J Cardiovasc Imaging. 2021 Apr;29(2):160-165
https://doi.org/10.4250/jcvi.2020.0176
pISSN 2586-7210·eISSN 2586-7296

Journal of Cardiovascular Imaging JCVI

Original Article

Implications of Alterations in Pre-test Probability in the 2019 Update of ESC Guidelines for Chronic Coronary Syndromes on Diagnostic Accuracy of Pharmacological Stress-Echocardiography: A Retrospective Cohort Study

Iryna Dykun, MD, Stefanie Hendricks, MD, Bastian Balcer, MD, Matthias Totzeck, MD, Fadi Al-Rashid, MD, Tienush Rassaf, MD, and Amir A. Mahabadi, MD

Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center Essen, University of Duisburg-Essen, Essen, Germany

Received: Sep 18, 2020
Revised: Dec 17, 2020
Accepted: Jan 5, 2021

Address for Correspondence:
Iryna Dykun, MD
Department of Cardiology and Vascular Medicine, West German Heart and Vascular Center Essen, University Hospital Essen, University of Duisburg-Essen, Hufelandstraße 55, Essen 45147, Germany.
E-mail: Iryna.dykun@uk-essen.de

ORCID iDs
Iryna Dykun
https://orcid.org/0000-0002-7350-1477
Matthias Totzeck
https://orcid.org/0000-0001-7898-3906
Fadi Al-Rashid
https://orcid.org/0000-0001-5229-9612
Tienush Rassaf
https://orcid.org/0000-0001-8001-0265
Amir A. Mahabadi
https://orcid.org/0000-0003-2336-7991

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Dykun I, Rassaf T, Mahabadi AA; Data curation: Hendricks S,

ABSTRACT

BACKGROUND: With the 2019 update of European Society of Cardiology (ESC) guidelines for chronic coronary syndromes, the pre-test probabilities (PTPs) based on age, sex, and symptoms have undergone major revisions. We aimed to determine implications of these alterations on diagnostic accuracy of dobutamine stress echocardiography (DSE).
METHODS: We retrospectively included consecutive patients undergoing pharmacological stress-echocardiography for evaluation of suspected obstructive coronary artery disease. DSE was performed as non-invasive imaging test and was indicated by individual treating physician's decision. Sensitivity, specificity, positive and negative predictive value as well as accuracy were assessed for detection of obstructive coronary artery disease, defined as revascularization therapy following DSE.
RESULTS: We included 206 patients (mean age 63.2 ± 12.4 years, 59.7% male). 51% of the cohort had a PTP of < 15% according to both scores. 9.2% of patients with PTP < 15% according to the original Diamond and Forrester score had a PTP > 15% according to 2019 ESC guidelines, predominantly due to the accountancy of dyspnea. In contrast, 13.6% of patient had a PTP ≥ 15% according to the original Diamond and Forrester score, while PTP was assessed below this threshold by updated guidelines. The differences in patient selection according to updated guidelines did not alter the diagnostic accuracy of DSE (68% for both).
CONCLUSIONS: Changes in assessment of PTP according to updated ESC guidelines from 2019 led to a relevant reclassification of patients with suspected coronary artery disease, ultimately changing the group of patients appropriate for DSE for evaluation of myocardial ischemia. Comparing the diagnostic performance in appropriate PTP groups, however, led to similar results.

Keywords: Stress echocardiography; Pretest probability; Chronic coronary syndrome; Diamond and Forrester

Journal of Cardiovascular Imaging JCVI

Balcer B, Totzeck M, Mahabadi AA; Formal analysis: Dykun I, Hendricks S, Balcer B, Mahabadi AA; Investigation: Hendricks S, Balcer B, Totzeck M, Al-Rashid F, Rassaf T; Methodology: Dykun I, Rassaf T, Mahabadi AA; Project administration: Dykun I, Rassaf T, Mahabadi AA; Supervision: Rassaf T, Mahabadi AA; Validation: Dykun I, Hendricks S, Balcer B, Totzeck M, Mahabadi AA; Writing - original draft: Dykun I, Hendricks S; Writing - review & editing: Balcer B, Totzeck M, Al-Rashid F, Rassaf T, Mahabadi AA.

