

Residual angina in female patients after coronary revascularization

Birgit Vogel^{a,1}, Ridhima Goel^{a,1}, Vijay Kunadian^b, Deborah N. Kalkman^{a,c}, Alaide Chieffo^d, Yolande Appelman^c, Roxana Mehran^{a,*}

^a Icahn School of Medicine at Mount Sinai, New York, NY, USA

^b Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom

^c Department of Cardiology, Amsterdam Universities Medical Center, location VU University Medical Center, Amsterdam, the Netherlands

^d San Raffaele Hospital, Milan, Italy

ARTICLE INFO

Article history:

Received 5 October 2018

Received in revised form 4 January 2019

Accepted 10 January 2019

Available online 11 January 2019

Keywords:

Stable angina

Residual angina

Revascularization

Percutaneous coronary intervention

Coronary artery bypass grafting

Sex-related differences

ABSTRACT

Coronary revascularization, either percutaneous by stent implantation or surgical, has been established as the treatment of choice for patients with significant coronary stenosis. One of the main targets of coronary revascularization – especially in patients with stable disease – is to alleviate symptoms and thereby improve quality of life. Residual angina after successful coronary revascularization is not uncommon and indeed frustrating for the patient as much as for the treating physician. Several studies have shown worse outcomes in females with regard to post-revascularization morbidity and mortality in percutaneous as well as surgical coronary procedures. Although none of the studies has specifically looked at sex-related differences in residual angina after revascularization, some studies have found that female compared to male sex was a predictor of post-revascularization angina. This review article aims to summarize the results of these studies as well as to discuss the potential underlying mechanisms of these findings.

© 2019 Elsevier B.V. All rights reserved.

1. Introduction

In July 1768 William Heberden gave a presentation to the Royal College of Physicians in London describing a disease with “*strong and peculiar symptoms*” and aptly said that “*the seat of it, and the sense of strangling, and the anxiety with which it is attended, may make it not improperly be called angina pectoris*”. The initial report was derived from an analysis of 20 males and 1 female while further studies included 100 patients of which 3 were females [1,2]. Of note, Heberden at that time associated these symptoms with a cramp and/or ulcer, and assumed it to be some disorder of the breast [1]. Today, we know that the symptoms observed by Heberden are associated with heart disease and in the majority of cases with significant obstructive coronary artery stenosis, respectively. Chronic angina pectoris affects about half of the 16.5 million adults (≥ 20 y) in the United States that have ischemic heart disease; about 4.5 million of them are females [3]. Coronary revascularization, either percutaneous by stent implantation or surgical, has been established as the treatment of choice for patients with significant coronary stenosis. One of the main targets of coronary revascularization – especially in patients with stable disease – is to alleviate symptoms and thereby improve

quality of life. Residual angina after successful coronary revascularization is not uncommon and indeed frustrating for the patient as much as for the treating physician. In terms of post-revascularization symptoms, one should differentiate between the following [4,5]:

- “Recurrent Angina”: re-occurrence of chest pain due to myocardial ischemia in a patient treated with percutaneous or surgical coronary revascularization.
- “Residual Angina”: persistence of chest pain due to myocardial ischemia in a patient treated with percutaneous or surgical coronary revascularization, with no period of complete dissolution of symptoms.

This review focused on residual anginal symptoms. However, most reports have failed to make a distinction between the different types of post-revascularization angina. Therefore we looked at the presence of symptoms in the early phase after the index coronary revascularization procedures as the best possible way to assess for residual angina.

2. Prevalence of post-revascularization angina

For patients with coronary artery disease (CAD) to have persistent anginal symptoms despite having undergone coronary revascularization can be an exceedingly disappointing experience [4]. The prevalence of (early) post-revascularization symptoms is high with up to almost 40% reported by studies in patients after percutaneous coronary intervention (PCI) as well as coronary artery bypass grafting (CABG)

* Corresponding author at: The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, NY, 10029, USA.

E-mail address: Roxana.Mehran@m Mountsinai.org (R. Mehran).

¹ Birgit Vogel and Ridhima Goel contributed equally to this work.

(Table 1). However, documented rates vary significantly throughout the literature.

While interpreting the varying rates of post-revascularization angina among the different studies the following points should be taken into account: In addition to the different sample sizes, the definitions of angina used as well as the baseline risk of the different study populations vary significantly. Furthermore, many of the studies reporting post-PCI symptoms have included patients who were treated with earlier used techniques such as either balloon angioplasty, implantation of bare-metal stents (BMS) or the first generation drug eluting stents (DES), which may have impacted respective outcomes [6–9]. Temporal trends towards improved outcomes and lower risk of post-PCI angina may not only be due to the development of newer devices but also owing to the increased use of anti-anginal medication [10]. Also of note is the fact that the incidence of CABG has been decreasing in the past decade, which resulted in fewer contemporary studies in CABG patients. For this review most importantly, however, females were under-represented in all of these studies with the majority of subjects being Caucasian males.

