Editorial

Myocardial revascularization: do age and sex matter?

Piroze M. Davierwala, Friedrich W. Mohr

Department of Cardiac Surgery, Heart Center, University of Leipzig, Leipzig Germany

Correspondence to: Piroze M. Davierwala. Herzzentrum, Universität Leipzig Struempellstrasse 39, Leipzig 04289, Germany. Email: pirarm@hotmail.com.

Submitted Aug 11, 2016. Accepted for publication Aug 19, 2016.
doi: 10.21037/jtd.2016.10.45
View this article at: http://dx.doi.org/10.21037/jtd.2016.10.45

The World Health Statistics 2016, which is World health Organization's annual compilation of health statistics for its 194 Member States, reported that the global average life span has dramatically increased by 5 years since 2000, making it the fastest rise since the 1960s (1). Globally, a 151% surge is expected in the population ≥85 years between 2005 and 2030, compared to an increase of only 104% in those aged ≥65 years (2). The American Heart Association predicts a significant rise in the burden of cardiovascular disease in the USA by 2030 due to this rise in the aging population (3). Approximately 25% of the population >75 years suffers from symptoms of cardiovascular diseases (4) and has resulted in a demographic shift in patients with coronary artery disease (CAD) requiring myocardial revascularization. The mean age of patients undergoing cardiac surgery increased from 55.8 years in 1990 to 68.8 years in 2007, of which, 9.8% were octogenarians (5). The healthcare challenges and clinical decision-making in elderly patients are real concerns in daily practice as they often present with several comorbidities existing concurrently, which not only complicates management of CAD, but also leads to development of newer disease states or worsening of preexisting conditions (6). Additionally, factors such as frailty, sarcopenia and cognitive decline, which are unique to the geriatric population, frequently compound multi-morbidity management and cause a hindrance to smooth postoperative recovery and rehabilitation despite uneventful procedures (7). Furthermore, such factors reduce the reserve capacity and strength of elderly patients to recover, sometimes, even from minor set-backs or complications.

Differences existing between individuals are not only age-related but also gender specific. The exponential increase in experimental and clinical studies investigating sex-related differences in cardiovascular system in the last 2 decades underscores the importance of this topic. The hormone estrogen, which regulates several metabolic factors, such as lipids, inflammatory markers and the coagulant system and promotes vasodilation through α and β receptors in the vessel wall (8), which still debatable, is presumed to confer the so-called protective effect against CAD in premenopausal women. Endogenous estrogen deficiency increases the risk of CAD in young women by 7 times (9). Sex-related differences are apparent even in the normal myocardium of healthy individuals (10). Additionally, differences exist in pathophysiology of atherosclerosis and vascular dysfunction such as slower progression of atheromas into vulnerable plaques in middle-aged women (11) and greater microvascular dysfunction of the coronary system and subendocardial ischemia in the presence of open coronary arteries due to distal embolization of microemboli from plaque erosions that are more often seen in women than men with acute coronary syndromes (12). Furthermore, gender dissimilarities have also been observed in the prevalence and relative weighting of cardiovascular risk factors among women <60 years (13), as indicated by the particularly more harmful effect of smoking in young women with respect to development of CAD, the higher prevalence of endothelial dysfunction, stroke, left ventricular hypertrophy and diastolic heart failure as a consequence of hypertension (14), greater occurrence of cardiovascular complications of type 2 diabetes mellitus (15) and higher levels of LDL cholesterol in women >65 years (16). The aforementioned alterations observed with aging and variations detected in women would presumably lead to age and sex-related differences in effectivity, interaction and side effects of therapeutic revascularization strategies.

The current guidelines recommend myocardial revascularization in all patients with CAD, who have a significant area of ischemic myocardium (>10% left ventricle) and/or presence of limiting angina unresponsive to optimal

