

Review Article

Old and New NICE Guidelines for the Evaluation of New Onset Stable Chest Pain: A Real World Perspective

Nazario Carrabba ¹, **Angela Migliorini**¹, **Silvia Pradella**², **Manlio Acquafresca**², **Marco Guglielmo**³, **Andrea Baggiano**³, **Giuseppe Moscogiuri**³, and **Renato Valenti**¹

¹Cardiovascular and Thoracic Department of Careggi Hospital, Florence, Italy

²Radiologic Department of Careggi Hospital, Florence, Italy

³Centro Cardiologico Monzino, IRCCS, Milan, Italy

Correspondence should be addressed to Nazario Carrabba; carrabban@aou-careggi.toscana.it

Received 6 June 2018; Revised 1 August 2018; Accepted 10 October 2018; Published 8 November 2018

Academic Editor: Cristiana Corsi

Copyright © 2018 Nazario Carrabba et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Stable chest pain is a common clinical presentation that often requires further investigation using noninvasive or invasive testing, resulting in a resource-consuming problem worldwide. At onset of 2016, the National Institute for Health and Care Excellence (NICE) published an update on its guideline on chest pain. Three key changes to the 2010 version were provided by the new NICE guideline. First, the new guideline recommends that the previously proposed pretest probability risk score should no longer be used. Second, they also recommend that a calcium score of zero should no longer be used to rule out coronary artery disease (CAD) in patients with low pretest probability. Third, the new guideline recommends that all patients with new onset chest pain should be investigated with a coronary computed tomographic angiography (CTA) as a first-line investigation. However, in real world the impact of implementation of CTA for the evaluation of new onset chest pain remains to be evaluated, especially regarding its cost effectiveness. The aim of the present report was to discuss the results of the studies supporting new NICE guideline and its comparison with European and US guidelines.

1. Introduction

In the last two years a great debate occurs about the value of anatomical information by coronary computed tomographic angiography (CTA) in comparison to functional imaging tests on the evaluation of patients with new onset chest pain and unknown coronary artery disease (CAD) [1–5]. Stable chest pain is a common clinical presentation that often requires further investigation using noninvasive or invasive testing [6–8]. Recently, PROMISE [9] and SCOT-HEART [10] studies suggest that an evaluation strategy based on CTA improves diagnostic certainty, as well as efficiency of triage to invasive catheterization; it also may reduce radiation exposure when compared with functional stress testing, with similar rates of cardiac events. Moreover, the EVINCI [11] trial supports the use of CTA for stable chest pain, highlighting a better performance in comparison to other imaging strategies. After the publication of these studies, the

National Institute for Health and Care Excellence (NICE) [12] recommended CTA as the first-line investigation for all patients presenting with chest pain due to suspected CAD.

2. Functional and Anatomical Tests for Suspicion of CAD

In current era of modern cardiology, the diagnostic workup test for patients with suspicion of CAD remains matter of debate [6–8]. Whatever the use of functional or anatomical tests, their additional values should be implied on guide the decision-making process to improve outcome, reducing cardiac death and nonfatal myocardial infarction [13–21]. For this purpose, it is conceivable that the first-line diagnostic test should have a high level of diagnostic accuracy as well as the ability to better stratify individuals risk and, finally, the ability to establish proper treatment regimes. In