Several studies have shown worse outcomes in females patients with regard to post-revascularization morbidity and mortality in percutaneous as well as surgical coronary procedures [11–13]. More specifically, an analysis of 368,492 patients from the British Cardiovascular Intervention Society (BCIS) database and 89,769 patients from the

Swedish Coronary Angiography and Angioplasty Registry (SCAAR) has identified female gender as an independent predictor of all-cause mortality at 30 days [14]. However, no study has specifically looked at sex-related differences in residual angina after coronary revascularization. Nevertheless, at least some studies have found that female sex was a predictor of post-revascularization angina.

2.1. Female sex as independent predictor of post-revascularization angina

2.1.1. Post PCI

Fanaroff et al. enrolled 10,870 patients as part of the TRANSLATE-ACS study, 3015 (27.7%) of those were females [15]. All patients were treated with PCI for myocardial infarction. Of the total population, 29.3% reported anginal symptoms at 6 weeks. Of these, 20.6% had daily/weekly angina. Patients with angina were more likely female compared with patients without angina. In a multivariate analysis female sex was shown to be an independent predictor of 6-week post-PCI angina [Odds ratio (OR) 1.41, 95% confidence interval (CI) 1.28–1.55; $p < 0.001$]. Venkitachalam et al. used the National Heart, Lung and Blood Institute-sponsored Dynamic Registry study database that enrolled 8879 patients in 5 “waves” between 1997 and 2006 to study the temporal trends in post-PCI angina [10]. Of the total population 22.0% received the initial PCI due to stable angina. In addition to a decrease of post-PCI angina over the years, also this study identified female sex as an independent predictor of post-

Table 1
Angina prevalence in patients after revascularization at short-term follow-up.

PCI studies								
SR #	Author	Study years	Patient population	Female (% of total)	Readmission/ total sample size	Follow up time	Outcome	Event rate (Percentage)
1.	Kwok et al. [67]	2013–14	All-comer PCI	32%	77,982/833,344	1 month	Coronary artery disease including angina	31.6% of cardiac readmissions (4.1% ^b)
2.	Tripathi et al. [68]	2013	Acute MI 58%	32.2%	24,889/206,869	1 month	Angina/Chronic ischemic heart disease	15.7% of readmissions (12.0%)
3.	McNeely et al. [69]	2012 ^a	Elective PCI 24.6%	40.1%	23,428/152,140	1 month	Chest pain/angina	6.5% of readmissions (15.4%)
4.	Fanaroff et al. [15]	2010–12	PCI for myocardial infarction	27.7%	NA/10,870	6 weeks	Angina	29.3% of total
5.	Grodzinsky et al. [70]	2009–11	PCI for stable AP	25.3%	NA/1080	1 month	Residual angina	24.0% of total
6.	Wasfy et al. [71]	2007–11	Elective PCI 18.1% ^c	35.5% ^c	893/9288	1 month	Chest pain or other symptoms concerning for angina	38.1% of readmissions (9.6%)
7.	Yost et al. [72]	2007–10	Elective PCI 28.2%	33.3%	262/3255	1 month	Stable angina	1.5% of readmissions (8.0%)
8.	Abdallah et al. [49]	2005–10	Stable patients with MVD and DM	26.8%	NA/953	1 month	Angina	26.6% of total
9.	Hannan et al. [73]	2007	All comer PCI; Acute MI 17.3%	33% ^c	4969/40093	1 month	Chest pain	10.8% of unplanned readmissions (12.4%)
10.	Cohen et al. [74]	2005–07	Stable patients with LM or MVD	23.6%	NA/903	1 month	Angina	35.6% of total
11.	Meadows et al. [75]	2006	Acute coronary syndrome	22.6%	555/6687	1 month	Chest pain	9.2% of CV-related readmissions (8.2%)
12.	Curtis et al. [76]	2005	All-comer PCI	42.0% ^b	45,964/315,241	1 month	Chest pain	6.7% of readmissions (14.6%)
CABG studies								
SR #	Author	Study years	Female (% of total)	Sample size	Follow up time	Outcome	Event rate (Percentage)	
1.	Lancey et al. [77]	2007–11	27.5%	4861	1 month	Myocardial infarction and/or recurrent angina	4.9% of readmissions (9.2%)	
2.	Price et al. [78]	2006–11	23%	1205	1 month	Recurrent myocardial ischemia/infarction	8.0% of readmissions (13.0%)	
3.	Li et al. [79]	2009–10	25%	11,823	1 month	Angina pectoris and chest pain	4.9% of readmissions (13.2%)	
4.	Abdallah et al. [49]	2005–10	30.2%	935	1 month	Angina	24.9% of total	
5.	Fox et al. [80]	2005–09	25.5%	63,911	1 month	Chest pain	6.9% of hospital-based acute care (readmission + ED visits; 23.9%)	
6.	Cohen et al. [74]	2005–07	21.1%	897	1 month	Angina	38.4% of total	
7.	Hannan et al. [81]	2005–07	26.5% ^c	30,953	1 month	Angina/chest pain	4.7% of readmissions (16.5%)	
8.	Vaccarino et al. [21]	1999–2001	27.8%	1113	6 weeks	Angina	3.3% ^b of total	

AP; angina pectoris, CV; cardiovascular, NA; not available, PCI; percutaneous coronary intervention, MI; myocardial infarction, LM; Left main coronary artery, MVD; multivessel disease, DM; diabetes mellitus, ED; emergency department.

