Bridging the Atlantic gap in clinical guidelines for non-ST-elevation acute coronary syndromes

Francesco Nudi, MD,^{a,b,c} Alessandro Nudi, MD,^c Giuseppe Biondi-Zoccai, MD, MStat,^{d,e} and Orazio Schillaci, MD^{e,f}

^a Service of Hybrid Cardio Imaging, Madonna Della Fiducia Clinic, Rome, Italy

^b Ostia Radiologica, Rome, Italy

^c Etisan, Rome, Italy

^d Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy

^e Department of AngioCardioNeurology, IRCCS Neuromed, Pozzilli, Italy

^f Division of Nuclear Medicine, Tor Vergata University, Rome, Italy

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Common sense is judgment without reflection, shared by an entire class, an entire nation, or the entire human race.

Giambattista Vico

PREAMBLE

American and European clinical practice guidelines for non-ST-elevation acute coronary syndromes (NSTEMACS) represent a unique opportunity to analyze in detail and reshape the role of cardiac imaging tests in the modern era of cardiovascular medicine.^{1,2} As it is often the case, differences and gaps should pose a constructive challenge, and prompt readers and practitioners to improve knowledge and decision making. Thus, we must be thankful to Prejean et al. for providing us in this issue of the Journal a detailed comparative analysis summarizing agreements between such guidelines while highlighting important discrepancies.³ As in guidelines on stable coronary artery disease (CAD),

even in NSTEMACS guidelines the clinical condition is the starting point which represents, in this case well, a potential complication in the natural history of CAD.

In stable CAD, nuclear cardiology has a key diagnostic and prognostic role, as in patients with a good prognosis, in whom it might seem irrelevant to proceed with revascularization in comparison to optimal medical therapy, myocardial perfusion imaging (MPI) recognizes the group of subjects at higher risk of severe adverse events.⁴ In patients with NSTEMACS the management approach is of course altogether different, but discrepancies are evident also on the diagnostic approach.^{1–3} Indeed, in NSTEMACS, at odds with stable CAD, pre-test probability of CAD receives much lesser emphasis. The first issue rests on goals of tests and key limitations of test results. While for stable CAD guidelines the key weakness of tests relies in false positives, in NSTEMACS it rests on false negatives, especially given the medico-legal liability implications. Another important feature is appraising the relationship among diagnostic tests which differ in role, in particular stress ECG, functional imaging tests (echocardiography, cardiac magnetic resonance [CMR], and myocardial perfusion imaging [MPI]), and anatomic imaging tests (coronary computed tomography [CT]). It is also important to distinguish functional tests based on the use of a dynamic vs pharmacologic stress.

INVASIVE STRATEGY

Patient heterogeneity in coronary anatomy in NSTEMACS is substantial, with many subjects lacking significant coronary lesions.⁵ Conversely, multivessel

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Reprint requests: Francesco Nudi, MD, Service of Hybrid Cardio Imaging, Madonna della Fiducia Clinic, Via Giuseppe Mantellini 3, 00179 Rome, Italy; francesco.nudi@gmail.com

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disease may have a prevalence ranging between 40% and 80%. Accordingly, unless very high-risk features mandating an immediate invasive strategy are present, a rule-in diagnosis is best sought in the emergency room (ER) or in the chest pain unit (CPU), given the multitude of causes of chest pain.^{1,2} Such approach is based on the triad of symptoms, ECG changes, and high-sensitivity troponin (hsT). In particular, symptoms may vary or lack altogether, even if when present the dominant type is prolonged (> 20 minutes) chest pain at rest (80%), followed by new-onset chest pain (10%), and worsening or post-myocardial infarction (MI) chest pain (10%). Typical ECG changes include transient ST elevation, persistent or transient ST depression (occasionally specular), negative or pseudonormalized T waves.^{1,2} Notably, ECG may be apparently normal in 30% of subjects, with left bundle branch block posing major diagnostic issues. While hsT has a high negative predictive value for ruling out MI, several conditions may cause an increase in hsT associated with chest pain, complicating the differential diagnosis. Accordingly, it is useful to evaluate the absolute value of hsT, especially when very high, given its strong positive predictive value for ruling in MI, in as much as 75%–80% of patients. In such subjects a default invasive approach is better than a selectively invasive one for most endpoints, including repeat hospitalizations and revascularizations after discharge, but timing is still debated. Indeed, while the overall rate of major adverse cardiac events (MACE) is similar in an early vs delayed invasive strategy, risk-stratification using clinical risk scores is useful to identify subjects who can gain a reduction in MACE risk with an early (< 24 hours) invasive management (i.e., those at high risk in comparison to those at moderate risk). The final decision on management strategy rests on both physician and patient, based on an accurate risk–benefit balance.

