Functional versus anatomical approach in stable coronary artery disease patients: Perspective of low- and middle-income countries

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Coronary artery disease (CAD) is the primary cause of death worldwide. Nevertheless, while mortality rates have decreased over the last decades in high-income countries, in many low- and middle-income countries, the situation is just the opposite. Thus, the utilization of the more rational approach to diagnose, risk-stratify, and guide cost-effective management in these patients is of utmost importance in a setting of limited financial resources. Topics such as function versus anatomy with the focus on prognosis in stable CAD patients, as well as future perspectives on noninvasive techniques, will be addressed.

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Coronary artery disease (CAD) is the primary cause of death worldwide.[1] Nevertheless, while mortality rates have decreased over the last decades in high-income countries (HICs), in many low- and middle-income countries (LMICs), the situation is just the opposite.[2] Thus, the utilization of the more rational approach to diagnose, risk-stratify, and guide cost-effective management in these patients is of utmost importance in a setting of limited financial resources.

Although recent appropriate use criteria (AUC) suggest that the use of diagnostic catheterization and revascularization should generally be preceded by documentation of ischemia,[3] in the real world, 15% of nearly 300,000 elective diagnostic catheterizations in subjects without prior CAD did not have a previous noninvasive test for ischemia,[4] while only 44.5% of those undergoing elective angioplasty had a prior stress test.[5]

FUNCTION VERSUS ANATOMY: FOCUS ON PROGNOSIS

For the clinician, including the cardiologist, it is sometimes a controversial decision what to prescribe as a first test in a patient with suspected or known CAD: a functional test to look for a stress-induced ischemia (stress test; stress echocardiography; myocardial perfusion SPECT and PET imaging, MPI; and stress cardiac magnetic resonance, CMR), or an anatomical test to detect the presence of obstructive or nonobstructive CAD, such as coronary computed tomography angiography (CCTA) or invasive coronary angiography (ICA). This editorial will address both MPI and CCTA.

MPI is a well-established imaging technique in Cardiology, with a proven prognostic value. Over the past few years, CCTA has become an important technique in a Cardiology setting, with its very high negative predictive values (NPV)[6] being the exclusion of CAD its major strength. However, although the presence of obstructive CAD as detected on coronary CCTA has been associated with increased risk of mortality and major adverse cardiac events (MACE) in several

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studies,[7-9] the short-term follow-up, small sample size, and single-center results are limitations to be taken into account. Thus, CCTA prognostic value is still not well established but hopefully the CONFIRM (Coronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry may contribute to fill this gap.[10-12]

In this issue of the Journal of Nuclear Cardiology, Karthikeyan et al[13] studied 303 patients, one-third women, from 6 centers in 6 LMICs. These mildly symptomatic patients with an intermediate likelihood of having CAD (based on the Diamond and Forrester criteria), and asymptomatic patients at intermediate risk of cardiac events by the ATP III criteria, underwent either initial stress-rest MPI (151) or CCTA (152).

In Karthikeyan's study, the primary outcome was downstream noninvasive or invasive testing at 6 months, while secondary outcomes included cumulative effective radiation dose (ERD) and costs at 12 months. The authors found that the initial MPI was abnormal in 29% and CCTA in 56% of patients. Patients undergoing stress MPI as the initial test were half as likely (adjusted OR 0.51, 95% CI 0.28-0.91, p = .023) as those undergoing CCTA to have further downstream testing at 6 months. There was a small increase in the median cumulative ERD with MPI (9.6 vs 8.8 mSv, $p = .04$) but no difference in costs between the two strategies at 12 months. In their study, Karthikeyan et al[13] concluded that in the initial evaluation of patients with suspected CAD, a strategy of functional testing with stress-rest MPI compared to CCTA may result in less downstream testing, but with a small increase in radiation exposure to patients.

For patients with pre-test likelihood consistent with high risk of CAD, the clinical management is clear. It is precisely in those with low-to-intermediate and intermediate risks, in whom a noninvasive test is reasonable and indicated per guidelines,[14] in whom the choosing of the right first test is crucial. Thus, randomized trials designed with this aim will contribute to fill this important gap.