INTRODUCTION

Accurate non-invasive detection of coronary artery disease (CAD) remains a challenge in daily clinical practice. More than forty years ago, Diamond and Forrester introduced a set of age, sex, and symptom-based pre-test probabilities (PTPs) for obstructive CAD estimation.[1] The updated guidelines on chronic coronary syndrome contained many updates. Most importantly, the role of non-invasive imaging tests, including dobutamine stress-echocardiography was strengthened. In addition, after several lines of evidence suggesting that these PTP may overestimate the presence of CAD, the guidelines of the European Society of Cardiology (ESC) on chronic coronary syndromes in their update from 2019 have undergone the major revision regarding the PTP and includes patients presenting with dyspnea as their main symptom.[2] Application of the new PTP may significantly reduce the need for non-invasive and invasive tests in patients with suspected stable CAD. Among the functional non-invasive tests for CAD diagnosis a dobutamine stress echocardiography (DSE) is used on routine basis in clinical practice for assessment of myocardial ischemia and recommended by the guidelines. This technique requires considerable experience but is widely accessible and is of comparable low cost. The reported diagnostic accuracy of DSE ranges with sensitivity of 72%–83% and specificity of 84%–95%.[3][4] Whether the shift in PTP according to the recent update in guidelines impacts the diagnostic accuracy has not been investigated so far.

Thus, the aim of this study was to determine the implications of alterations in PTP in the 2019 update of ESC guidelines for chronic coronary syndrome on diagnostic performance of pharmacological stress-echocardiography.

METHODS

Study subjects

We retrospectively included consecutive patients undergoing pharmacological stress-echocardiography for suspected obstructive CAD between April 2018 and November 2019 on a single tertiary care center in Germany. Patients with acute coronary syndrome or with other indications for DSE (e.g., evaluation of low-flow-low-gradient aortic valve stenosis) were not included into the analysis. Patients with moderate or severe valvular disease or heart failure with reduced ejection fraction were excluded from this analysis.

Demographic characteristics, cardiovascular risk factors (systolic and diastolic blood pressure [BP], smoking status, positive family history of premature coronary artery disease manifestation, and body mass index), medical history, and medical therapy were assessed from available patient records. The analysis was approved by the local ethics committee (20-9218-BO) without the need of informed consent from the included patients, given the retrospective nature of the study with anonymous data assessment.

Pharmacological stress echocardiogram

Echocardiography was performed in the lateral decubitus position using an Epiq 7C system with an X5-1 probe (Philips Medical Systems, Eindhoven, The Netherlands). Rate-control medication was withheld at least 48h before the examination. The target heart rate (HR) was prespecified as 85% of the maximal HR, as dependent on the patient's age. Dobutamine was infused intravenously at an initial dose of 10 μg/kg/min and increased every 3 minutes to a

https://doi.org/10.4250/jcvi.2020.0176

Journal of Cardiovascular Imaging JCVI

maximum dose of 40 mc/kg/min. Atropine was given as required up to a maximum dose of 1 mg in divided doses (0.25 mg) to achieve target HR.[5] Dobutamine was discontinued when the target HR was reached, extensive new wall motion abnormalities, major arrythmias, hypertension (BP ≥ 240/120 mmHg) or hypotension (drop of > 30 mmHg in BP) or severe angina occurred. Two-dimensional echocardiographic images were recorded at rest, low-dose stage, upon reaching peak HR and in recovery. Parasternal long axis, short axis and apical 4-, 2-, and 3-chamber views were acquired and analyzed by an experienced investigator (> 500 examinations). Definition of positive and negative DSE was made in accordance with the current guidelines.[6] In brief, a segment that is normokinetic at rest and normal or hyperkinetic during stress is accounted as a normal response. Hypokinesis, akinesis, or dyskinesis in at least two adjacent segments are accounted as positive test.

Coronary angiography

The decision to perform coronary angiography was obtained by the referring physician as in the real-world scenario with results of the DSE being available to the physician. During invasive coronary angiography procedures, revascularization therapy was performed as indicated by the responsible interventional cardiologist. Decision for interventional therapy was made by interventional cardiologist based on angiographic findings, functional testing including instantaneous wave-free ratio and fractional flow reserve and intravascular imaging. For sensitivity analysis of this project, we additionally assessed anatomically relevant CAD as secondary endpoint, which was defined as > 50% luminal stenosis for sensitivity analysis. For this, an experienced interventional cardiologists, who was blinded to the clinical characteristics and the DSE-results of the patient, reviewed all coronary angiography images, defining lesions > 50% luminal stenosis.

Statistical analysis

The baseline characteristics are presented as mean ± standard deviation for continuous variables and as frequency and percentages for categorical variables. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) as well as overall accuracy were calculated based on positive results of DSE as well as revascularization therapy. Sensitivity analysis was performed using the secondary endpoint, defined as any anatomically relevant CAD. All analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

RESULTS

Overall, 206 patients were included in the final analysis. The mean age was 63.2 ± 12.4 years with 123 male patients (59.7%), mean systolic BP 134.0 ± 17.7 mmHg and diastolic BP 74.8 ± 11.1 mmHg. 74.8% used antihypertensive medication and 58.7% cholesterol-lowering therapy. Detailed patient characteristics are depicted in **Table 1**. Typical and atypical angina were equally frequent present, while 35% of patients complained of dyspnea.