^a Only data for the most recent year of study enrollment (2012) was considered.

^b Calculated value.

^c Percentage of readmissions only.

PCI symptoms with a reported relative risk of 1.30 (95% CI 1.15–1.47, $p < 0.001$) compared with male sex. Of note, these results refer to one-year follow-ups and no differentiation between recurrent and residual angina was made. Similarly, a patient-pooled analysis of the TWENTE and DUTCH PEERS Trials ($N = 3202$; 27.7% females) reported 1- and 2-years prevalence of chest pain in patients after implantation of newer generation DES. Multivariate analysis demonstrated that female sex independently predicted clinically relevant chest pain during both daily activities and at minimum physical exertion/at rest [16]. Ben-Yehuda et al. did not provide short-term post-PCI outcomes either when they analyzed outcomes of 51,710 patients (22% stable angina) from a multi-payer database [17]. No distinction was made between recurrent and residual angina when authors reported that 30.4% of females versus 24.3% of males had chest pain at 1 year follow-up. Nevertheless, the study has also shown that post-PCI angina was associated with higher costs related to inpatient care, outpatient care and outpatient pharmacy services. Arnold et al. aimed to create a model to predict patients at high risk for post-revascularization symptoms [18]. Data from the Outcomes of PCI Study (OPS)/Personalized Risk Information Services Manager™ (PRISM) study were used and angina follow-up evaluation was performed with the help of the Seattle Angina Questionnaire (SAQ) a 19-item self-administered questionnaire that measures five dimensions of health in patients with coronary artery disease [19,20]. At six months after PCI, 24% of the 2573 patients experienced angina in the preceding 4 weeks. Although patients with angina were more likely female, sex was not included in the final multivariable prediction model. The most important predictor was the severity of angina, as assessed by the SAQ angina frequency score, prior to PCI.

2.1.2. Post CABG

With regard to post-CABG symptoms, Vaccarino et al. conducted a prospective study of patients undergoing CABG to analyze sex-related differences in post-op recovery. Of the 1113 patients included in the final analysis, 309 were females (29.6%). It was documented that more females than males (6.0% vs. 2.3%; $p = 0.002$) reported angina 6 weeks after surgery, along with complaints of dyspnea, depression, lower physical function and other surgery-related side effects [21].

3. Possible causes of post-revascularization angina

Several factors can result in post-revascularization angina. One of the most important scenarios leading to residual angina is incomplete revascularization due to reasons such as small vessel disease or more diffuse coronary lesions. Other causes include stent 'stretch' pain, coronary spasm and microvascular disease. Early recurrent angina may result from early stent failure and thrombosis after PCI or bypass graft failure, technical surgical errors and poor target vessel runoff after CABG. Contributing factors include biological and pathophysiological components as well as disease presentation and treatment. With regard to these factors sex-related differences have been documented and may explain the increased risk and prevalence of post-revascularization angina in females compared to males (Fig. 1).

3.1. Factors contributing to the increased risk of post-revascularization angina in females compared to males

3.1.1. Underlying biological differences

Anatomically female hearts are smaller and lighter with smaller LV dimensions and narrower caliber of coronary arteries compared to male hearts [22–27]. Inherent differences in the physiology like cardiac muscle contractility as well as oxygen transportation and delivery to tissue due to lower hemoglobin levels in females have been described as having implications in CVD divergence between the sexes [28–30]. Smaller diameter of female coronary arteries may influence the post-CABG outcomes associated with higher risk of poor distal run-off with potential early graft occlusion due to graft thrombosis and kinking

[31,32]. Worse outcomes have also been documented after PCI of small (reference vessel diameter < 2.75 mm) versus larger vessel diameter with higher risk of restenosis [33].