addition, taking into account a reduced economical resource of the health system around the world, in the practice the cost-effective clinical aspects may play a pivotal role in planning a diagnostic workup test for CAD. Several studies have compared different stress imaging modalities in order to detect obstructive CAD. However, there are no strict recommendations based on the evidence of one diagnostic test' superiority over another [9–21]. Specifically, diagnostic functional tests are encumbered by a high rate of false-positive results. The low prevalence of obstructive CAD following elective ICA has been clearly demonstrated in the registry data, raising more criticisms regarding the ability of functional test in detecting markers of significant myocardial ischemia [22, 23]. All this has generated a great debate as to which test is best placed to serve as a “gatekeeper” to invasive coronary angiography (ICA). The rationale for the use of noninvasive testing prior to ICA is established in the recent publication of Clinical Evaluation of Magnetic Resonance Imaging in Coronary Artery Disease 2 (CE-MARC-2), confirming that risk models may overestimate the presence of obstructive CAD [21]. Ideally, considering several noninvasive tests available, ICA is only rarely mandatory to confirm the diagnosis of obstructive CAD and should be reserved for those likely to have coronary intervention. In the last decade, the additional values of coronary CTA to improve diagnostic accuracy and risk stratification of coronary artery disease have been evaluated in depth from several studies. Recently, two ‘test-and-treat’ multicenter randomized control trials furnished evidences into whether coronary CTA could be incorporated into chest pain care pathways [9, 10]. In similar way, both trials were focused on the evaluation if the incorporation of noninvasive test into a care pathway may confer benefit to patients with suspicion of CAD. Namely, the Prospective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) trial enrolls a large cohort from USA and Canadian centers in order to settle whether an initial assessment of suspected stable CAD using CTA improves outcomes, reducing major adverse cardiovascular events [9]. This study demonstrated that coronary CTA was associated with more ICA within the first 90 days; however the use of coronary CTA reduced invasive angiograms without obstructive CAD. Moreover, at 2-year follow-up, the use of CTA was not associated with improvement in death, myocardial infarction, or major procedural complication in comparison to functional strategy. Differently, the Scottish Computed Tomography of the HEART (SCOT-HEART) trial recruited UK patients referred for recent onset chest pain to cardiology clinics with suspected angina [10], all of whom presented with chest pain and one-third reported typical angina symptoms. In comparison with a PROMISE trial, a higher rate of obstructive CAD was reported in CTA arm of SCOT-HEART. Moreover, there was a nonsignificant reduction in cardiac death and myocardial infarction (hazard ratio 0.62, 95% confidence interval 0.38–1.01, $p=0.0527$). In the SCOT-HEART study, differently from the PROMISE study, coronary CTA did not replace functional testing but was added to a standard care protocol with exercise ECG for most. In these two studies the low prevalence of CAD and the low occurrence of MACE in patients with stable

chest pain were reported, raising questions concerning the use for new imaging test. Generally, it is well known that, in patients with low CAD prevalence, the probability of CAD may be overestimated by standard prediction rules [9, 10]. Indeed, the prevalence of CAD in PROMISE was low 8.8% in comparison to the 53% predicted probability by the Diamond and Forrester model. In the SCOT-HEART study, a higher rate of obstructive CAD was reported in the CTA arm compared with the PROMISE trial. Moreover, in the SCOT-HEART study, after 50 days clinicians reviewed the test result and started preventive medical therapy. From this time, post hoc landmark analysis was associated with an impressive reduction rate of cardiac death and myocardial infarction (hazard ratio 0.50, 95% confidence interval 0.28–0.88, $p=0.020$) [23]. Thus, not surprisingly, the findings of randomized SCOT-HEART study confirmed the results previously reported from the observational CONFIRM registry, where for the first time the beneficial effect of statin therapy in individuals with subclinical atherosclerosis was demonstrated [24]. Importantly, the longer-term impact of coronary CTA use in clinical practice remains unexplored. Until recently, the long-term clinical outcomes of the SCOT-HEART trial was published [25], showing that the use of CTA in comparison to than standard care alone is associated with a lower rate of death or nonfatal myocardial infarction (2.3% versus 3.9%; HR 0.59; 95% CI 0.41 to 0.84; $P = 0.004$). These results are mainly related to the change of treatment based on CTA findings. In addition, the use of CTA is associated with an increase rate of ICA in the short follow-up, but 5 years the use of ICA and coronary revascularization were not different. Moreover, according to design of study, the SCOT-HEART trial encouraged the secondary prevention strategy in patients with nonobstructive CAD. This strategy may be very important, considering that near the half of subsequent myocardial infarctions occurred among patients with nonobstructive CAD. The clinical, social, and financial implications of this consideration could be very relevant in the next future, considering the exponential increase of the subclinical and nonobstructive coronary atherosclerosis reported from CTA in patients with suspicion of CAD.

3. NICE Guidelines Update 2016

Specifically, the NICE guideline update (2016) makes three key changes to the 2010 version [12]. The first is the recommendation for a clinical assessment of the likelihood of CAD, based on the typicality of the chest pain into typical, atypical, or noncardiac, instead of the previous pretest probability (PTP) risk score (RS). The second change in the guideline is that a zero calcium score is no longer used to rule out CAD in patients with low PTP. Thirdly, and most radically, NICE now recommends that all patients with new onset chest pain with atypical or typical anginal features, as well as those with noncardiac chest pain and an abnormal resting ECG, should first be investigated with CTA using a 64-slice (or above) CT scanner. Functional imaging tests are now reserved for the assessment of patients with chest pain symptoms who are known to have CAD and for patients where the CTA has been nondiagnostic or has shown CAD of uncertain significance.