Imaging for patients with suspected or established NSTEMI/ACS remains crucial in different clinical and temporal scenarios, in particular in the acute phase, during the hospitalization, and after discharge.^{1–3}

ROLE OF IMAGING AT ADMISSION

The acute phase is clearly characterized by patient heterogeneity, including clinical features.^{1,2} Among subjects acutely presenting with suspected NSTEMI/ACS, chest pain may be caused by non-coronary cardiac conditions in 15%, and non-cardiac conditions in 50%. Accordingly, the role of imaging is paramount, when findings from symptoms, ECG, or markers are not explicitly in favor of a default invasive strategy. Even if patients have no coronary instability, they might still have stable CAD on top of a non-coronary or non-

cardiac cause of chest pain, benefiting from early diagnosis and risk-stratification for subsequent management, as well as differential diagnosis. Imaging is not indicated in patients at high or very high risk (for whom it is necessary, respectively, an early or an immediate invasive strategy), with the exception of echocardiography to exclude mechanical complications according to European guidelines.^{1–3} Instead, imaging is crucial in particular for low-risk patients in whom a selective invasive strategy is envisioned. Imaging may also be beneficial in those subjects who undergo revascularization within 72 hours from symptom onset but not acutely. These are intermediate risk subjects, who include several clinical conditions, in particular: 1) for diabetics and those with renal failure it is important to appraise the extent and severity of myocardial ischemia; 2) in patients with reduced ejection fraction it is paramount to recognize myocardial viability, contractile reserve, and dyssynchrony; 3) in subjects with prior revascularization it is crucial to evaluate ipsi- or contralateral ischemia, especially in case of incomplete revascularization; and 4) in patients with prior evidence of myocardial ischemia at imaging, it is paramount to appraise defect progression. For these reasons, stress imaging tests are preferred to stress ECG tests. Other indications pertain to the appraisal of possible neuronal injury, for instance, in subjects with significant ventricular arrhythmias. Furthermore, a rest imaging test can occasionally be performed as a stand alone.

In patients in whom a delayed invasive strategy is probable, echocardiography and CMR are useful in the evaluation of myocardial viability as an alternative to MPI, using myocardial wall thickness and fibrosis as markers.^{1,2} Radioprotection issues are also relevant for hospital personnel and materials if invasive procedures or intensive patient management follow shortly MPI.

ROLE DURING HOSPITAL STAY AND AFTER DISCHARGE

Since accessing the ER or CPU and throughout, imaging tests remain pivotal to establish short and long-term risk.^{1,2} Higher risk patients are admitted for invasive management and revascularization. In other subjects, it is necessary to identify the best treatment spanning between delayed invasive and discharge with optimal medical therapy only. When revascularization is envisioned, it is paramount to distinguish the role of percutaneous coronary interventions vs coronary artery bypass grafting. For instance, in subjects in whom revascularization is indicated, it is useful to identify the culprit lesion or, conversely, the lack of benefit subsequent to treating a lesion associated with necrotic myocardium, especially in patients with prior or recent

MI. Another pro of imaging tests rests on the functional appraisal of coronary collaterals, as concomitant non-culprit or culprit occlusions are present in up to 25% of NSTEMI. In addition, two-thirds of these patients have coronary collaterals, with a variable degree of ischemia.

Even after revascularization for NSTEMI or before discharge, imaging can provide details on reverse remodeling and highlight patients with moderately or severely reduced left ventricular systolic function, who might need an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT).

After discharge for a suspected or established NSTEMI, progression of CAD remains a major cause of morbidity and mortality.^{1,2} Accordingly, even after an apparently successful management of NSTEMI, cardiac imaging tests are important to diagnose and risk-stratify disease progression. General recommendations apply to all patients, of course, but specific subgroups of patients may require more attentive management because of heightened risk or more complex differential diagnosis, such as the elderly, women, subjects with multivessel disease, acute or chronic heart failure, diabetes mellitus, renal failure, peripheral artery disease, or comorbidities. The reviewed guidelines and Prejean et al. offer important insights on such populations.^{1,2} Yet, whenever prognostic accuracy is important, such as in high-risk patients both acutely as well as at discharge, the functional details become the major player. Indeed, the higher the patient risk, the greater the need to upscale diagnostic alternatives. Finally, pharmacologic stress testing remains crucial during hospital stay, whereas exercise stress testing is very useful before discharge.