Females are known to have a protective effect during pre-menopause with respect to CVD and it has been postulated that estrogen plays a significant role in this phenomenon [3,34]. Effects of estrogen on the arterial wall such as remodeling, vasodilation, platelet aggregation, thrombogenesis and lipid metabolism have been described as influencing the CVD manifestations in females in a positive manner [27,28,34,35]. Male androgens have a distinct effect on cardiovascular tissue in genetic male and genetic female bodies, as shown by studies where genetic female hearts undergo remodeling and progressive vessel enlargement when exposed to male androgen hormones [36,37]. Conditions such as periodic fluctuation of hormones during the menstrual cycle as well as disorders affecting the hypothalamic-pituitary-ovarian axis, and/or resulting in irregular menstrual cycles, (e.g. polycystic ovarian disease, hyperandrogenism or hypothalamic amenorrhea) are known to adversely affect CVD outcomes in females [38–40]. Also, early menopause increases the cardiovascular risk of a female significantly [41].

Due to the protective effect of estrogen, female compared to male patients develop coronary artery disease at an older age. Thus, females are more likely than men to present with age associated comorbidities such as anemia, dyslipidemia, hypertension, diabetes mellitus (DM), and congestive heart failure (CHF) and kidney dysfunction [26,42–45]. These risk factors are known to be associated with worse outcome in general, but some of them may be specifically linked with post-revascularization angina. Of particular mention is the association of DM with extensive and diffuse atherosclerosis and faster disease progression. The former is associated with increased difficulty for optimal revascularization, which may lead to increased risk of residual angina, while together with the latter, it may contribute to worse post-revascularization outcomes.

3.1.2. Sex-related differences in presentation, treatment and complications

CAD presents very heterogeneously in females with atypical symptoms being more common and precipitating factors of myocardial infarction (MI) being less frequent. This may result in delayed diagnosis and treatment initiation, both pre and post revascularization [46,47], and may also impact post-revascularization outcomes and symptoms. Several studies have documented that female patients are more likely to have increased time-to-hospital presentation, resulting in delayed diagnosis and treatment which in turn may lead to worse post-revascularization outcomes for these patients [13,48–50].

An analysis from the SWEDEHEART study suggested that female compared to male patients treated for MI were less likely to receive evidence-based treatment at discharge ($p < 0.001$ for β -blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, statins, and P2Y12 antagonists) [51]. In addition, it was documented that compliance with prescribed medication was lower in females compared to male patients [52]. With regard to PCI, another study documented that females compared to male patients were also less likely to be treated with DES, despite their better performance in smaller diameter vessels [45,53]. It was also documented that female patients are less likely to receive PCI via radial versus femoral approach compared to male patients [54–56]. This may further increase the generally higher risk of bleeding in females compared with males [57] and may, in addition, have impact on consecutive antithrombotic treatment.

In female subjects undergoing CABG, it has been noted that fewer females receive internal mammary artery (IMA) grafts as compared to saphenous vein grafts (SVG) which are known to have worse outcomes with early graft failure. Sometimes the latter may occur as early as 48 h post-operative, leading to ongoing post-operative anginal pain [58]. However, also arterial grafts seem to have higher risk of occlusions in female compared to male patients [59]. In addition, total arterial revascularization can lead to spasm of the arteries in an early phase

