed when available.

Evaluation of clinical utility of diagnostic techniques

Based on the previously published *Take home figure* in Knuuti *et al.*,[10] we revisited the ranges of PTP in which a positive or negative test result can confidently rule-in or rule-out (by driving the *post-test probability* below 15% or above 85%) the presence of significant CAD [i.e. as determined by ICA and fractional flow reserve (FFR) evaluation] based on the likelihood ratio values of the following techniques: exercise ECG, ICA, CCTA, PET, stress CMR, and SPECT.

Subsequently, we calculated the ranges of PTP in which ruling-out CAD is possible by driving the *post-test probability* to <10% and <5% (as a refinement from the traditionally considered single-value threshold of <15%). Then, we integrated the updated PTP table with these graded PTP ranges for ruling-out CAD and created a new colour-coded tabular *diagnostic technique selection tool* (a previous version was published in *Supplemental Figure S2 in Knuuti et al. 2018*[10]). The intended goal of this tool is to help in selecting a particular technique, depending on its diagnostic power, for a specific patient category when suspecting obstructive CAD.

Finally, we graphically represented the Bayesian relationship between PTP and the theoretical rate of diagnostic errors (false positives) in relative and absolute terms for every diagnostic technique to complement the characterization of their utility.

Results

The search string can be consulted in the Supplementary data online, *Resource S1*, although the included studies were provided by the authors after cross-referencing. Three large-scale trials were analysed: Foldyna *et al.*,[11] Reeh *et al.*,[12] and Cheng *et al.*,[7] which conveyed a combined population of 15 815 patients (mean age of 59 ± 11 years old). All three studies considered significant CAD as any luminal narrowing of >50%. A summary of the characteristics and procedures of the included studies can be consulted in the Supplementary data online, *Resource S2*.

Baseline characteristics per study and resulting pooled estimates are shown in *Table 1*. The studies documented balanced proportions of males and females. The oldest mean age and highest body mass

Table 1 Summary of population characteristics

Baseline variables	Pooled estimate	Foldyna et al. (PROMISE)	Reeh et al.[a]	Cheng et al. (CONFIRM)[b]
Sample, *n*	15 815	4415	3294	8106
CAD cases, *n*	2350	615	243	1492
CAD prevalence (%)	14.9	13.9	7.4	18.4
Men, *n* (%)	7573 (48)	2132 (48)	1453 (44)	3999 (49)
Women, *n* (%)	8222 (52)	2283 (52)	1841 (56)	4107 (51)
Age (years)	59	60.50	58.05	57.8
Age (SD)	11	8.2	13.8	11.3
BMI (kg/m^2)	28.2	30.40	27.07	27.4
BMI (SD)	5.5	5.9	5.2	5.3
HTN, *n* (%)	8691 (55)	2829 (64)	1678 (43)	4184 (52)
DM, *n* (%)	2485 (16)	908 (21)	465 (12)	1112 (14)
Dyslipidaemia, *n* (%)	9432 (60)	2965 (67)	1764 (45)	4703 (58)
Family history of CAD, *n* (%)	5184 (33)	1441 (33)	1213 (31)	2530 (31)
Smokers, *n* (%)	5494 (35)	2256 (51)	1907 (49)	1331 (16)[c]

BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HTN, arterial hypertension; SD, standard deviation.
[a]The reported sample and number of cases with obstructive CAD consider only patients reported in the typical angina, atypical angina, and non-anginal pain categories, while the rest of the baseline characteristics were extracted considering the whole sample of the study.
[b]The reported sample, number of cases with obstructive CAD, and the rest of the baseline characteristics consider only patients reported in the typical angina, atypical angina, and non-anginal pain categories.
[c]The definition of smokers differed across studies.

index were reported in the PROMISE study,[11] while the other two reports were closely comparable regarding these baseline characteristics. There were seemingly more smokers in the study by Foldyna *et al.*[11] Of note, data from the registry reported by Reeh *et al.*[12] showed the lowest prevalence of CV risk factors as it included a broad un-selected patient sample.

Pooled population composition and updated PTPs of significant CAD

In the pooled population, the largest groups of participant subjects were those with atypical angina (59%), then those with non-anginal pain (25%), and finally, the smallest groups were the ones with typical angina (16%) (see Supplementary data online, *Resource S3A* for a stacked depiction of the number of participants across clinical categories provided by each study). The distribution of patients into different categories between trials was not profoundly different. However, the study by Reeh *et al.*[12] reported more patients classified as having non-anginal pain than the other two reports.

Of the patients with significant CAD, patients with atypical angina (58%) conveyed the largest proportion, while the percentage of such cases with typical angina and non-anginal pain represented 29 and 14%, respectively. The stacked depiction of the number of obstructive CAD cases provided by each study across clinical categories can be consulted in the Supplementary data online, *Resource S3B*.