medical therapy (17). Patients with three-vessel disease (3VD) usually fall in the above category. The chief objective of revascularization, whether percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), is to prolong survival and improve the quality of life by relieving ischemia and increasing the ability to exercise. CABG has been associated with lower rates of cardiac death, myocardial infarction (MI), repeat revascularization and major adverse cardiac and cerebrovascular events at long-term follow-up than PCI in patients with severe multivessel CAD (18,19), which should make it the obvious choice of revascularization for such patients. However, PCI, being the less invasive procedure than CABG, leads to a general perception that it would be associated with a lower early mortality than CABG in elderly patients (>75 years) with significant comorbidities, in whom the main goal of revascularization is to reduce early mortality and relieve angina. Furthermore, previous studies have shown that women are at a higher risk of post-procedural death after PCI or CABG irrespective of age (20,21). There is a paucity of evidence in literature with respect to safety and efficacy of PCI in comparison to CABG in such elderly patients, particularly in relation to gender. Yamaji *et al.* have tried to fill this gap in knowledge through their study published in Circulation in spring this year, which evaluated the effects of the age and sex on clinical outcomes after PCI relative to CABG in a pooled population of Cohorts 1 and 2 (era of bare-metal and drug-eluting stents, respectively) of the CREDO-Kyoto (Coronary Revascularization Demonstrating Outcome Study in Kyoto) all-comer registry (22).

The study involved a total 5651 consecutive patients including 3,998 men and 1653 women with 3VD, who had undergone PCI [3,165] or CABG [2,486]. The authors evaluated the patients, initially, by dividing the whole cohort into 3 groups based on the age of patients: ≤65 years (n=1972), 66 to 73 years (n=1820), and ≥74 years (n=1,859) and then into 2 groups based on gender. The whole cohort and each group were further subdivided into CABG and PCI subgroups. All-cause mortality was the primary outcome and cardiac death, sudden death, noncardiac death, MI, stroke, heart failure (HF) hospitalization, and any coronary revascularization were other outcome measures. The mean age of patients and the percentage of women undergoing PCI were higher than those undergoing CABG for the whole cohort, but comorbidities such as prior stroke, non-dialysis dependent renal insufficiency, insulin-dependent diabetes mellitus, and anemia and cardiac parameters like prior MI and atrial fibrillation were more commonly observed in the CABG subgroup. The complexity of CAD was also significantly greater in the CABG subgroup as evidenced by higher SYNTAX scores and higher number of occluded vessels and proximal LAD lesions. A similar trend in differences in demographics and comorbidities was also observed between the PCI and CABG subgroups, when the three age-related tertiles (groups) were individually analyzed. Of note, however, was that patients aged ≥74 years demonstrated an increased incidence of HF and other comorbidities than younger patients. Analysis of gender-related groups revealed that women were older than men, had more comorbidity, but less often had left ventricular dysfunction, prior MI, and peripheral vascular disease.

The main findings of the study demonstrated that patients in the PCI subgroup for the whole cohort and for the age group ≥74 years had significantly higher all-cause mortality than those in the CABG subgroup (even after adjustment of confounders) with no difference observed in the younger age group categories, giving rise to a significant interaction between age tertile and the mortality risk of PCI relative to CABG. A similar difference in all-cause mortality was also observed between PCI and CABG in both, men and women, resulting in no interaction between gender and all-cause death. Other outcomes such as cardiac death, MI, hospitalization for HF, and any coronary revascularization also occurred more frequently after PCI compared with CABG irrespective of age and sex. Contrarily, stroke rate was significantly greater after CABG than PCI and was chiefly driven by the particularly high occurrence of postoperative stroke in elderly women (≥74 years), resulting in an interaction of borderline significance between sex and the effect of PCI relative to CABG for stroke.

The findings of the study by Yamaji *et al.* further confirm the superiority of CABG to PCI as a modality of treatment in patients with multivessel CAD. The primary and secondary outcomes are similar to those reported by two contemporary landmark trials (18,19) and recent meta-analyses that have included most of the relevant recent trials (23,24). However, this study, which involves analysis of data from a large registry, is more representative of real world practice. Furthermore, stratification of the patient cohort based on age and sex contributes a different insight into the field of myocardial revascularization. One of the unforeseen results revealed by this study was that the elderly population (≥74 years) undergoing PCI was at a greater mortality risk compared to those undergoing CABG, despite the higher prevalence of comorbidities in the latter. This could be