According to 2013 guidelines, mean PTP was 21.7% ± 30.3% (range: 0%–93%), whereas PTP according to 2019 guidelines was 12.7% ± 14.5% (range: 0%–52%). **Table 2** shows the distribution of the patient cohort according to the original Diamond and Forrester score as well as according to the updated ESC guidelines. Approximately 50% of the cohort had a PTP of below 15% according to both scores. 9.2% of patients with PTP ≤ 15% according to the original Diamond and Forrester score had a PTP > 15% according to 2019 ESC guidelines,

https://doi.org/10.4250/jcvi.2020.0176

Journal of Cardiovascular Imaging JCVI

Table 1. Patient characteristics

Variable	All patients (n = 206)
Age (years)	63.2 ± 12.4
Sex, male	123 (59.7)
Systolic BP (mmHg)	134.0 ± 17.7
Diastolic BP (mmHg)	74.8 ± 11.1
Diabetes mellitus	31 (15.2)
Family history of CAD	45 (21.8)
Current smoker	27 (13.1)
Cholesterol-lowering therapy	121 (58.7)
Antihypertensive therapy	154 (74.8)
Angina pectoris	
Typical	42 (20.4)
Atypical	42 (20.4)
CCS class	
CCS I	35 (17.0)
CCS II	14 (6.8)
CCS III	28 (13.6)
Dyspnea	73 (35.4)
NYHA I	133 (64.6)
NYHA II	51 (24.8)
NYHA III	22 (10.6)

Values are presented as mean ± standard deviation or number (%).
BMI: body mass index, BP: blood pressure, CAD: cardiac artery disease, CCS: Canadian Cardiovascular Society grading of angina pectoris, NYHA: New York Heart Association Functional Classification.

predominantly due to the accountancy of dyspnea as symptoms in the updated score. In contrast, 13.6% of patient had a PTP > 15% according to original Diamond and Forrester, while PTP was assessed below this threshold by updated guidelines.

From the included cohort, 39 patients underwent invasive coronary angiography after DSE. Obstructive CAD was detected in 17 of those patients. Sensitivity, specificity, NPV, and PPV as well as diagnostic accuracy of DSE was assessed for comparison of the overall cohort with the subsets of patients with certain PTP groups but not for evaluation of the overall diagnostic performance of DSE. For the overall cohort, sensitivity and specificity of DSE was 59% and 72% with a NPV of 95% and an accuracy of 71% (**Table 3**). For the subset of patient with a PTP of 15%–85% according to Diamond and Forrester, sensitivity and specificity of DSE was 70% and 67% with a NPV of 93% and overall accuracy of 68%. While including a relevantly different subset of patients, updated ESC guidelines led to identical predictive probabilities (sensitivity: 67%, specificity: 68%, NPV: 93%, overall accuracy: 68%; **Table 3**). In sensitivity analysis, we compared the diagnostic performance to anatomically defined obstructive CAD (> 50% luminal stenosis). Overall, there was a slight improvement of diagnostic performance using this endpoint (**Supplementary Table 1**). However, overall diagnostic performance was not relevantly altered by updated guidelines, using anatomically defined CAD as endpoint.

Table 2. Categorization using PTP values for the probability thresholds recommended by the 2013 vs. 2019 ESC guidelines[2)7)]

ESC-DF PTP categories 2019	ESC-DF PTP categories 2013				
	< 15%	15%–65%	66%–85%	> 85%	Total
≤ 15%	107 (51.9)	28 (13.6)	0	0	135 (65.5)
> 15%	19 (9.2)	16 (7.8)	30 (14.6)	6 (2.9)	71 (34.5)
Total	126 (61.1)	44 (21.4)	30 (14.6)	6 (2.9)	206 (100.0)

Values are presented as number (%).
DF: Diamond and Forrester, ESC: European Society of Cardiology, PTP: pre-test probability.

https://doi.org/10.4250/jcvi.2020.0176

Table 3. Sensitivity, specificity, PPV and NPV, as well as overall accuracy of DSE for the detection of obstructive CAD for the overall cohort, according to Diamond and Forrester (as suggested by ESC 2013 guidelines) as well as updated 2019 ESC guidelines

Variables	Overall cohort (n = 206)	PTP 15%–85% according to ESC 2013 guidelines (n = 74)	PTP > 15% according to ESC 2019 guidelines (n = 71)
Sensitivity	59%	70%	67%
Specificity	72%	67%	68%
NPV	95%	93%	93%
PPV	16%	25%	23%
Accuracy	71%	68%	68%

CAD: coronary artery disease, DSE: dobutamine stress echocardiography, ESC: European Society of Cardiology, NPV: negative predictive value, PPV: positive predictive value, PTP: pre-test probability.