The pooled prevalence of significant CAD in subjects with typical angina, atypical angina and non-anginal pain was 23, 14, and 8%, respectively. Patients with significant CAD were older, more often males, and mostly had atypical angina. Notably, the prevalence of significant CAD in the patients with atypical angina was higher in the CONFIRM trial than the other populations, while the other data were consistent between the studies.

The updated pooled PTPs of obstructive CAD across the clinical patient categories are shown in *Table 2* (and graphically depicted in the Supplementary data online, *Resource S4*). The overall prevalence of significant CAD in the pooled population ranged from 1 to 52% with a mean of 14.9% (see *Table 1* for the prevalence estimates across the three included studies), which corresponds to about a 66% decrease in average from the values defined by Genders *et al.* 2011 used in the 2013 ESC guidelines across all patient categories.

The study by Reeh *et al.*[12] provided prevalence estimates in the categories corresponding to >80 years of age, while both the studies by Foldyna *et al.*[11] and Cheng *et al.*[7] did not. Therefore, the counts for cases and totals in the 80+ years old categories were pooled into the ≥70 years old categories. The absolute pooled counts for each patient category can be consulted in the Supplementary data online, *Resource S5*.

Patients with dyspnoea

The supplementary pooling of patients in the clinical categories of dyspnoea [either as the predominant symptom (as considered by Reeh *et al.*[12]) or as the only symptom (as considered by Cheng *et al.*[7])] was only performed, due to availability, with data from such two studies. The corresponding pooled prevalence of obstructive CAD, absolute number of cases, and subjects in this category are shown in *Table 2* and Supplementary data online, *Resources S4* and *S5*. The resulting PTP distribution resembled mostly that of the patients with atypical angina.

Table 2 Pre-test probabilities of obstructive CAD in symptomatic patients according to age, gender, and the nature of symptoms in pooled analysis

	Typical (%)		Atypical (%)		Non-anginal (%)		Dyspnoea[a] (%)	
Age (years)	Men	Women	Men	Women	Men	Women	Men	Women
30–39	3	5	4	3	1	1	0	3
40–49	22	10	10	6	3	2	12	3
50–59	32	13	17	6	11	3	20	9
60–69	44	16	26	11	22	6	27	14
70+	52	27	34	19	24	10	32	12

[a]In addition to the classic Diamond and Forrester classes, patients with dyspnoea only or dyspnoea as primary symptom are included. The dark green shaded regions denote the groups in which non-invasive testing is most beneficial (pre-test probability >15%). The light green shaded regions denote the groups with pre-test probability of CAD between 5 and 15% in which the testing for diagnosis may be considered based on clinical judgement.

Clinical utility of techniques and diagnostic technique selection tool

Figure 1 shows the updated ranges of PTP in which a positive or negative test result can rule-in or rule-out significant CAD against both reference standards: ICA and FFR. In particular, it depicts the calculated colour *gradient* according to the PTP ranges in which it is possible to rule-out the disease by driving the *post-test probability* below the following thresholds of *post-test probability*: <15, <10, and <5%. As expected, it is much easier to achieve a *post-test probability* below 15% than below 5%. It is also clearly shown that CCTA performs better when considering ICA than when considering FFR as the reference standard, and conversely, that functional tests perform better when the reference standard is FFR.

By considering the aforementioned significant shift of the distribution of PTPs towards a lower average prevalence (14.9%) in comparison with the traditional assumptions considered in the ESC Guidelines (former average PTP = 44.5%), as well as the calculated thresholds for every technique for ruling-out disease with increasing levels of confidence, we updated the colour-coded *diagnostic technique selection tool*. This is shown in *Figure 2* again considering FFR (and ICA for completeness) as reference standard. The ruling-out capabilities of the included techniques were remarkable in ruling-out CAD across all clinical patient categories with a *post-test probability* of at least <15%. On the other hand, the greatest capacity to rule-out disease (i.e. with a post-test probability <5% as shown in darkest green) reached all age and type of chest pain categories when utilizing CCTA, PET, and stress CMR in women, but not in men. Notably, there was only one clinical instance in which an overlapping ruling-out and ruling-in potential was reflected by two techniques namely, in male patients 70 years and older with typical angina when opting for PET or stress CMR. ICA demonstrated the most restricted profile for ruling-out FFR-significant CAD, particularly, in clinical groups that convey the highest PTP estimates (males with typical anginal above 50 years old). Alternatively, stress ECG showed the least favourable ruling-out profile for ICA-significant CAD. The diagnostic capabilities of each analysed technique given the updated PTP table can be individually consulted in the Supplementary data online, *Resource S6*. The diagnostic utility of all techniques was additionally depicted for the categories of patients who presented with dyspnoea as the only or predominant symptom in the report by Reeh *et al.*[12] and the CONFIRM study.[7] The profile resembled that of the categories of patients with atypical angina (see right panels in *Figure 2* and Supplementary data online, *Resource S6*).