4. Comparison with European and American Recommendations

The 2013 European Society of Cardiology (ESC) guideline on stable chest pain recommends the use of a PTP RS that is calculated using age, gender, and typicality of chest pain, but not cardiovascular risk factors [26]. This RS is based on an updated Diamond-Forrester method, which adjusts the likelihood of CAD for a more contemporary population [26]. The ESC recommends that patients with an intermediate RS (15–85%) have a functional imaging test and, if there is limited availability, exercise ECG is recommended as an alternative in patients with RS 15–65% and CTA for patients with RS 15–50%. The 2012 guidelines from the American cardiology societies on stable chest pain recommend clinical evaluation of the PTP of CAD [27]. Patients able to exercise with interpretable resting ECGs and a low to intermediate likelihood of CAD are recommended to have an exercise ECG. Patients with uninterpretable ECG and patients with intermediate to high likelihood of CAD are recommended to have functional imaging tests. Patients with low to intermediate PTP, who are unable to exercise, may also undergo CTA as an alternative to exercise stress testing.

5. The 2016 Update to NICE CG95 Guideline

The PTP model was based on USA cohorts of patients undergoing invasive coronary angiography (ICA) in the 1970s who had a much higher prevalence of CAD than current rapid access chest pain clinic populations. Thus, in the latest guidance, NICE has parted from its PTP model; it may overestimate the risk in current rapid access chest pain clinic populations [28, 29]. Since the ESC RS was based on a contemporary population and has been externally validated and shown to be a good predictor of risk [29, 30], there was an expectation that NICE may adopt it. Not surprisingly, the most striking change in the new NICE guideline is the expansion of the use of CTA to all patients with new onset of chest pain. NICE no longer recommends coronary artery calcium scoring followed by CTA if the calcium score is above zero because of case reports of significant coronary stenoses in patients with a zero calcium score. Another reason is that the radiation dose from CTA on high-specification CT scanners is now as low as the radiation dose for the calcium score itself (less than 1 mSv). More controversially, NICE expanded the recommendation for CTA as first line to patients with intermediate and high likelihood of CAD based on their cost-effectiveness analysis suggesting that this would be a lower cost strategy. While recent clinical trials, such as PROMISE, demonstrated that patients investigated with CTA and functional tests had similar clinical outcomes [9], one has to remember that this trial was in a low-intermediate disease prevalence population with only approximately 11% having CAD. Although the SCOT-HEART trial had a higher prevalence of CAD and demonstrated that the use of CTA in patients with chest pain improves the diagnosis when added to standard of care, the standard of care was the exercise ECG and not functional imaging tests [10]. In fact, there are no published data demonstrating the diagnostic accuracy or cost

effectiveness of CTA in patients with chest pain and higher likelihood of CAD, making the NICE recommendations for CTA in this population somewhat surprising. Interestingly, however, there are UK data demonstrating higher utilization rates of the costly ICA following a CTA strategy [31].

6. Disinvestment in Stress Imaging Services in Favor of CT Imaging: A New Question

The advance in management and the adoption of modern effective treatment have reduced the cardiovascular mortality for patients with acute coronary syndrome worldwide, but not for patients with stable CAD. Currently, healthcare system focused their efforts on delivering management of stable CAD that is both clinical and cost effective. Notably, the populations with stable CAD increase in age and consequently their access to the healthcare system may increase exponentially worldwide. This picture of stable CAD is true worldwide; thus the treatment for stable CAD should be not only efficacious but also sustainable for healthcare system. Moreover, differently to the previous two decade, now the rapid clinical assessment of patients with suspected angina is necessary for the community of cardiology to select out high-risk individuals [32]. In this way, the attending physician may avoid the risk of potential complications following the onset of chest pain symptoms, as well as may avoid unnecessary diagnostic tests. In current clinical practice, the ICA remains the more precise test to confirm or to exclude the presence of obstructive CAD against which all other noninvasive tests have been validated. Since the hospitalization is required to perform ICA, this examination remains the most expensive diagnostic investigation and, importantly, it exposes individuals to the highest risk of procedural complications, although the radial access may reduce the burden of complications and now should be the preferred approach [33]. After a number of publications, now coronary CTA is recognized as accurate diagnostic test to evaluate the presence of coronary atherosclerosis. The publication of the updated NICE guideline CG95 confirms and reinforces this message, but in the same time it rises some concerns about the impact of the use of coronary CTA as first-line investigation on the resource of healthcare system. In England the adoption of this strategy for CAD diagnosis has been estimated as favorable, since it will be associated with an annual savings of £16 million, by prompt exclusion of significant CAD and more effectively use of resources [34]. However, caution needs in interpretation these findings, since the availability of CT scan in other countries may be different in comparison to the UK, and the applicability of this model in other healthcare system remains to be explored. On this regard, the British Society of Cardiovascular Imaging/British Society of Cardiovascular CT (BSCI/BSCCT) estimated an impressive increase of near 700% in coronary CTA across the UK [35]. The situation is quite similar in most European countries as well as in USA, although the UK has a relatively low number of CTA scanners per head of population [35]. Thus, the potential adoption for most western countries of updated NICE recommendations for stable CAD may require a substantial investment in CTA technology and training.