attributed to several factors. First, PCI patients in the age group ≥74 years had a higher SYNTAX score than those in the younger age group. PCI can be challenging and at times unsuccessful in presence of complex bifurcation or totally occluded lesions, which results in a higher incidence of incomplete revascularization. Patients with persisting areas of ischemic myocardium are at an increased risk of developing HF (17% in the current study), which was associated with an extremely elevated mortality risk in present series (51.9%). In contrast, significantly lower number of elderly CABG patients developed HF (11%) at follow-up, which may have contributed to lower all-cause mortality. Secondly, this study is a retrospective analysis without the use of propensity score to iron out the differences in baseline parameters of patients undergoing PCI or CABG, which could at least reduce if not nullify the potential selection bias. Therefore, this study may have included patients in whom only one treatment modality was considered appropriate based on certain parameters assessed at the time of decision-making. Age could be one of them as evidenced by the significantly higher mean age of PCI patients in the elderly age group. The observation that prevalence of most comorbidity was higher in patients undergoing CABG, which opposes reasoning, underscores the fact that there must have been other confounding factors not captured in the registry's database. One such important factor is frailty, which was defined by Bergman *et al.* as enhanced vulnerability to stressors because of impairments in multiple, inter-related systems that lead to decline in homeostatic reserve and resiliency (25). Frailty scores increase exponentially with increasing age (26) and may deteriorate following a more invasive procedure (27). Sarcopenia or relative deficiency of skeletal muscle mass and strength is another factor that increases rapidly after 65 years of age and is significantly associated with functional limitation and physical disability (28). Cognitive deficiencies, particularly executive function, also hinder recovery after interventional procedures and the improvement in quality of life achievable by therapy are controversial (29). Such factors, although not included in most databases, play a very important role in outcomes of patients undergoing myocardial revascularization. PCI is usually the preferred choice of revascularization in such patients as they have a very low reserve and a minor complication or infection in addition to surgical stress following CABG can lead to irreversible deterioration. But PCI in such patients would also be associated with an increased mortality risk than healthier individuals, which could also be a contributing factor to the higher mortality observed after PCI in the elderly patients in the present study. Therefore, lower mortality associated with CABG in elderly patients with more comorbidity in the present series should be addressed with caution. An integrated approach involving a heart team including a cardiologist and a cardiac surgeon for preoperative assessment and decision-making with addition of an anesthesiologist and intensivist for perioperative care would be prudent to adequately address the peculiarities, susceptibilities and formulate individualized therapeutic strategies for such patients.

Although all outcomes except stroke were significantly higher in both, men and women undergoing PCI as compared to CABG, a striking observation of this study was the better clinical outcome rates apart from stroke after CABG in women compared with men, in spite of the higher incidence of cardiovascular risk factors and comorbidities among the former. Historically, female gender has been associated with increased mortality especially following CABG (20,21). This has been attributed to difficulty and delay in diagnosis, underutilization of diagnostic tests and therapies, and anatomical (small and fragile coronary arteries), physiological and genetic differences in women. Additionally, women undergoing CABG are less likely to receive an internal mammary graft and complete revascularization (30). Although the authors have not provided any justification for the same, one of the explanations for these improved results in women in this series could be the high percentage of single (96%) and bilateral (23%) internal mammary artery use in women. One can also speculate that Japanese surgeons, similar to most Asian surgeons are more adept at grafting smaller vessels, because they encounter such arteries on an everyday basis. This could have led to better patency and higher complete revascularization rates, resulting indirectly in reduction of occurrence of heart failure and death. Clearly other cofounding and unknown factors must have contributed to these outcomes, elucidation of which will require more sex-specific investigations.

Acknowledgements

None

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Kai Zhu (Department of Cardiac Surgery,

Zhongshan Hospital Fudan University, Shanghai, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Yamaji K, Shiomi H, Morimoto T, *et al.* Effects of Age and Sex on Clinical Outcomes After Percutaneous Coronary Intervention Relative to Coronary Artery Bypass Grafting in Patients With Triple-Vessel Coronary Artery Disease. Circulation 2016;133:1878-91.