The relationship between the PTP and *post-test probability* was explored graphically and is shown in *Figure 3*. There was a clear non-linear function linking the PTP with the rate of false positive and negative findings at each extreme of PTP. The range of contemporary PTPs across clinical patient categories (see *Table 2*) shows a clear predominance in the lower 50% of PTP in which the main challenge is the increasing rates of false positive results.

Figure 4 shows the impact of lower PTPs on false positive findings. As the PTP gets smaller, the fraction of false positive findings rapidly increased. At very low levels of PTP the fraction of false positives approaches 100%. However, as the PTP decreases, the absolute number of patients eventually having significant CAD gets also lower. This partly cancels out the exponential increase in relative numbers of false positives and leads to only a modest increase in absolute number of patients with false positive diagnosis. Such absolute numbers, in turn, may aid in depicting the most favourable techniques to utilize.

Discussion

The present analysis conveys several clinically important messages. First, we provide the pooled updated PTPs of significant CAD across traditionally established symptomatic patient categories. Second, this information is integrated with the performance profiles of available diagnostic techniques for ruling-in or ruling-out CAD. Third, we propose a new *diagnostic technique selection tool* taking into account the changes in prevalence of CAD, the performance of the tests, and an updated probability threshold for ruling-out CAD.

PTP of CAD

The pooling of data concerning the contemporary prevalence of CAD has demonstrated that the current average PTP of CAD is substantially lower as compared to the earlier assumption suggested in clinical guidelines (14.9% vs. 44.5%). This notion has been also suggested in the recent EVINCI prospective trial.[13] The three included reports have independently put forward timely prevalence estimates