In spite of the relatively small size of the sample and the short-term follow-up, and considering the standardization and pre-specification of the downstream test use with effect-estimates adjusted for physician preference, the study of Karthikeyan et al,[13] sponsored by the International Atomic Energy Agency (IAEA), reflects the real world situation in the LMICs scenario. Note that this scenario included different countries with different environments and health policies. Larger studies previously published, such as the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial and the SCOT-HEART,[15,16] were conducted in more limited geographic areas and only reflect the situation in HICs with more financial resources and availability of imaging techniques.

Nevertheless, several other aspects need to be taken into account as well:

- First, Karthikeyan's study[13] was not powered to detect differences in clinical outcomes which could potentially result from the differences in the rates of downstream testing, while in the PROMISE trial,[15] the primary endpoint was a composite of death, myocardial infarction, hospitalization for unstable angina, or major procedural complication. The PROMISE trial showed that after a median follow-up of 25 months, there was no significant difference in time to the primary composite endpoint in the CCTA-based strategy as compared to functional testing, or any of its components. Nevertheless, when compared with the functional testing group, those patients in PROMISE trial undergoing an initial CCTA were 50% more likely to undergo catheterization, and almost twice as likely to undergo revascularization. These additional procedures, however, did not show any clinical benefit during the follow-up as measured by the primary outcome measure (3.3% in the CCTA group vs. 3.0% in the functional testing group).
  Thus, CCTA resulted in more radiation (cautiously assumed because functional testing with no radiation exposure: exercise, ECG, and stress echocardiography were also included to a lesser extent in these calculations), more catheterizations, and more revascularizations, without any improvement in clinical outcomes. It can be considered that the results from the PROMISE trial suggest that functional testing is the best initial noninvasive test in symptomatic patients with suspected CAD, congruent with the results in the Karthikeyan's study.
  However, the CRESCENT trial[17] (another small, randomized single-country study conducted in four Dutch hospitals that included 350 patients with stable angina followed during 1 year) showed that the cumulative radiation dose was slightly higher in the CCTA group, and the event-free survival was 96.7% for patients randomized to CCTA and 89.8% for those randomized to functional testing ($p = .011$). After CCTA, the final diagnosis was established sooner ($p < .0001$), and additional downstream testing was required less frequently (25% vs. 53%, $p < .0001$), resulting in significantly lower cumulative diagnostic costs.
- Second, SPECT testing in most asymptomatic patients is considered rarely appropriate, according to current AUC recommendations.[18] The only instance in which MPI is Appropriate in asymptomatic patients is in those considered at high risk for CAD.

– Third, gender differences (if any) according to functional or anatomical tests results were not accounted for in the study of Karthikeyan et al. Considering that women are frequently underrepresented in clinical trials, this may be considered as a continued line of research.
Hemal et al,[19] analyzing the patients from PROMISE trial, found that compared with men, all risk scores characterized women as being at lower risk. They were more often referred to imaging tests (adjusted odds ratio: 1.21; 95% confidence interval: 1.01 to 1.44) than nonimaging tests, and were less likely to have a positive test (9.7% vs. 15.1%; $p < .001$).
Although univariate predictors of test positivity were similar, in multivariable models, age, body mass index, and Framingham risk score were predictive of a positive test in women, while Framingham and Diamond and Forrester risk scores were predictive in men.[19] Thus, patient's gender influences the diagnostic pathway for possible CAD, from baseline risk factors and presentation to noninvasive test outcomes, as well as highlights the need for gender-specific approaches for the evaluation of CAD.
Schulman-Marcus et al.[11] analyzing gender-specific associations among CONFIRM patients, concluded that there is no significant observed interaction of gender between MACE and increasing per-vessel extent of obstructive CAD. Their results show that CCTA has prognostic significance to predict MACE and nonfatal myocardial infarction in both women and men.
According to Pagidipati et al,[20] the prognostic value of a noninvasive imaging test result varies according to test type and patient gender. Women seem to derive more prognostic information from a CCTA, while men tend to derive similar prognostic value from both test types.
But beyond anatomic information, CCTA can also be used to assess the significance of visualized plaques. This aspect might be helpful in understanding the increased adverse cardiac events risk associated with nonobstructive CAD, which is more frequent in women.
– Fourth, the impact of CCTA results on subsequent medical therapy and risk factors[21-23] has been reported. Hulten et al[21] in a study of 2839 patients with mean follow-up of 3.6 years, found that aspirin prescription increased from 17% to 72% for those with < 50% stenosis, and from 25% to 89% for those with ≥50% stenosis. The odds of physician intensification of lipid-lowering therapy significantly increased for those with nonobstructive CAD (odds ratio, 3.6; 95% confidence interval, 2.9-4.9; $p < 0.001$) and obstructive CAD (odds ratio, 5.6; 95% confidence interval, 4.3-7.3; $p < 0.001$).
Among patients with nonobstructive but extensive CAD, statin use after CCTA was associated with a reduction in cardiovascular death or myocardial infarction (hazards ratio, 0.18; 95% confidence interval, 0.05-0.66; $p = 0.01$).[21] This may constitute another interesting line of research, mainly in LMICs, where prevention results are particularly important. But it is not limited to CCTA; it has also been shown that the identification of small to moderate ischemia can lead to the intensification of aspirin and lipid-lowering therapies as well as to a more aggressive control of risk factors.
– Fifth, although the majority of patients included in PROMISE and SCOT-HEART cohorts[15,16] were symptomatic and had a high-risk factor burden, they had low cardiovascular event rates, just 1% to 2% per year. This can logically influence in the assessment of risk, because it reflects the fact that the majority of patients had either normal coronary arteries or mild CAD.