TESTING ALTERNATIVES

Stress ECG, while commonplace and affordable, is inadequate to stratify patients with NSTEMI at low or moderate risk and is fraught by a substantial likelihood of false-negative results, as well as false-positive ones, in terms of diagnostic yield, but even worse of prognostic yield, notwithstanding the poor or absent correlation between test results and culprit lesion, disease extent, left ventricular geometry, function, and viability.^{1,2} Conversely, stress ECG rests strong on easier interpretation, and does not require extensive training nor expensive equipment. For instance, MPI scoring systems enable a more detailed characterization of the patient, but are more demanding.⁶ Some differences regarding the use of diagnostic tests between American and European guidelines can be explained by the fact that access to invasive angiography is easier and more proactive in the US, resulting in fewer non-invasive imaging tests.³ The same explanation may

apply to the stronger recommendations favoring CT and anatomic details in American guidelines. Indeed, despite the established fact that on average only half of angiographically significant coronary stenoses cause ischemia, myocardial ischemia is not chosen as the key decisional criterion.⁷

As malpractice and financial issues are substantial, unless expedited invasive management is chosen, an imaging test is indeed useful already before admission to decide whether to actually admit the patient or discharge him/her after temporary observation, as well as to minimize the risk of sudden death or MI after discharge. For this purpose, a CT scan and/or a cadmium-zinc-telluride/CT camera should be available to all centers given the limited dimensions and ease of exam.⁸ Indeed, as alternatives to MPI, CT, echocardiography, and cardiac magnetic resonance (CMR) are all appealing. Specifically, CT focuses on anatomic detail and thus it best maximizes negative predictive value, minimizing useless admissions.⁹ Our goal of accurately characterizing each patient has however improved with perfusion CT and fractional flow reserve (FFR)-CT, despite this being often at odds with anatomic CT, as even anatomically significant lesions may be associated with normal FFR values.¹⁰ This clearly reinforces the importance of the functional detail, despite the fact that FFR validity has been questioned in the acute phase of myocardial injury. Several other limitations to CT apply, including protocol issues, variability in interpretation, need for an expert reader, coronary calcium, prior stenting, heart rate, arrhythmias, and so forth.

Echocardiography still rests strong given its non-invasiveness and lack of radiation exposure, access, ease of use, as well as plethora of additional details such as non-coronary findings and complications. In addition, left ventricular geometry and function, whose prognostic role is unparalleled, is finely appraised by echocardiography.¹¹ Finally, CMR is very potent to appraise cardiac geometry and function, but less accessible and still limited by lack of coronary details.¹²

Myocardial perfusion imaging (MPI) remains a powerful test in NSTEMI for its ease, access, reliability, and thus may maintain a dominating role among the available cardiac imaging tests.^{1,2,13-15} Yet, virtually all institutions have no 24/7 access to MPI. In addition, in very high- and high-risk patients, MPI is not useful for diagnostic purposes or short-term prognosis as diagnosis is already quite established and accordingly the indication to invasive management. The main contribution of MPI in this setting rests on viability, but this is typically affected later (as it applies to neuronal damage), unless the admission is for reinfarction rather than de novo NSTEMI. In addition, neuronal injury (informing on prognosis and benefits of beta-blocker therapy and ICD)

can be measured with meta-iodo-benzyl-guanidine (MIBG) tests.¹⁶ Overall, the main advantage of MPI is that it provides with a one-stop-shop approach a comprehensive set of functional results with a wide spectrum of characterizing features to best define patient prognosis. Yet, specific settings where MPI may be particularly advantageous include patients with reduced systolic function and limited viability or hibernation/stunning, left ventricular dyssynchrony, or myocardial dyssinnervation/denervation.

Irrespective of the choice of its core components, anatomic-functional hybrid imaging appears particularly appealing for patients with NSTEMI, given their high risk of adverse events during follow-up (> 10% 1-year MACE rate).^{4,7} For instance, CT-derived anatomic imaging, which provides for instance details on lesion location, plaque features, vessel remodeling, calcium score, and stenosis severity can be seamlessly combined with MPI-derived functional imaging, which yields several functional parameters provided by MPI, including, most recently, coronary flow reserve.^{6,13–15} Thus, hybrid imaging provides many important results which are complementarily associated with pre-test and stress features, enabling the best clustering of the patient into a low-risk group, or otherwise prompting expedited invasive assessment, or guiding post-discharge management and follow-up.

FUTURE PERSPECTIVES AND CONCLUSIONS

American and European guidelines provide specific guidance for most patients, from bread-and-butter cases to special cases such as the very elderly.^{1,2,15} Yet, individualized management requires also careful and proactive follow-up. Indeed, the importance of the quest for optimal care shortly and long-after discharge for an otherwise correctly managed NSTEMI is proven by ongoing efforts at improving and streamlining patient empowerment, interactive follow-up, and patient-physician communication with novel information technology platforms such as the Recipe tools developed by Replycare (Rome, Italy).¹⁷

In conclusion, the main goal of any guideline is its application to the single patient. American and European guidelines on NSTEMI offer important and constructive insights to practising cardiovascular specialists. Imaging specialists remain key in capitalizing agreements and resolving discrepancies.

Disclosure

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