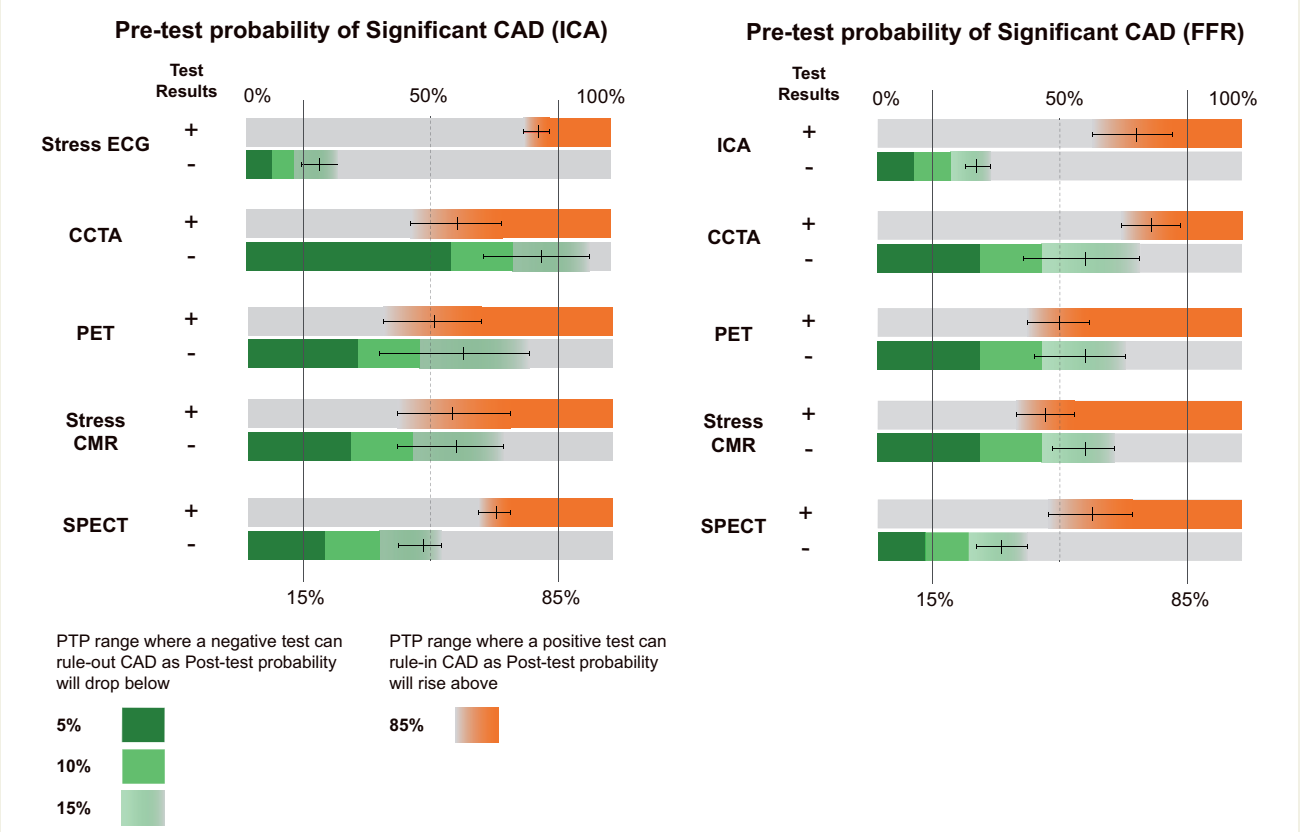

Figure 1 PTP ranges in which significant CAD can be ruled-in or ruled-out according to the result of a test. Left panel shows ICA as reference standard, while right panel uses significant CAD by abnormal FFR. The applied colour gradient (or test band-width) depicts the PTP ranges and thresholds with which a negative result can rule-out disease by driving the post-test probability below 15, 10, or 5. CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; FFR, fractional flow reserve; ICA, invasive coronary angiography; PET, positron emission tomography; SPECT, single photon emission computed tomography. Adapted from Knuuti *et al.*[10]

with directional convergence according to the type of study performed. The present work takes the next step forward by combining data from these trials to obtain estimates of the current disease base rates as displayed in *Table 2*. The decrease in overall PTP may be a result of both epidemiological and methodological factors. For instance, progressive changes risk factor prevalence (lifestyle improvement), preventive therapeutics (e.g. statins), clinical presentation and a consequent evolution of the natural history of CAD on the one hand, and a decreased selection bias in the evaluated studies on the other. Of note, one of the studies included in this analysis[12] evaluated all-comers from the general population.

The pooled proportions of subjects with obstructive CAD across sex, age, and type of chest complaints categories confirmed an increasing gradient of PTP with increasing age and typicality of complaints, along with higher PTPs consistently found in men when compared with women. Although expected, these phenomena were not constant across the studies. The most common symptom in the patient with suspected CAD is atypical angina (59%). However, also the patients with non-anginal pain were common (25%). Although the prevalence of CAD in the patients with non-anginal pain was 8%, this group formed 14% of all patients with significant CAD. Therefore, our analysis does not support the proposed approach by NICE guidelines,[14] in which patients with non-anginal pain with normal resting ECG can be automatically ruled-out. It should, however, be noted that the PTP presented in this study is based mainly on low CV risk countries and may vary between different regions and countries.

The pooling of patients in categories of dyspnoea as an angina equivalent provided an interesting nuance about the possible utilization of such clinical designation. Dyspnoea has been shown to be a prognostic marker in patients referred for cardiac stress testing.[15] The prevalence of significant CAD in such patients closely resembles the one found in patients who present with atypical angina. As such, further discussion is certainly warranted around the most adequate equivalence of dyspnoea as a clinically relevant cluster of patients.

A substantial fraction of symptomatic patients do not demonstrate obstructive CAD, e.g. the prevalence of obstructive CAD was only 11% in women 60–69 years old with atypical angina. It is understood that symptoms may arise from abnormal coronary flow reserve related to diffuse atherosclerosis or dysfunction at the level of the