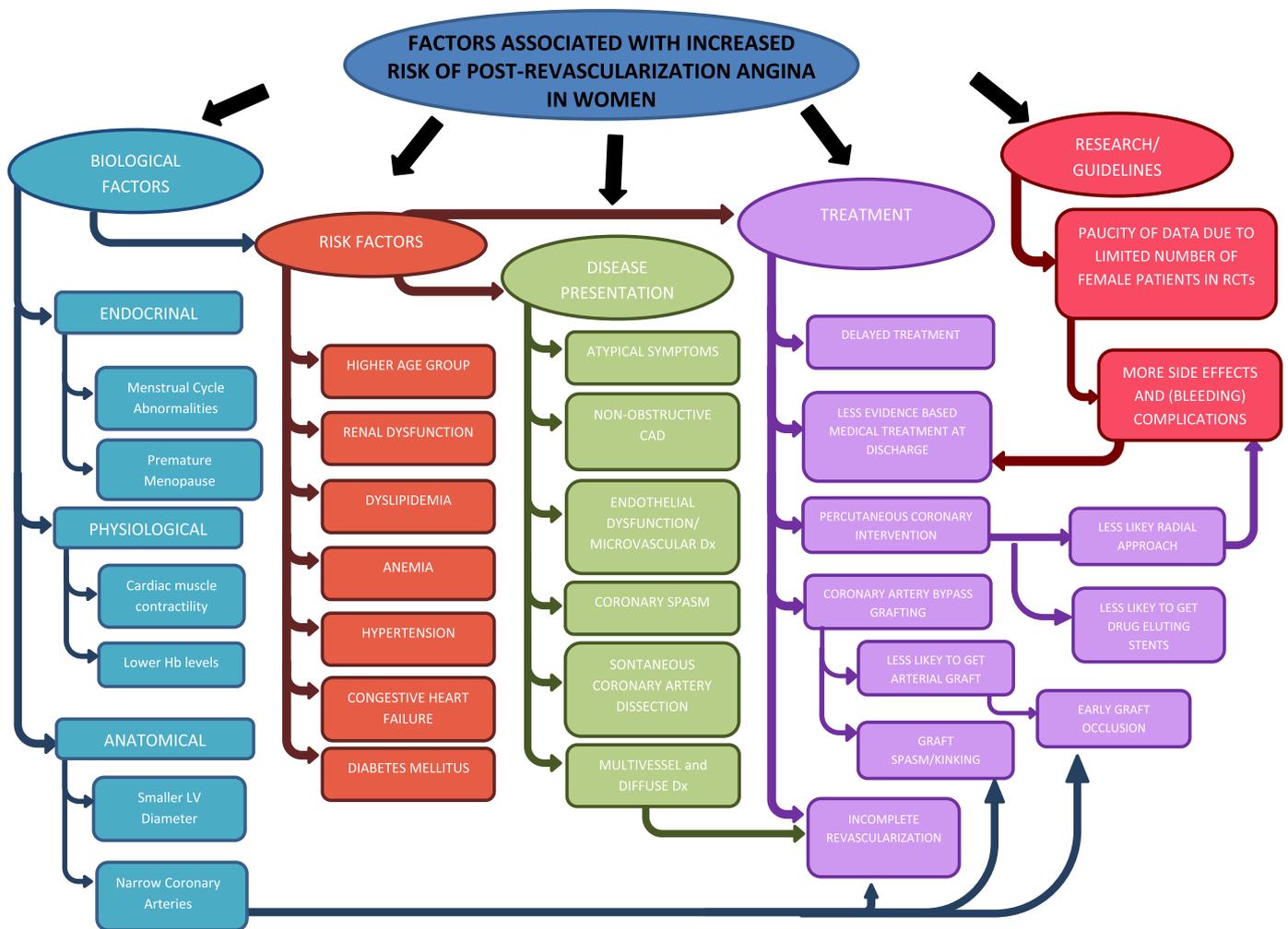


Fig. 1. Factors associated with increased risk of post-revascularization angina in females. Adjusted from Abbate et al. [4] and Sandoval et al. [82]. Dx; disease, Hb; hemoglobin, LV; left ventricle.

after CABG [60]. Postoperatively, it was shown that females have worse functional status and mental health compared with males [21].

3.1.3. Pathophysiology of angina pectoris

Studies have shown that plaque morphology differ between the sexes with almost 60% of females having no flow-limiting stenosis [61]. The underlying causes of angina pectoris in female patients include significant coronary stenosis, but also microvascular disease (MVD), coronary spasm and spontaneous coronary artery dissection (SCAD). Revascularization and stent placement are not appropriate treatment options for these conditions. Nevertheless, especially patients with SCAD are often treated with PCI and stenting and have high rates of recurrent symptoms and rehospitalization [62]. The special role of microvascular dysfunction, vascular inflammation, hormonal influences and coronary reactivity in ischemic heart disease in females has been identified in previous studies, but are still not very well understood [44,61]. Despite the fact that MVD is mostly discussed in the context of absent obstructive coronary disease, it may also be a factor contributing to increased risk of post-revascularization angina in patients treated for a significant stenosis artery disease [63]. However, the aforementioned pathophysiologic mechanisms as coronary spasm or MVD are not routinely investigated during angiography. As a consequence, it stays uncertain if they play an important role in recurrent angina.

3.1.4. Incomplete revascularization

One of the most important reasons for residual angina after PCI is incomplete revascularization. As mentioned previously, female patients tend to have smaller coronary arteries, which are more challenging for revascularization. Furthermore, females compared to males more likely present with diabetes, which is associated with more diffuse and multivessel coronary artery disease. Multivessel PCI or even CABG might be indicated, but increased age and higher prevalence of comorbidities in females vs. males may preclude these patients from undergoing complex coronary interventions or surgery, respectively [64,65].

3.1.5. Underrepresentation of females in cardiovascular clinical trials

Another important point to mention is the limited number of female patients included in clinical trials evaluating CVD outcomes [3,66]. Despite the fact that most evidence on antithrombotic and other medical treatment is derived from predominantly male populations, identical dosing regimens are applied to females compared to males. This may result in an increased occurrence of side effects, which may in turn explain the poorer compliance found in females compared with males as described above. In case of antithrombotic therapy, it may also contribute to the increased rate of bleeding in females compared to males and may explain the reluctance to prescribe guideline recommended therapy in females compared to males as discussed previously. Efforts by the

Food and Drug Administration (FDA) to include more females in cardiovascular trials and initiatives focusing on females may eventually result in better knowledge on optimal treatment in female patients. Once more evidence on sex-related pathophysiology of cardiovascular disease, impact of different therapies in female patients and rarer predominantly female diseases (e.g. SCAD) exists respective data can be included in international practice guidelines, which may then provide sex-specific recommendations. Until then physicians need to be extra cognizant and may think of alternative causes and treatment in women and especially young women with coronary artery disease and/or acute coronary syndrome in order to provide optimal care.