Out of the setting of randomized and well conducted trial, in clinical practice the use of CTA will generate a number of equivocal CTA test, due to the nonoptimal expertise in exam execution and image interpretation. Consequently, in order to solve the doubt raise from the equivocal tests the attending physician may require in the diagnostic workup more additional functional imaging test. Thus, it is likely that the potential disinvestment in stress imaging services in favor of CTA imaging could not occur in the next years. Notably, the rapid development of new CT technologies may help us to reduce the burden of false-positive CTA for patients with stable CAD. In this setting, the routine use of fractional flow reserve CTA and CT perfusion (CTP) appears to be the most promising and valuable tool, even if the accuracy of both techniques remains to be demonstrated on revascularized patients with recurrent chest pain [36–38]. In addition the availability of both modern techniques is very restricted in some dedicated centers. Moreover, in case of wide dissemination of coronary CTA in western countries, the preservation of quality imaging is very important, since it is strongly related to the diagnostic accuracy of coronary CTA. In this regard, current recommendation should be followed in order to optimize image quality in cardiac CTA [39, 40], and, moreover, standardized informative reports of CTA studies should be provided by the physician as well as the radiation dose exposure should be reported on this report. Recently, CAD-RADS reporting and data system are also available for the structured reporting of cardiac CTA, which may facilitate and simplify the communication of results to clinicians and patients [41]. Especially, this program may optimize downstream investigations in order to avoid an increase in the use of ICA when cardiac CTA identifies nonobstructive CAD. Not surprisingly, in setting of chest pain patients with suspicion of CAD the nonobstructive CAD was the most common pattern of coronary atherosclerosis disease and its detection may increase with the increase availability and use of coronary CTA. Currently, the management of nonobstructive CAD represents in the community of cardiology one of the major challenge. The concept of stenosis severity alone for the classification of CAD appears old and it does not feet with the continuum of risk associated with nonobstructive atherosclerotic plaque. The identification of features of vulnerability in coronary plaques rather than the luminal narrowing in isolation may improve the risk stratification of future cardiac events [42–56]. This concept is very important, especially in women with suspicion of CAD showing frequently a nonobstructive CAD or minimal coronary lesion from CTA, associated with features of microvascular dysfunction [57].

7. The Radiation Dose

The practical implementation of the new guidelines will meet many challenges. The recommendations are in part based on the assumption that the radiation dose of CTA is in the order of 1–2 mSv, which is achievable in most patients with the latest generation CT scanners [58–62]. However, most UK hospitals do not have these and instead use 64-slice CT scanners that can perform a CTA with a

radiation dose of 3–5 mSv, provided prospective gating is used, which requires a heart rate of 60 bpm; otherwise, CTA is performed with retrospective gating, which allows for a heart rate up to 70 bpm, but with radiation doses of 10–15 mSv, a similar radiation dose to MPS. In PROSPECT, a trial comparing CTA and MPS in patients with intermediate risk chest pain, the total radiation dose was high in both arms (24 versus 29 mSv) and no difference was found in the rates of ICA between the two strategies. To implement the NICE guidelines without increasing the radiation burden on the population, the National Health Service (NHS) will need to make a significant investment in high-specification CT scanners and/or carefully consider the choice of the follow on functional imaging test, based on the patient's age, sex, and their cumulative radiation dose, from other radiation-based investigations. This UK picture is similar to that observed in the majority of the European country, highlighting that the investment in the latest generation CT scanners should be planned as an appropriate and rationale strategy rather than occasional investment. A further major challenge, if the NICE recommendations are to be adopted on the next European guidelines, will be to identify and train the increased requirement for radiographers and consultants (both cardiologist and radiologist) to perform and report the additional CTA.