References

1. World Health Organization 2016. Life expectancy—major gains but still large differences. In: World health statistics 2016: monitoring health for the SDGs, sustainable development goals. Geneva: WHO Press. 2016:7-9.
2. National Institute of Aging. Why Population Aging Matters: A Global Perspective. [published 2011 Sept; updated 2015 Jan 22]. Available online: https://www.nia.nih.gov/publication/why-population-aging-matters-global-perspective/trend-3-rising-numbers-oldest-old
3. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation 2010;121:586-613.
4. National Center for Health Statistics, Vital Statistics of the United States US Government Printing Office, vol. 2, Washington, DC, USA, 1992.
5. Friedrich I, Simm A, Kötting J, et al. Cardiac surgery in the elderly patient. Dtsch Arztebl Int 2009;106:416-22.
6. Bell SP, Orr NM, Dodson JA, et al. What to Expect From the Evolving Field of Geriatric Cardiology. J Am Coll Cardiol 2015;66:1286-99.
7. Chaudhry SI, Wang Y, Gill TM, et al. Geriatric conditions and subsequent mortality in older patients with heart failure. J Am Coll Cardiol 2010;55:309-16.
8. Murphy E. Estrogen signaling and cardiovascular disease. Circ Res 2011;109:687-96.
9. Bairey Merz CN, Johnson BD, Sharaf BL, et al. Hypoestrogenemia of hypothalamic origin and coronary artery disease in premenopausal women: a report from the NHLBI-sponsored WISE study. J Am Coll Cardiol 2003;41:413-9.
10. Legato MJ, Leghe JK. Gender and the heart: sex-specific differences in the normal myocardial anatomy and physiology. In: Legato MJ (ed.). Principles of Gender-Specific Medicine. Elsevier Inc: Amsterdam, Boston, Heidelberg, London, New York, Oxford, Paris, San Diego, San Francisco, Singapore, Sydney, Tokyo. 2010:151-61.
11. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. J Am Coll Cardiol 2009;54:1561-75.
12. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. JAMA 2005;293:477-84.
13. Anand SS, Islam S, Rosengren A, et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J 2008;29:932-40.
14. Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001;345:1291-7.
15. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73-8.
16. Abbey M, Owen A, Suzakawa M, et al. Effects of menopause and hormone replacement therapy on plasma lipids, lipoproteins and LDL-receptor activity. Maturitas 1999;33:259-69.
17. Authors/Task Force members, Windecker S, Kolh P, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541-619.
18. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629-38.
19. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375-84.
20. Lempereur M, Magne J, Cornelis K, et al. Impact of gender difference in hospital outcomes following percutaneous coronary intervention. Results of the Belgian Working Group on Interventional Cardiology (BWGIC) registry. EuroIntervention 2016;12:e216-23.
21. Pollock B, Hamman BL, Sass DM, et al. Effect of gender and race on operative mortality after isolated coronary artery bypass grafting. Am J Cardiol 2015;115:614-8.
22. Yamaji K, Shiomi H, Morimoto T, et al. Effects of Age and

Sex on Clinical Outcomes After Percutaneous Coronary Intervention Relative to Coronary Artery Bypass Grafting in Patients With Triple-Vessel Coronary Artery Disease. Circulation 2016;133:1878-91.
23. Sipahi I, Akay MH, Dagdelen S, et al. Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease: meta-analysis of randomized clinical trials of the arterial grafting and stenting era. JAMA Intern Med 2014;174:223-30.
24. Smit Y, Vlayen J, Koppenaal H, et al. Percutaneous coronary invervention versus coronary artery bypass grafting: a meta-analysis. J Thorac Cardiovasc Surg 2015;149:831-8.e1-13.
25. Bergman H, Ferrucci L, Guralnik J, et al. Frailty: an emerging research and clinical paradigm--issues and controversies. J Gerontol A Biol Sci Med Sci 2007;62:731-7.
26. Mitnitski A, Rockwood K. The rate of aging: the rate of deficit accumulation does not change over the adult life span. Biogerontology 2016;17:199-204.
27. Gill TM, Allore HG, Gahbauer EA, et al. Change in disability after hospitalization or restricted activity in older persons. JAMA 2010;304:1919-28.
28. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002;50:889-96.
29. Cannon JA, McMurray JJ, Quinn TJ. 'Hearts and minds': association, causation and implication of cognitive impairment in heart failure. Alzheimers Res Ther 2015;7:22.
30. Vaccarino V, Koch CG. Long-term benefits of coronary bypass surgery: are the gains for women less than for men? J Thorac Cardiovasc Surg 2003;126:1707-11.

Cite this article as: Davierwala PM, Mohr FW. Myocardial revascularization: do age and sex matter? J Thorac Dis 2016;8(10):E1244-E1248. doi: 10.21037/jtd.2016.10.45