4. Conclusion

Evidence exists that female sex is a predictor of residual angina after coronary revascularization. Explanations for these findings include sex-related differences in coronary anatomy, pathophysiology as well as differences in presentation and treatment of patients with angina pectoris. Careful and comprehensive evaluation of symptoms is crucial to initiate timely and appropriate treatment. Further, studies on endothelial- and microvascular dysfunction, vascular inflammation, hormonal influences and coronary reactivity in ischemic heart disease in females are mandated.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

- [1] W. Heberden, Some account of a disorder in the breast, *Med. Trans. Coll. Physns.* 2 (59–67) (1772) (pp. 59–60, 63).
- [2] W. Heberden, *Commentaries on the History and Cure of Diseases*, T. Payne, 1802.
- [3] E.J. Benjamin, S.S. Virani, C.W. Callaway, A.M. Chamberlain, A.R. Chang, S. Cheng, S.E. Chiuve, M. Cushman, F.N. Delling, R. Deo, S.D. de Ferranti, J.F. Ferguson, M. Fornage, C. Gillespie, C.R. Isasi, M.C. Jiménez, L.C. Jordan, S.E. Judd, D. Lackland, J.H. Lichtman, L. Lisabeth, S. Liu, C.T. Longenecker, P.L. Lutsey, J.S. Mackey, D.B. Matchar, K. Matsushita, M.E. Mussolino, K. Nasir, M. O'Flaherty, L.P. Palaniappan, A. Pandey, D.K. Pandey, M.J. Reeves, M.D. Ritchey, C.J. Rodriguez, G.A. Roth, W.D. Rosamond, Sampson UKA, G.M. Satou, S.H. Shah, N.L. Spartano, D.L. Tirschwell, C.W. Tsao, J.H. Voeks, J.Z. Willey, J.T. Wilkins, J.H. Wu, H.M. Alger, S.S. Wong, P. Muntner, Heart disease and stroke statistics—2018 update: a report from the American Heart Association, *Circulation* 137 (2018) e67–e492.
- [4] A. Abbate, G.G.L. Biondi-Zoccai, P. Agostoni, M.J. Lipinski, G.W. Vetrovec, Recurrent angina after coronary revascularization: a clinical challenge, *Eur. Heart J.* 28 (2007) 1057–1065.
- [5] P.A. Lemos, A. Hoye, P.W. Serruys, Recurrent angina after revascularization: an emerging problem for the clinician, *Coron. Artery Dis.* 15 (Suppl. 1) (2004) S11–S15.
- [6] C. Varenhorst, M. Lindholm, G. Sarno, et al., Stent thrombosis rates the first year and beyond with new- and old-generation drug-eluting stents compared to bare metal stents, *Clin Res. Cardiol.* 107 (9) (2018) 816–823.
- [7] S. Bangalore, B. Toklu, N. Patel, F. Feit, G.W. Stone, Newer generation ultra-thin strut drug-eluting stents versus older second-generation thicker strut drug-eluting stents for coronary artery disease: a meta-analysis of randomized trials, *Circulation* 138 (2018) 2216–2226.
- [8] S.V. Rao, C.N. Hess, D. Dai, C.L. Green, E.D. Peterson, P.S. Douglas, Temporal trends in percutaneous coronary intervention outcomes among older patients in the United States, *Am. Heart J.* 166 (2013) 273–281.e4.
- [9] U. Landes, T. Bental, A. Levi, et al., Temporal trends in percutaneous coronary interventions thru the drug eluting stent era: Insights from 18,641 procedures performed over 12-year period, *Catheter. Cardiovasc. Interv.* (2017) 1–9.
- [10] L. Venkatchalam, K.E. Kip, S.R. Mulukutla, F. Selzer, W. Laskey, J. Slater, H.A. Cohen, R.L. Wilensky, D.O. Williams, O.C. Marroquin, K. Sutton-Tyrrell, C.H. Bunker, S.F. Kelsey, Temporal trends in patient-reported angina at 1 year after percutaneous coronary revascularization in the stent era, A Report From the National Heart, Lung, and Blood Institute–Sponsored 1997–2006 Dynamic Registry, 2, 2009, pp. 607–615.
- [11] J.H. Wasfy, K. Rosenfield, K. Zelevinsky, R. Sakhuja, A. Lovett, J.A. Spertus, N.J. Wimmer, L. Mauri, S.L. Normand, R.W. Yeh, A prediction model to identify patients at high risk for 30-day readmission after percutaneous coronary intervention, *Circ. Cardiovasc. Qual. Outcomes* 6 (2013) 429–435.