8. Conclusions

CTA is an excellent rule-out test for CAD when used in the appropriate disease prevalence population. Despite the good performance of CTA in recent PROMISE, SCOT-HEART, and EVINCI trials, there is little clinical or health economic data to support the use of CTA over other noninvasive imaging tests in patients at intermediate-high risk of CAD in real world. Furthermore, the availability of latest generation scanners in European country is limited. Thus the potential for high cumulative radiation dose exposure from multiple serial CTA investigations could be a big problem. Finally, in real world the implementation of CTA for the evaluation of new onset chest pain fundamentally depends on the new health strategy based on the reconfiguration of current finances and staffing levels.

Conflicts of Interest

The author declares that there are no conflicts of interest regarding the publication of this paper.

References

- [1] M. J. Wolk, S. R. Bailey, J. U. Doherty et al., “Multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease. American College of Cardiology Foundation Appropriate Use Criteria Task Force,” *Journal of the American College of Cardiology*, vol. 63, no. 2, pp. 380–406, 2014.
- [2] E. Maffei, S. Seitun, C. Martini et al., “CT coronary angiography and exercise ECG in a population with chest pain and low-to-intermediate pre-test likelihood of coronary artery disease,” *Heart*, vol. 96, no. 24, pp. 1973–1979, 2010.

