Editorial

Variation in treatment strategy for NSTEMI: A complex phenomenon

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The mainstay treatments for patients presenting with non-ST-elevation myocardial infarction (NSTEMI) include guideline-directed medical therapy, coronary angiography, and revascularization when appropriate. The benefits of an invasive strategy are well established [1,2], however, what is less certain is the optimal timing of coronary angiography. Regardless of whether the weight of evidence supports an earlier invasive strategy (EIS) (i.e., within 24 h after diagnosis) for reduction of the incidence of major adverse cardiovascular events and recurrent ischemia compared with a delayed invasive strategy [3], this potential benefit seems strongly associated with the patient's risk profile [4,5]. Indeed, in prespecified subgroup analyses from the TIMACS and VERDICT trials, patients with a GRACE risk score > 140 benefited from an EIS compared with a delayed strategy, while those with a GRACE risk score ≤ 140 did not [4,5]. Moreover, the clinical presentation is heterogeneous and may range from patients who are free of symptoms to those with ongoing ischaemia, cardiogenic shock, and even cardiac arrest. Therefore, the acute management of patients with NSTEMI remains a clinical challenge.

In the journal Park et al [6] reported the results of a study in which they used a Korean, prospective, observational, multicenter online registry (The Korean Acute Myocardial Infarction Registry (KAMIR)-National Institute of Health (NIH)) to evaluate region and hospital level variations in the selection of an EIS after NSTEMI. The authors enrolled 7037 NSTEMI patients from November 2011 to November 2015 from 20 hospitals in 3 regions. Interestingly, EIS was selected in 84.4% of patients, and rates varied from 61.3% to 97.9%. After adjusting for patient-level covariates, the authors found significant hospital- and region-level variation in the selection of an EIS, and in the final model there was a notable rate of site-level variation with a median rate ratio (MRR) of 2.14 (95% confidence interval [CI]:1.70–2.48), indicating significant variation. Male sex and recurrent or ongoing chest pain were positively associated with EIS selection; conversely among high-risk criteria, new onset heart failure and GRACE score > 140 were negatively associated with the selection of an EIS. Therefore, an early conservative strategy (ECS) was often chosen when an EIS would provide more benefit [4,5]. Although we know that the benefit of EIS cannot be determined from non-randomized studies [7], the in-hospital rate of MACE (a composite of mortality or major bleeding) was significantly lower in patients with an EIS than with an early conservative strategy (ECS) (3.6% versus 6.3%, $p < 0.001$), including mortality (2.4% versus 3.8%, $p < 0.001$), whereas there was no significant difference in MACE between an EIS and ECS in patients without high-risk criteria.

The authors have reported important data regarding NSTEMI management in East Asia. This information is critical to understand the divergence of practice from current recommendations and also for better understanding the treatment gaps for some patient categories.

Strengths of the study include the large sample size derived from a whole-country registry and that all-comer patients were included.

However, the registry data were based on reported diagnoses and were not independently verified; only all-cause mortality and not cardiac-specific mortality was available. Moreover, the EIS was defined as within 48 h after diagnosis, a different time range compared with the current accepted guideline definition of EIS, i.e., within 24 h after diagnosis [8,9]. Despite these limitations, this cohort study confirms clear variation in the management of NSTEMI [10] and the wide presence of the treatment risk paradox - higher-risk patients are less likely to receive EIS despite the fact that they stand to benefit the most [11–14]. The reasons for this variation are difficult to ascertain and are probably multifactorial (Fig. 1).

Timing of angiography could be influenced by resource availability [15] and calibrated on the number of catheterization laboratories and personnel in the hospital, as well as the presence of specific hospital protocols. In this sense we do not know if hospitals at which EIS was more common also had stricter adherence to guideline-recommended therapies. Potential influence of hospital resources vs EIS would have been interesting to evaluate. Variations in practice may also have to do with the experience and skill of the operators. Interestingly, 15.6% of patients received an ECS, and among them 38.3% of patients received only medical therapy. Was this a neglect of the neediest or a "wise" clinical selection? For example, the frailty associated with advanced age or absence of revascularization options in patients with recent angiography may not be recorded. In the "real world," critical reasoning and the clinical judgment of physicians could be able to detect specific patients in whom early invasive procedures are unlikely to be beneficial, and additionally, physicians may take into consideration patient preference, life expectancy, cognitive and functional status, comorbidities, and inherent bleeding risk. Indeed, in some specific situations, extensive comorbidities may outweigh the benefits of revascularization.

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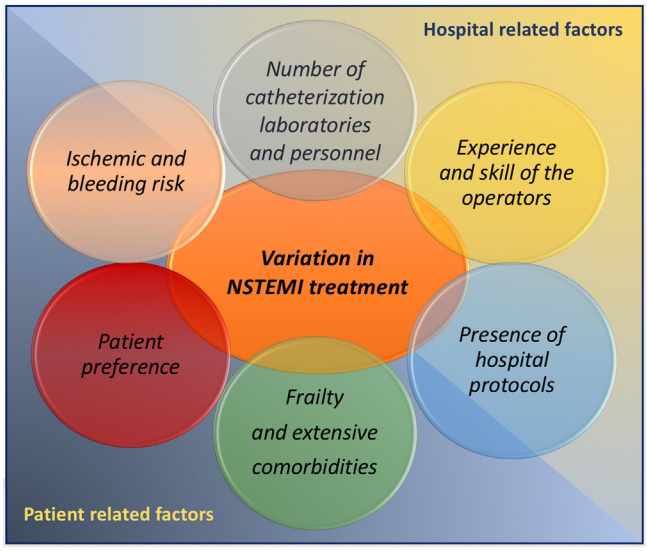

Fig. 1. Potential factors influencing variation in NSTEMI treatment.

Male sex was independently associated with the selection of an EIS, however, females were nearly a decade older than men at the time they presented with NSTEMI and were more likely to have comorbidities. It has been shown that the lower use of an EIS in women is not responsible for a higher crude rate of in hospital mortality, which could be explained by older age and greater comorbidity burden [16]. On the other hand, there is evidence that the mortality benefit from invasive management might extend to NSTEMI patients aged 80 years or older [17], and age per se should not be a reason for avoidance of an indicated revascularization procedure. In the last decade, even though the rising complexity of patients undergoing PCI has contributed to increase the incidence of ischemic stroke after PCI [18], the greater utilization of EIS in the United States has been associated with reduced in-hospital mortality and decreased length of stay [19].

Strictly following the more recent European guidelines [9], EIS should be the recommended approach in the vast majority of NSTEMI cases. Physicians should improve the appropriate use of EIS in high-risk patients, and they should not be tempted to bring in the cath lab only the easiest cases. At the same time, it is also true that a rigid one size fits all approach should not be applied to a markedly diverse group of NSTEMI patients. In the past, questions regarding invasive vs conservative management have been addressed [20] but the debate continues for the best timing of an invasive strategy. In the modern era of interventional cardiology and continuous sub-specialization in the pursuit of technical virtuosity, there is still room for wise clinical judgment. This seems even more crucial in the management of increasing numbers of complex cardiac patients in order to achieve patient-centered goals.

Declaration of Competing Interest

Dr. Fabris has nothing to disclose. Dr. Bhatt discloses the following relationships - Advisory Board: Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Level Ex, Medscape Cardiology, MyoKardia, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, MyoKardia, Owkin, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda.

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