- [12] S.P. de Boer, J.W. Roos-Hesselink, M.A. van Leeuwen, M.J. Lenzen, R.J. van Geuns, E. Regar, N.M. van Mieghem, R. van Domburg, F. Zijlstra, P.W. Serruys, E. Boersma, Excess mortality in women compared to men after PCI in STEMI: an analysis of 11,931 patients during 2000–2009, *Int. J. Cardiol.* 176 (2014) 456–463.
- [13] A. Hassan, M. Chiasson, K. Buth, G. Hirsch, Women have worse long-term outcomes after coronary artery bypass grafting than men, *Can. J. Cardiol.* 21 (2005) 757–762.
- [14] V. Kunaadian, W. Qiu, B. Lagerqvist, N. Johnston, H. Sinclair, Y. Tan, P. Ludman, S. James, G. Sarno, National Institute for Cardiovascular Outcomes R, Swedish Coronary A, Angioplasty R, Gender differences in outcomes and predictors of all-cause mortality after percutaneous coronary intervention (data from United Kingdom and Sweden), *Am. J. Cardiol.* 119 (2017) 210–216.
- [15] A.C. Fanaroff, L.A. Kaltenbach, E.D. Peterson, C.N. Hess, D.J. Cohen, G.C. Fonarow, T.Y. Wang, Management of persistent angina after myocardial infarction treated with percutaneous coronary intervention: insights from the TRANSLATE-ACS study, *J. Am. Heart Assoc.* 6 (2017), e007007.
- [16] M.M. Kok, L.C. van der Heijden, H. Sen, P.W. Danse, M.M. Löwik, R.L. Anthonio, J. (Hans), W. Louwerenburg, F.H.A.F. de Man, G.C.M. Linssen, M.J.J. zerman, C.J.M. Doggen, A.H.E.M. Maas, R. Mehran, C. von Birgelen, Sex difference in chest pain after implantation of newer generation coronary drug-eluting stents: a patient-level pooled analysis from the TWENTE and DUTCH PEERS trials, *J. Am. Coll. Cardiol. Interv.* 9 (2016) 553–561.
- [17] O. Ben-Yehuda, D.S. Kazi, M. Bonafede, S.W. Wade, S.F. Machacz, L.A. Stephens, M.A. Hlatky, J.B. Hernandez, Angina and associated healthcare costs following percutaneous coronary intervention: a real-world analysis from a multi-payer database, *Catheter. Cardiovasc. Interv.* 88 (2016) 1017–1024.
- [18] S.V. Arnold, J.-S. Jang, F. Tang, G. Graham, D.J. Cohen, J.A. Spertus, Prediction of residual angina after percutaneous coronary intervention, *Eur. Heart J. Qual. Care Clin. Outcomes* 1 (2015) 23–30.
- [19] J.A. Spertus, J.A. Winder, T.A. Dewhurst, R.A. Deyo, J. Prodzinski, M. McDonell, S.D. Fihn, Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease, *J. Am. Coll. Cardiol.* 25 (1995) 333–341.
- [20] J.A. Spertus, J.A. Winder, T.A. Dewhurst, R.A. Deyo, S.D. Fihn, Monitoring the quality of life in patients with coronary artery disease, *Am. J. Cardiol.* 74 (1994) 1240–1244.
- [21] V. Vaccarino, Z.Q. Lin, S.V. Kasl, J.A. Mattera, S.A. Roumanis, J.L. Abramson, H.M. Krumholz, Gender differences in recovery after coronary artery bypass surgery, *J. Am. Coll. Cardiol.* 41 (2003) 307–314.
- [22] D. Levy, D.D. Savage, R.J. Garrison, K.M. Anderson, W.B. Kannel, W.P. Castelli, Echocardiographic criteria for left ventricular hypertrophy: the Framingham heart study, *Am. J. Cardiol.* 59 (1987) 956–960.
- [23] G. de Simone, R.B. Devereux, M.J. Roman, A. Ganau, S. Chien, M.H. Alderman, S. Atlas, J.H. Laragh, Gender differences in left ventricular anatomy, blood viscosity and volume regulatory hormones in normal adults, *Am. J. Cardiol.* 68 (1991) 1704–1708.
- [24] C.S. Roberts, W.C. Roberts, Cross-sectional area of the proximal portions of the three major epicardial coronary arteries in 98 necropsy patients with different coronary events. Relationship to heart weight, age and sex, *Circulation* 62 (1980) 953–959.
- [25] J.T. Dodge, B.G. Brown, E.L. Bolson, H.T. Dodge, Lumen diameter of normal human coronary arteries. Influence of age, sex, anatomic variation, and left ventricular hypertrophy or dilation, *Circulation* 86 (1992) 232–246.