- [3] G. Pontone, A. Guaricci, D. Neglia, and D. Andreini, "State of the art: non-invasive imaging in ischaemic heart disease," *EuroIntervention*, vol. 13, no. 6, pp. 654–665, 2017.
- [4] J. Abdulla, S. Z. Abildstrom, O. Gotzsche, E. Christensen, L. Kober, and C. Torp-Pedersen, "64-Multislice detector computed tomography coronary angiography as potential alternative to conventional coronary angiography: a systematic review and meta-analysis," *European Heart Journal*, vol. 28, no. 24, pp. 3042–3050, 2007.
- [5] E. Maffei, C. Martini, and C. Tedeschi, "Diagnostic accuracy of 64-slice computed tomography coronary angiography in a large population of patients without revascularisation: registry data in NSTEMI acute coronary syndrome and influence of gender and risk factors," *La radiologia medica*, vol. 116, no. 7, pp. 1014–1026, 2011.
- [6] J. A. Ladapo, S. Blecker, and P. S. Douglas, "Physician decision making and trends in the use of cardiac stress testing in the United States: An analysis of repeated cross-sectional data," *Annals of Internal Medicine*, vol. 161, no. 7, pp. 482–490, 2014.
- [7] G. Montalescot, U. Sechtem, and S. Achenbach, "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," *European Heart Journal*, vol. 34, no. 38, pp. 2949–3003, 2013.
- [8] G. Pundziute, J. D. Schuijf, J. W. Jukema et al., "Head-to-head comparison of coronary plaque evaluation between multislice computed tomography and intravascular ultrasound radiofrequency data analysis," *JACC: Cardiovascular Interventions*, vol. 1, no. 2, pp. 176–182, 2008.
- [9] P. S. Douglas, U. Hoffmann, M. R. Patel et al., "Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease," *The New England Journal of Medicine*, vol. 372, no. 14, pp. 1291–1300, 2015.
- [10] D. E. Newby, M. Williams, A. Hunter et al., "CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial," *The Lancet*, vol. 385, no. 9985, pp. 2383–2391, 2015.
- [11] D. Neglia, D. Rovai, C. Caselli et al., "Detection of Significant Coronary Artery Disease by Noninvasive Anatomical and Functional Imaging," *Circulation: Cardiovascular Imaging*, vol. 8, no. 3, 2015.
- [12] National Institute for Health and Care Excellence, "Chest pain. NICE pathway. Manchester: NICE, 2017;" <https://pathways.nice.org.uk/pathways/chest-pain>.
- [13] J. M. van Werkhoven, J. D. Schuijf, O. Gaemperli et al., "Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients with suspected coronary artery disease," *Journal of the American College of Cardiology*, vol. 53, no. 7, pp. 623–632, 2009.
- [14] G. Pontone, A. I. Guaricci, and D. Andreini, "Prognostic benefit of cardiac magnetic resonance over transthoracic echocardiography for the assessment of ischemic and nonischemic dilated cardiomyopathy patients referred for the evaluation of primary prevention implantable cardioverter-defibrillator therapy: clinical perspective," *Circulation: Cardiovascular Imaging*, vol. 9, no. 10, p. e004956, 2016.
- [15] C. Cheruvu, B. Precious, and C. Naoum, "Long term prognostic utility of coronary CT angiography in patients with no modifiable coronary artery disease risk factors: results from the 5 year follow-up of the confirm international multicenter registry," *Journal of Cardiovascular Computed Tomography*, vol. 10, no. 1, pp. 22–27, 2016.
- [16] G. Pontone, D. Andreini, E. Bertella et al., "Prognostic value of dipyridamole stress cardiac magnetic resonance in patients with known or suspected coronary artery disease: a mid-term follow-up study," *European Radiology*, vol. 26, no. 7, pp. 2155–2165, 2016.
- [17] E. Maffei, S. Seitun, C. Martini et al., "Prognostic value of computed tomography coronary angiography in patients with chest pain of suspected cardiac origin," *La radiologia medica*, vol. 116, no. 5, pp. 690–705, 2011.
- [18] N. Gaibazzi, T. Porter, V. Lorenzoni et al., "Effect of coronary revascularization on the prognostic value of stress myocardial contrast wall motion and perfusion imaging," *Journal of the American Heart Association*, vol. 6, no. 6, p. e006202, 2017.
- [19] G. Pontone, A. I. Guaricci, and D. Andreini, "Prognostic stratification of patients with ST-segment-elevation myocardial infarction (PROSPECT): a cardiac magnetic resonance study," *Circulation: Cardiovascular Imaging*, vol. 10, no. 11, p. e006428, 2017.
- [20] M. R. Patel, E. D. Peterson, D. Dai et al., "Low diagnostic yield of elective coronary angiography," *The New England Journal of Medicine*, vol. 362, no. 10, pp. 886–895, 2010.
- [21] M. R. Patel, D. Dai, A. F. Hernandez et al., "Prevalence and predictors of nonobstructive coronary artery disease identified with coronary angiography in contemporary clinical practice," *American Heart Journal*, vol. 167, no. 6, pp. 846–852.e2, 2014.
- [22] J. P. Greenwood, D. P. Ripley, C. Berry et al., "Effect of Care Guided by Cardiovascular Magnetic Resonance, Myocardial Perfusion Scintigraphy, or NICE Guidelines on Subsequent Unnecessary Angiography Rates," *Journal of the American Medical Association*, vol. 316, no. 10, pp. 1051–1060, 2016.
- [23] M. C. Williams, A. Hunter, A. S. Shah et al., "Use of Coronary Computed Tomographic Angiography to Guide Management of Patients With Coronary Disease," *Journal of the American College of Cardiology*, vol. 67, no. 15, pp. 1759–1768, 2016.
- [24] B. J. Chow, G. Small, Y. Yam et al., "Prognostic and therapeutic implications of statin and aspirin therapy in individuals with non-obstructive coronary artery disease: results from the CONFIRM (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry) registry," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 35, no. 4, pp. 981–989, 2015.
- [25] The SCOT-HEART Investigators, "Coronary CT Angiography and 5-Year Risk of Myocardial Infarction," *The New England Journal of Medicine*, 2018.
- [26] T. S. Genders, E. W. Steyerberg, H. Alkadhi et al., "A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension," *European Heart Journal*, vol. 32, no. 11, pp. 1316–1330, 2011.
- [27] S. D. Fihn, J. M. Gardin, J. Abrams et al., "Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons," *Circulation*, vol. 126, no. 25, pp. e354–e471, 2012.
- [28] V. Y. Cheng, D. S. Berman, A. Rozanski et al., "Performance of the traditional age, sex, and angina typicality-based approach