DISCUSSION

The Diamond and Forrester score for assessment of PTP has been first described in 1979 and has been used since then for the estimation of the probability of obstructive coronary artery disease.[1] Likewise, the 2013 guidelines for stable coronary artery disease of the European Heart Association recommended the Diamond and Forrester score for PTP assessment. However, recent data suggest that the original Diamond and Forrester score overestimates the probability of obstructive coronary angiography, which led to a modification in the 2019 update of the ESC.[7] According to the updated risk score, the PTP was downgraded for all age- and sex groups, independent of type of chest pain. In addition, dyspnea as additional symptom was added. When comparing the original Diamond and Forrester score and the updated version as recommended in the 2019 guidelines, we found that a relevant proportion of patients were downgraded according to the updated guidelines. However, also several patients with PTP < 15% according to Diamond and Forrester reached an intermediate PTP according to the updated score due to dyspnea as leading symptom. Interestingly, when comparing the sensitivity and specificity when applying appropriate subgroups qualifying for non-invasive imaging-based test according to 2013 and 2019 guidelines led to similar results. Therefore, our results suggest that DSE can be performed with identical accuracy with the updated assessment of PTP according to 2019 ESC guidelines.

In our study, indication for DSE were made by treating physicians. With also availability of other imaging-based modalities for assessment of suspected myocardial ischemia including stress magnetic resonance imaging, single photon emission computed tomography, and coronary computed tomography at our center, individualized decisions were made according to the patient's profile and in agreement with the patient. Characteristics promoting DSE were good imaging quality in echocardiography, patient's request to avoid; e.g., examinations with radiation exposure, and availability. At our center, DSE can routinely be performed with high availability without prearrangement in an outpatient setting. While we found that changes of PTP in updated ESC guidelines relevantly changed patient populations, qualifying for imaging-based assessment of suspected CAD, we found comparable diagnostic performance of appropriate groups according to 2013 and 2019 recommendations. Further research is needed to examine, whether this also applies for other imaging tests.

There are several limitations of this study. First, our results are based on a retrospective cohort. Secondly, DSE indication was made based on referring physician's decision with a relevant proportion of our cohort being not within the PTP range suggested for DSE according to guidelines. But the assessment of patients with PTP above or below suggested range made comparison of different PTP-scores as part of this analysis possible. Lastly, only a minority of patients undergoing DSE were ultimately referred for invasive coronary angiography, as this decision was also made by treating physicians. This may have biased our sensitivity and

specificity as well as PPV towards the null. Lastly, only a minority of patients undergoing DSE were ultimately referred for invasive coronary angiography, as this decision was also made by treating physicians. This may have biased our sensitivity and specificity as well as PPV towards the null and also leaves uncertainties regarding false and true negatives. Therefore, the reported estimates on accuracy allow for comparison of different assessments of PTP but may not reflect the overall performance of DSE. A larger prospective study on patients undergoing both DSE and invasive coronary angiography in all patients is needed to confirm our results.

In conclusion, changes in assessment of PTP according to updated ESC guidelines from 2019 led to a relevant up- and down-classification of patients undergoing DSE with suspected obstructive coronary artery disease. Applying appropriate PTP groups based on 2013 vs. 2019 guidelines ultimately changed the group of patients qualifying for DSE for evaluation of potential myocardial ischemia. Comparing the diagnostic performance in appropriate PTP groups, however, led to similar results.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Sensitivity, specificity, PPV and NPV, as well as overall accuracy of DSE for the detection of anatomically significant coronary artery stenosis (> 50% luminal stenosis) for the overall cohort, according to Diamond and Forrester (as suggested by ESC 2013 guidelines) as well as updated 2019 ESC guidelines

Click here to view

REFERENCES

1. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;300:1350-8.
PUBMED | CROSSREF
2. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41:407-77.
PUBMED | CROSSREF
3. Picano E, Molinaro S, Pasanisi E. The diagnostic accuracy of pharmacological stress echocardiography for the assessment of coronary artery disease: a meta-analysis. *Cardiovasc Ultrasound* 2008;6:30.
PUBMED | CROSSREF
4. Heijenbrok-Kal MH, Fleischmann KE, Hunink MG. Stress echocardiography, stress single-photon-emission computed tomography and electron beam computed tomography for the assessment of coronary artery disease: a meta-analysis of diagnostic performance. *Am Heart J* 2007;154:415-23.
PUBMED | CROSSREF
5. Pellikka PA, Arruda-Olson A, Chaudhry FA, et al. Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease: from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2020;33:1-41.e8.
PUBMED | CROSSREF
6. Sicari R, Nihoyannopoulos P, Evangelista A, et al. Stress echocardiography expert consensus statement—Executive summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur Heart J* 2009;30:278-89.
PUBMED | CROSSREF
7. Task Force MembersMontalescot G, Sechtem U, et al. 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;34:2949-3003.
PUBMED | CROSSREF