FUTURE PERSPECTIVES

Two aspects may be considered as future perspectives with the use of CCTA in cardiac patients:

– An advantage of CCTA over ICA is the ability to visualize the vessel wall, providing the potential to identify high-risk features of coronary plaque,[24] with a reported sensitivity of 93% and specificity of 92 % when compared with intravascular ultrasound (IVUS).[25]
– Recent developments in the calculation of fractional flow reserve noninvasively (FFR_{CT}): The accuracy of FFR_{CT} has been compared adequately with invasive FFR measurements.[26] The high NPV of FFR_{CT} has raised awareness for its potential to exclude ischemia caused by intermediate grade lesions, potentially avoiding unnecessary ICA.[27] Recently, the nonrandomized Prospective LongitudinAl Trial of FFR_{CT}: Outcome and Resource Impacts (PLATFORM) study investigated the clinical use of FFR_{CT}, showing that CCTA with FFR_{CT} led to a marked reduction in the number of ICA with no obstructive CAD,[28] as well as it was associated with less resource use and lower costs within 90 days than evaluation with invasive coronary angiography.[29] Over 1 year, in patients with stable chest pain and planned ICA, CCTA and selective FFR_{CT}-guided management were associated with equivalent clinical outcomes and lower costs.[30] Nevertheless, as Hulten and DiCarli proposed,[31] randomized trials comparing FFR_{CT}, CCTA, and stress testing are needed to further evaluate changes in cost and outcomes with FFR_{CT} before including it in the clinical practice.

Finally, the more or less widespread utilization of technology relates to factors ranging from financial

resources and political willingness to invest, to the level of information on the value of a given technology to help deliver cost-effective care.[32]

CONCLUSIONS

In understanding why a specific imaging test is chosen to evaluate a symptomatic patient with suspected CAD, we should remember that as Medicine is practiced today is still a combination of art and science. What clinicians prescribe will depend on their clinical instincts as well as the most recent guidelines and appropriateness criteria. These are certainly very important, but the regional clinical picture and the medical judgment cannot be overlooked.

Up to now, generally current studies have found no clear differences between testing strategies with regard to clinical or management outcomes that would allow recommendation of one strategy over another for any given pre-test risk group. However, some hints can be given: in patients with low- and low-intermediate risks for CAD with normal rest electrocardiogram and being able to exercise, given the overall good prognosis as well as low need for downstream testing, the stress test represents a reasonable initial testing option.

For intermediate-risk patients, an anatomical approach with a CCTA, due to its very high NPV, can be a good option; while in those with intermediate-high risk, a functional approach with stress imaging (either MPI or stress echo) seems to be a best option. In this sense, the study of Karthikeyan et al raises the topic in the LMICs setting, where to date, the introduction of CCTA has not affected significantly the utilization of MPI, and being considered more often complimentary than competitive.

In LMICs, where the best use of available financial and technological resources is mandatory, it is necessary to adequately combine guidelines and clinical criteria before prescribing noninvasive testing to cardiac patients.

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