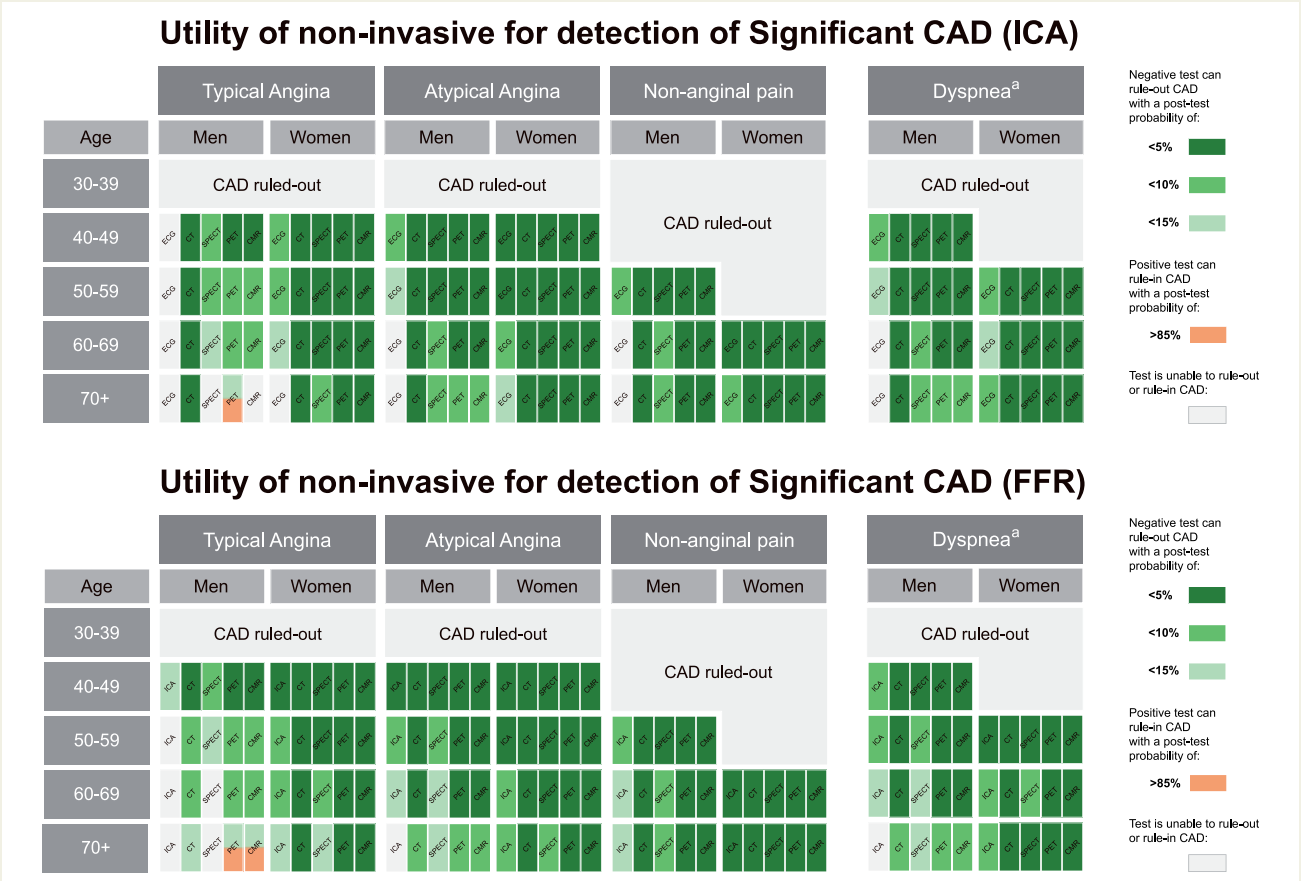

Figure 2 Updated *diagnostic technique selection tool* for all patient categories based on sex, age, and type of chest pain, considering both ICA (upper panel) and FFR (lower panel) as the reference standard. The colour gradients inform the confidence with which a negative result can rule-out disease (i.e. by driving the *post-test probability* below 15, 10, or 5). CAD is directly rule-out with a PTP ≤5. [a]The categories corresponding to dyspnoea as the predominant or only symptom; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; FFR, fractional flow reserve; ICA, invasive coronary angiography; PET, positron emission tomography; SPECT, single photon emission computed tomography. Adapted from Knuuti *et al.*[10]

microvasculature in a proportion of these patients.[16,17] This is relevant as it supports future optimization of angiographic disease definition in population studies beyond focal obstruction.

One main limitation of this simplified determination of PTP is that it does not take into account the other risk factors but is based only on age, gender and symptoms. Therefore, it is important to keep in mind that risk factors such as family history, smoking, hypercholesterolaemia, hypertension, and diabetes have major impact on individual PTP and risk, and should be part of the clinical assessment.[18,19] Comparisons of models predicting likelihood of CAD indicate that inclusion of risk factors and resting ECG changes significantly improve identification of patients with obstructive CAD by CCTA as compared with models based on age, sex, and type of chest pain.[19–22] For example, the Duke Clinical Risk score has shown a net reclassification improvement of 51% as compared with the Diamond and Forrester method, particularly improving identification of patients with low likelihood of obstructive CAD.[22] Furthermore, coronary calcium score refines estimates of PTP of CAD compared with clinical models.[20,23] However, a simple algorithm that would combine risk factors for a more accurate assessment of individual clinical likelihood of CAD is not available, and warrants research.

The performance of diagnostic tests in contemporary populations

Application of the new PTP may substantially reduce the need for non-invasive and invasive tests in patients with suspected stable CAD. However, deferring diagnostic testing in patients with new PTP <15% will result in a large increase in the proportion of symptomatic patients in whom diagnostic testing is not recommended. When using a criterion of <15% post-test probability for ruling-out CAD, up to 15 patients out of 100 will potentially have significant CAD but may not get the appropriate diagnosis.