- for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography: Results from the multinational coronary CT angiography evaluation for clinical outcomes: An international multicenter registry (CONFIRM)," *Circulation*, vol. 124, no. 22, pp. 2423–2432, 2011.
- [29] O. M. Demir, P. Dobson, N. D. Papamichael, J. Byrne, S. Plein, and K. Alfakih, "Comparison of ESC and NICE guidelines for patients with suspected coronary artery disease: evaluation of the pre-test probability risk scores in clinical practice," *Clinical Medicine*, vol. 15, no. 3, pp. 234–238, 2015.
- [30] M. S. Bittencourt, E. Hulten, T. S. Polonsky et al., "European society of cardiology-recommended coronary artery disease consortium pretest probability scores more accurately predict obstructive coronary disease and cardiovascular events than the diamond and forrester score," *Circulation*, vol. 134, no. 3, pp. 201–211, 2016.
- [31] K. Alfakih, J. P. Greenwood, and S. Plein, "The 2016 update to NICE CG95 guideline for the investigation of new onset stable chest pain: More innovation, but at a cost?" *Clinical Medicine*, vol. 17, no. 3, pp. 209–211, 2017.
- [32] D. E. Newby, K. A. Fox, L. L. Flint, and N. A. Boon, "A 'same day' direct-access chest pain clinic: improved management and reduced hospitalization," *QJM: An International Journal of Medicine*, vol. 91, no. 5, pp. 333–337, 1998.
- [33] M. Tavakol, S. Ashraf, and S. J. Brenner, "Risks and Complications of Coronary Angiography: A Comprehensive Review," *Global Journal of Health Science*, vol. 4, no. 1, pp. 65–93, 2011.
- [34] E. Nicol, S. Padley, G. Roditi, On behalf of the British Society of Cardiovascular Imaging/ British Society of Cardiovascular Computed Tomography et al., *The challenge of national CT coronary angiography (CTCA) provision in response to NICE CG95 update*, 2016.
- [35] <https://www.oecd.org/els/health-statistics-2014-frequently-requested-data.htm>.
- [36] H. Kitabata, J. Leipsic, M. R. Patel et al., "Incidence and predictors of lesion-specific ischemia by FFR CT: Learnings from the international ADVANCE registry," *Journal of Cardiovascular Computed Tomography*, vol. 12, no. 2, pp. 95–100, 2018.
- [37] G. Pontone, D. Andreini, and A. I. Guaricci, "Incremental diagnostic value of stress computed tomography myocardial perfusion with whole-heart coverage CT scanner in intermediate-to high-risk symptomatic patients suspected of coronary artery disease," *JACC: Cardiovascular Imaging*, 2018.
- [38] N. Carrabba, J. D. Schuijff, F. R. de Graaf et al., "Diagnostic accuracy of 64-slice computed tomography coronary angiography for the detection of in-stent restenosis: A meta-analysis," *Journal of Nuclear Cardiology*, vol. 17, no. 3, pp. 470–478, 2010.
- [39] S. Harden, R. Bull, R. Bury et al., "The safe practice of CT coronary angiography in adult patients in UK imaging departments," *Clinical Radiology*, vol. 71, no. 8, pp. 722–728, 2016.
- [40] S. Abbara, P. Blanke, C. D. Maroules et al., "SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: A report of the society of Cardiovascular Computed Tomography Guidelines Committee: Endorsed by the North American Society for Cardiovascular Imaging (NASCI)," *Journal of Cardiovascular Computed Tomography*, vol. 10, no. 6, pp. 435–449, 2016.
- [41] R. C. Cury, S. Abbara, S. Achenbach et al., "CAD-RADSTM Coronary Artery Disease – Reporting and Data System. An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the North American Society for Cardiovascular Imaging (NASCI). Endorsed by the American College of Cardiology," *Journal of Cardiovascular Computed Tomography*, vol. 10, no. 4, pp. 269–281, 2016.
- [42] A. Arbab-Zadeh and V. Fuster, "The Risk Continuum of Atherosclerosis and its Implications for Defining CHD by Coronary Angiography," *Journal of the American College of Cardiology*, vol. 68, no. 22, pp. 2467–2478, 2016.
- [43] A. Ahmadi, J. Leipsic, R. Blankstein et al., "Do plaques rapidly progress prior to myocardial infarction?" *Circulation Research*, vol. 117, no. 1, pp. 99–104, 2015.
- [44] A. P. Burke, A. Farb, G. T. Malcom, Y. Liang, J. Smialek, and R. Virmani, "Coronary risk factors and plaque morphology in men with coronary disease who died suddenly," *The New England Journal of Medicine*, vol. 336, no. 18, pp. 1276–1282, 1997.
- [45] A. I. Guaricci, G. Pontone, N. D. Brunetti et al., "The presence of remodeled and mixed atherosclerotic plaques at coronary ct angiography predicts major cardiac adverse events — The café-pie study," *International Journal of Cardiology*, vol. 215, pp. 325–331, 2016.
- [46] E. Romagnoli, F. Burzotta, F. Giannico, and F. Crea, "Culprit lesion seen 1 hour before occlusion: Limits of coronary angiography in detecting vulnerable plaques," *Circulation*, vol. 113, no. 5, pp. e61–e62, 2006.
- [47] C. Thomsen and J. Abdulla, "Characteristics of high-risk coronary plaques identified by computed tomographic angiography and associated prognosis: A systematic review and meta-analysis," *European Heart Journal—Cardiovascular Imaging*, vol. 17, no. 2, pp. 120–129, 2016.
- [48] A. I. Guaricci, T. Arcadi, N. D. Brunetti et al., "Carotid intima media thickness and coronary atherosclerosis linkage in symptomatic intermediate risk patients evaluated by coronary computed tomography angiography," *International Journal of Cardiology*, vol. 176, no. 3, pp. 988–993, 2014.
- [49] A. C. Kwan, K. N. Aronis, V. Sandfort, R. S. Blumenthal, and D. A. Bluemke, "Bridging the gap for lipid lowering therapy: plaque regression, coronary computed tomographic angiography, and imaging-guided personalized medicine," *Expert Review of Cardiovascular Therapy*, vol. 15, no. 7, pp. 547–558, 2017.
- [50] L. La Grutta, M. Marasà, and P. Toia, "Integrated non-invasive approach to atherosclerosis with cardiac CT and carotid ultrasound in patients with suspected coronary artery disease," *La radiologia medica*, vol. 122, no. 1, pp. 16–21, 2017.
- [51] S. Novo, P. Carità, E. Corrado et al., "Preclinical carotid atherosclerosis enhances the global cardiovascular risk and increases the rate of cerebro- and cardiovascular events in a five-year follow-up," *Atherosclerosis*, vol. 211, no. 1, pp. 287–290, 2010.
- [52] A. I. Guaricci, G. Pontone, L. Fusini et al., "Additional value of inflammatory biomarkers and carotid artery disease in prediction of significant coronary artery disease as assessed by coronary computed tomography angiography," *European Heart Journal - Cardiovascular Imaging*, vol. 18, no. 9, pp. 1049–1056, 2017.
- [53] S. Motoyama, H. Ito, M. Sarai et al., "Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up," *Journal of the American College of Cardiology*, vol. 66, no. 4, pp. 337–346, 2015.

