for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373:723–31.

5. Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation 2010;122:2131–41.

Immediate Versus Delayed Invasive Intervention for Non–ST-Segment Elevation Myocardial Infarction Patients (RIDDLE-NSTEMI Study)

A Game Changer for Interventional Cardiologists?

We read with great interest the recent study published by Milosevic et al. (1) assessing clinical outcomes at 30-day and 1-year follow-up in patients with non-ST-segment elevation myocardial infarction (MI) in stable condition undergoing immediate versus delayed percutaneous coronary intervention in a single-center, prospective, randomized study (RIDDLE-NSTEMI [Randomized Study of Immediate Versus Delayed Invasive Intervention in Patients With Non ST-Segment Elevation Myocardial Infarction]). The median time from onset of chest pain to coronary angiography was 6.4 h in the immediate-intervention group and 67.5 h in the delayed-intervention group. At 30-day and 1-year follow-up, significant differences in the rates of primary (death and new MI) and secondary (death, new MI, or recurrent ischemia) outcomes were observed between the 2 treatment strategies, with differences notable mostly in the pre-catheterization period. No significant differences were seen in the time period from 31 days to 1-year follow-up.

We believe that several factors may have skewed outcomes in favor of the immediate-intervention strategy. First, the definition of new MI did not include troponin I levels, as suggested in the "reinfarction" definition outlined in the third universal definition of MI (2), if ischemic symptoms and electrocardiographic changes occurred within the first 24 h of randomization ("early new MI"). In contrast, a rise in troponin I >20% (if initial elevated values were stable or decreasing) occurring >24 h to 7 days from randomization, in the presence of symptoms and electrocardiographic changes, was defined as a "late new MI." Perhaps the investigators adopted this definition to avoid overdiagnosis of "new early MI" in patients with initially elevated cardiac troponin I, thus making it difficult to discriminate between the occurrence of new MI and the initial index event. Nevertheless, because patients randomized to the immediate-intervention arm underwent PCI <24 h from randomization, could it be possible that recurrent MIs in this early period were undiagnosed or attributed to the percutaneous coronary intervention procedure (type 4a MI) (2)?

Second, it is unclear why more patients in the delayed-intervention group were referred for coronary artery bypass grafting and had a higher proportion of GRACE (Global Registry of Acute Coronary Events) score (3) >140. This suggests that these patients had a greater coronary artery disease burden and thus were "sicker" and at higher risk than those in the immediate-intervention group. Considering that these high-risk patients were not crossed over to the immediate-intervention strategy, as recommended in the most recent European Society of Cardiology (4) and American College of Cardiology and American Heart Association (5) guidelines, one could argue that the occurrence of adverse clinical events would be expectedly higher in this patient subgroup.

This study suggests benefits of an early invasive intervention strategy in high-risk patients with non-ST-segment elevation MI, with reductions of death and new MI at 30 days and 1 year. We agree with the investigators that an investigation with larger sample size, longer clinical follow-up, and precise definitions of new MI, reinfarction, and periprocedural MI is required to assess the long-term benefits of such a strategy given its potential impact on the health care system and the delivery of care in the catheterization laboratory.

Marie-Jeanne Bertrand, MD, MSc
***Jean-François Tanguay, MD**
*Université de Montréal
Montreal Heart Institute
5000 Bélanger Street
Montreal QC H1T 1C8
Canada
E-mail: jean-francois.tanguay@icm-mhi.org

http://dx.doi.org/10.1016/j.jcin.2016.04.032

Please note: Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Milosevic A, Vasiljevic-Pokrajcic Z, Milasinovic D, et al. Immediate versus delayed invasive intervention for NSTEMI patients: the RIDDLE-NSTEMI study. J Am Coll Cardiol Intv 2016;9:541–9.

2. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.

3. Bradshaw PJ, Ko DT, Newman AM, et al. Validity of the GRACE (Global Registry of Acute Coronary Events) acute coronary syndrome prediction model for six month post-discharge death in an independent data set. Heart 2006;92:905–9.

4. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267–315.

5. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139–228.

REPLY: Immediate Versus Delayed Invasive Intervention for Non–ST-Segment Elevation Myocardial Infarction Patients (RIDDLE-NSTEMI Study)

A Game Changer for Interventional Cardiologists?

We thank Drs. Bertrand and Tanguay for their in-depth analysis and constructive comments on our study (1), which demonstrated improved clinical outcomes in patients with non-ST-segment elevation myocardial infarction (MI) treated with an immediate versus a delayed invasive strategy, and we agree with the conclusion that such results, if confirmed by a larger, multicenter study, may have a significant impact on health care infrastructure. Because of inherent problems of determining periprocedural MI in the setting of early percutaneous coronary intervention (PCI) in patients with non-ST-segment elevation MI, we adopted a time-specific definition of MI similar to the hitherto largest study on this subject, the TIMACS (Timing of Intervention in Acute Coronary Syndromes) trial (2). This definition allowed differential assessment of new MI between the treatment groups, with a possibility of biomarker-based adjudication preferentially in the delayed-intervention group. However, the definition also required new-onset ischemic symptoms >20 min, and our records show that in all cases of new MI after PCI in the delayed-intervention group, there was a supporting electrocardiographic correlate of ischemia as well. Importantly, the main difference in the primary outcome resulted from the higher rate of precatheterization MI in delayed-intervention patients (10 vs. 0 new MIs in the delayed- vs. immediate-intervention group, respectively). An additional 6 patients in the delayed-intervention group had new MI after PCI and up to 30-day follow-up. Of these, 4 patients had biomarker elevations within 24 to 48 h post-PCI, accompanied by new-onset chest pain lasting >20 min and corresponding new ischemic electrocardiographic changes. In the remaining 2 patients, new MI occurred after hospital discharge. Hence, we believe that the definition of new MI had no significant impact on the overall study results.

In our study, baseline risk profile, as expressed by GRACE (Global Registry of Acute Coronary Events) and TIMI (Thrombolysis In Myocardial Infarction) risk scores, was similar in the immediate- and delayed-intervention groups (1). The higher rate of surgical revascularization in patients assigned to undergo delayed invasive intervention is listed as a potential limitation of our study. More specifically, 38 and 20 patients were treated with coronary artery bypass grafting in the delayed- and immediate-intervention groups, respectively. The final decision on revascularization strategy for these patients was made by the institutional heart team, blinded to randomization code. However, even after excluding patients referred for coronary artery bypass grafting from the analysis, immediate intervention was still associated with reduced rates of death or MI at both 30 days (2.1% vs. 13.9%, $p < 0.001$) and 1 year (3.5% vs. 17.2%, $p < 0.001$). Therefore, the observed difference in the rate of coronary artery bypass grafting seems not to have significantly influenced the overall study results, and nor has the time-specific definition of new MI. However, we agree that further studies are needed to corroborate our findings, as they may have substantial implications for health care systems in terms of increased resource allocation to expedite early invasive treatment in patients with ischemic electrocardiographic changes and biomarker elevation on admission.

Aleksandra Milosevic, MD
Zorana Vasiljevic-Pokrajcic, MD, PhD
Dejan Milasinovic, MD
Vladan Vukcevic, MD, PhD
Milika Asanin, MD, PhD
***Goran Stankovic, MD, PhD**

*Clinical Center of Serbia
Department of Cardiology and Faculty of Medicine
University of Belgrade
26 Visegradska
Belgrade 11000
Serbia
E-mail: gorastan@sbb.rs

http://dx.doi.org/10.1016/j.jcin.2016.04.047

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

REFERENCES

1. Milosevic A, Vasiljevic-Pokrajcic Z, Milasinovic D, et al. Immediate versus delayed invasive intervention for non-STEMI patients: the RIDDLE-NSTEMI study. J Am Coll Cardiol Intv 2016;9:541–9.

2. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360:2165–75.