In data derived from the current pooled analysis 57% of patients are classified to a PTP <15%. Studies suggest that clinical outcomes in patients with a contemporary PTP up to 15% are good (annual risk of CV death or myocardial infarction <1%).[11,12] Hence, it may be safe to defer routine testing in such patients with a PTP <15%. However,

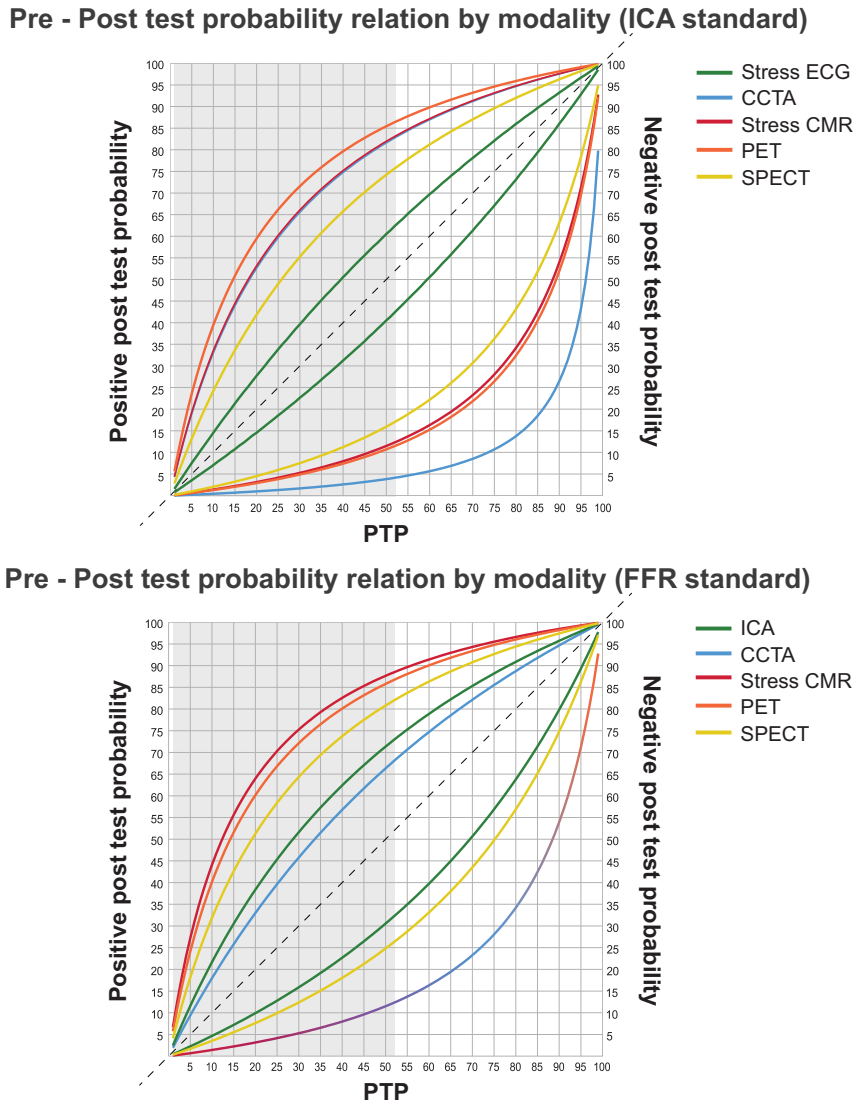

Figure 3 The Bayesian relationship between PTP and post-test probability across diagnostic techniques for both reference standards. The light-grey area borders the contemporary range of PTPs presented in *Table 2*. CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; ICA, invasive coronary angiography; PET, positron emission tomography; SPECT, single photon emission computed tomography.

recent evidence has also demonstrated that the true observed prevalence of obstructive CAD has been <5% in patients commonly considered to have a PTP <15% according to the PTP estimates by Genders *et al.*[12,24] Therefore, performing diagnostic testing also in patients with PTP of 5–15% may more closely reflect current clinical practice. The large discrepancy between the estimated and observed prevalence of obstructive CAD points towards a need for more research on outcomes and tools to further identify patients with a minimal event risk, such as coronary calcium imaging.[19,20] Naturally, patient preference, local resources and availability of tests, clinical judgement, and appropriate patient information remain important for the decision to proceed with non-invasive diagnostic testing in an individual patient when PTP is 5–15% and the higher likelihood of a false positive test result must be considered. Patients with PTP ≤5% can be assumed to have such a low probability of disease that diagnostic testing should be performed only for compelling reasons. Implementation of the updated PTP also indicates that patients should not be routinely referred to invasive assessment unless clinical or other data indicate a high likelihood of obstructive CAD.

The updated estimates of PTP of CAD have major impact on the clinical utility of diagnostic techniques. For instance, coarse diagnostic techniques (i.e. with rather modest negative likelihood ratios) may be able to deliver a low-enough *post-test probability* of disease to the clinician, in order to effectively rule-out significant CAD at the individual level.

We assessed the performance of various tests to achieve a post-test probability of <15, <10, and <5%. The lower thresholds become of substantial relevance with a decreasing prevalence of CAD.