- [54] H.-B. Park, R. Heo, B. Ó Hartaigh et al., "Atherosclerotic plaque characteristics by CT angiography identify coronary lesions that cause ischemia: A direct comparison to fractional flow reserve," *JACC: Cardiovascular Imaging*, vol. 8, no. 1, pp. 1–10, 2015.
- [55] R. Nakazato, H. Park, and H. Gransar, "Additive diagnostic value of atherosclerotic plaque characteristics to non-invasive FFR for identification of lesions causing ischaemia: results from a prospective international multicentre trial," *EuroIntervention*, vol. 12, no. 4, pp. 473–481, 2016.
- [56] S. Gaur, K. A. Øvrehus, and D. Dey, "Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions," *European Heart Journal*, vol. 37, no. 15, pp. 1220–1227, 2016.
- [57] C. J. Pepine, K. C. Ferdinand, L. J. Shaw et al., "Emergence of nonobstructive coronary artery disease: a womans problem and need for change in definition on angiography," *Journal of the American College of Cardiology*, vol. 66, no. 17, pp. 1918–1933, 2015.
- [58] E. Maffei, C. Martini, S. De Crescenzo et al., "Low dose CT of the heart: a quantum leap into a new era of cardiovascular imaging," *La Radiologia Medica*, vol. 115, no. 8, pp. 1179–1207, 2010.
- [59] S. Leschka, S. Seitun, M. Dettmer et al., "Ex vivo evaluation of coronary atherosclerotic plaques: characterization with dual-source CT in comparison with histopathology," *Journal of Cardiovascular Computed Tomography*, vol. 4, no. 5, pp. 301–308, 2010.
- [60] D. R. Obaid, P. A. Calvert, and D. Gopalan, "Dual-energy computed tomography imaging to determine atherosclerotic plaque composition: a prospective study with tissue validation," *Journal of Cardiovascular Computed Tomography*, vol. 8, no. 3, pp. 230–237, 2014.
- [61] R. Fazel, H. M. Krumholz, Y. Wang et al., "Exposure to low-dose ionizing radiation from medical imaging procedures," *The New England Journal of Medicine*, vol. 361, no. 9, pp. 849–857, 2009.
- [62] J. M. Levsky, D. M. Spevack, M. I. Travin et al., "Coronary Computed Tomography Angiography Versus Radionuclide Myocardial Perfusion Imaging in Patients With Chest Pain Admitted to Telemetry," *Annals of Internal Medicine*, vol. 163, no. 3, p. 174, 2015.