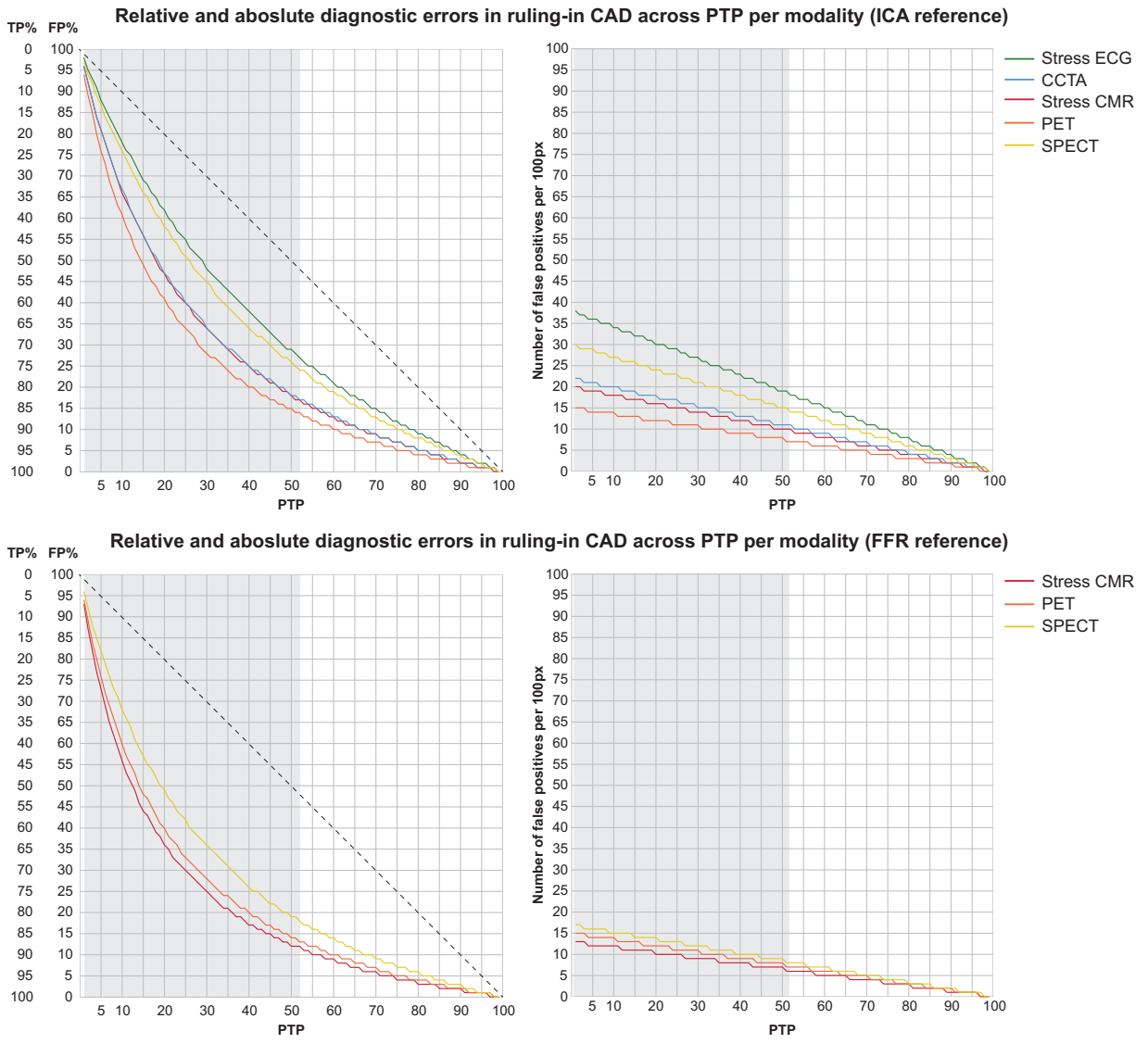

Figure 4 The relationship between PTP and false positive findings across diagnostic techniques in relative and absolute terms for both reference standards: ICA and FFR. The right side graph shows the expected number of patients with false positive test result when a sample of 100 patients is assessed at each PTP value. The light-grey area borders the contemporary range of PTPs presented in *Table 2*. CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; FP, percentage of false positive finding; ICA, invasive coronary angiography; PET, positron emission tomography; SPECT, single photon emission computed tomography; TP, percentage of true positive findings.

We found that in many patient categories, several tests can achieve post-test probability even as low as <5% (*Figure 2*).

On the other hand, there is only one clinical instance in which CAD could be ruled-in by a positive test result, i.e. driving the post-test probability above 85%. This can be achieved only by using the techniques with the highest positive diagnostic likelihood ratios and in men aged 70+ years with typical angina. Accordingly, the *overlap* of optimal performance of a test (the range of PTPs in which the technique can confidently both rule-in or rule-out CAD[10]) was only discernible in this category of patients. This should encourage further characterization of the additive value of sequential or multiple testing for adequate ruling-in of significant CAD.

What should be the PTP limit to rule-out CAD?

The clinical application resulting from the exploration of PTP thresholds for ruling-out CAD with a post-test probability of <15, <10, and <5% is currently feasible, given the contemporary lower average PTP of obstructive CAD. In our perspective, there are advantages of

refining these ruling-out thresholds. An example is pertinent: if one starts from assuming a PTP of 26% (which corresponds to that of males between the ages of 60–69 years and with atypical angina), a negative test result with PET will deliver a post-test probability of 4%. Conversely, if we rather would utilize ICA as the sole diagnostic tool, the obtained post-test probability would equal to 13%. The latter approach produces three times as many false negatives, while the currently utilized threshold of <15% would deem both approaches equally acceptable. This example clearly demonstrates the potential for improvement in the precision of our diagnostic estimates in suspected CAD. As explained above, the operational threshold that has been already utilized corresponds to <5% in practice. Applying this new threshold together with new PTP table would not increase the number of patients entering diagnostic testing. In a recent analysis, 2.5% in the PROMISE and 19.8% in the SCOT-HEART trials belonged to the category of <15%, i.e. the group in which no further testing is recommended.[24] When applying the contemporary PTP data, 14% of patients (2224 patients out of 15 815) were classified as having PTP <5%.

The main challenge of testing patients with low PTP is that the fraction of false positive results will increase rapidly. This is clearly true in relative terms. However, as shown by the analysis in *Figures 3* and *4*, the increase in false positive cases in absolute terms is less striking as the prevalence of disease is decreasing with decreasing PTP.

How to select a diagnostic technique for each patient?

Based on the analysis above, we have proposed a new *diagnostic technique selection tool* in patients with suspected CAD and stable angina (*Figure 2* and Supplementary data online, *Resource S6*). The patient categories having PTP <5% are classified as having CAD already ruled-out. For other categories, we have colour-coded the performance of the tests to achieve a post-test probability <5% (the ideal target) but also <10 and <15%. As currently, both functional (FFR) and anatomical (ICA) reference standards are applied, we have created tables for both reference standards. As shown earlier,[10] CCTA performs better in ruling-out ICA-defined anatomical disease while functional imaging tests are better in ruling-out functionally significant CAD. Somewhat surprisingly, there is generally no big difference between the tests in ruling-out power for obstructive CAD. When the detection of non-obstructive CAD is considered important, as it was suggested by the recent study (i.e. the 5-year follow-up of SCOT-HEART trial[25]), CCTA may be the preferred technique. However, this is at the cost of more false positive findings as compared to functional imaging tests due to the lower specificity of CCTA (see *Figure 4*).

Albeit the studies are less recent and did not include FFR as gold standard, the performance of exercise ECG in ruling-out of CAD seems clearly worse than any imaging test. Therefore, even in the setting of a reduced PTP, this test cannot be used to rule-out obstructive CAD. However, exercise ECG provides complementary clinically useful information beyond ECG changes and valuable prognostic information. Therefore, exercise ECG is useful in selected patients to complement clinical evaluation for assessment of symptoms, exercise tolerance, inducibility of arrhythmias, blood pressure response, and risk assessment.

The present analysis has some limitations. It was based on the prevalence of CAD in three contemporary studies that had specific inclusion criteria. We assumed that the patients in these trials represent the current clinical symptomatic populations in which diagnostic testing is considered. For PTP estimations, CCTA was used in many patients for the detection of CAD. It is well-known that CCTA overestimates the degree of coronary artery stenosis. Therefore, it is possible that the true PTP values maybe even lower than in the current analysis, but not likely higher. Further, this analysis was focused on diagnostic power for classifying patients as having CAD or not, but not on the severity of the disease, the assessment of risk or the performance of the tests to guide therapeutic decisions. Lastly, not all modalities have accumulated a similar repository of data. Therefore, comparing the relative performance of imaging modalities must be done with caution.

In conclusion, the contemporary PTP of significant CAD across symptomatic patient categories based on sex, age, and type of chest complaints is substantially lower than currently assumed. A significant number of patients with obstructive CAD can be detected in all symptomatic categories. With a low prevalence of the disease, non-invasive testing can rarely rule-in CAD and the focus should shift to ruling-out obstructive CAD. The rule-out power of the imaging tests appears quite comparable. The large proportion of false positive findings must be taken into account when patients with low PTP are investigated. Further individual refinement of disease probability based on additional pre-test information is warranted. When a higher clinical likelihood of CAD is assumed, functional tests are more powerful to rule-in CAD.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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