- [26] A.J. Lansky, V.G. Ng, A. Maehara, G. Weisz, A. Lerman, G.S. Mintz, B. De Bruyne, N. Farhat, G. Niess, I. Jankovic, D. Lazar, K. Xu, M. Fahy, P.W. Serruys, G.W. Stone, Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes, *JACC Cardiovasc. Imaging* 5 (2012) S62–S72.
- [27] C.J. Pepine, R.A. Kerensky, C.R. Lambert, K.M. Smith, G.O. von Mering, G. Sopko, C.N. Bairey Merz, Some thoughts on the vasculopathy of women with ischemic heart disease, *J. Am. Coll. Cardiol.* 47 (2006) S30–S35.
- [28] S. Wingate, Cardiovascular anatomy and physiology in the female, *Crit. Care Nurs. Clin. North Am.* 9 (1997) 447–452.
- [29] M.-Y. Kim, S.H. Jee, J.E. Yun, S.J. Baek, D.-C. Lee, Hemoglobin concentration and risk of cardiovascular disease in Korean men and women - the Korean heart study, *J. Korean Med. Sci.* 28 (2013) 1316–1322.
- [30] J. Capasso, R. Remily, R. Smith, E. Sonnenlück, Sex differences in myocardial contractility in the rat, *Basic Res. Cardiol.* 78 (1983) 156–171.
- [31] P. Parang, R. Arora, Coronary vein graft disease: pathogenesis and prevention, *Can. J. Cardiol.* 25 (2009) e57–e62.
- [32] F.H. Edwards, J.S. Carey, F.L. Grover, J.W. Bero, R.S. Hartz, Impact of gender on coronary bypass operative mortality, *Ann. Thorac. Surg.* 66 (1998) 125–131.
- [33] G. Biondi-Zoccai, C. Moretti, A. Abbate, I. Sheiban, Percutaneous coronary intervention for small vessel coronary artery disease, *Cardiovasc. Revasc. Med.* 11 (2010) 189–198.
- [34] A.C. Boese, S.C. Kim, K.-J. Yin, J.-P. Lee, M.H. Hamblin, Sex differences in vascular physiology and pathophysiology: estrogen and androgen signaling in health and disease, *Am. J. Phys. Heart Circ. Phys.* 313 (2017) H524–H545.
- [35] R.H. Knopp, P. Paramsothy, B.M. Retzlaff, B. Fish, C. Walden, A. Dowdy, C. Tsunehara, K. Aikawa, M.C. Cheung, Sex differences in lipoprotein metabolism and dietary response: basis in hormonal differences and implications for cardiovascular disease, *Curr. Cardiol. Rep.* 8 (2006) 452–459.
- [36] N.A. Herity, S. Lo, D.P. Lee, M.R. Ward, S.D. Filardo, P.G. Yock, P.J. Fitzgerald, S.A. Hunt, A.C. Yeung, Effect of a change in gender on coronary arterial size. A longitudinal intravascular ultrasound study in transplanted hearts, 41 (2003) 1539–1546.
- [37] R.J. McCredie, J.A. McCrohon, L. Turner, K.A. Griffiths, D.J. Handelsman, D.S. Celermajer, Vascular reactivity is impaired in genetic females taking high-dose androgens, *J. Am. Coll. Cardiol.* 32 (1998) 1331–1335.
- [38] C.G. Solomon, F.B. Hu, A. Dunaif, J.E. Rich-Edwards, M.J. Stampfer, W.C. Willett, F.E. Speizer, J.E. Manson, Menstrual cycle irregularity and risk for future cardiovascular disease, *J. Clin. Endocrinol. Metab.* 87 (2002) 2013–2017.
- [39] B. Meczekalski, K. Katulski, A. Czyzyk, A. Podfigurna-Stopa, M. Maciejewska-Jeske, Functional hypothalamic amenorrhea and its influence on women's health, *J. Endocrinol. Invest.* 37 (2014) 1049–1056.
- [40] C. Maric-Bilkan, E.L. Gilbert, M.J. Ryan, Impact of ovarian function on cardiovascular health in women: focus on hypertension, *Int. J. Women's Health* 6 (2014) 131–139.

- [41] M. Wellons, P. Ouyang, P.J. Schreiner, D.M. Herrington, D. Vaidya, Early menopause predicts future coronary heart disease and stroke: the Multi-Ethnic Study of Atherosclerosis, *Menopause* 19 (2012) 1081–1087.
- [42] F. Nicolini, A. Vezzani, D. Fortuna, G.A. Contini, D. Pacini, D. Gabbieri, C. Zussa, R. De Palma, T. Gherli, Gender differences in outcomes following isolated coronary artery bypass grafting: long-term results, *J. Cardiothorac. Surg.* 11 (2016) 144.
- [43] G. Brandrup-Wognsen, H. Berggren, M. Hartford, A. Hjalmarson, T. Karlsson, J. Herlitz, Female sex is associated with increased mortality and morbidity early, but not late, after coronary artery bypass grafting, *Eur. Heart J.* 17 (1996) 1426–1431.
- [44] C.N. Bairey Merz, L.J. Shaw, S.E. Reis, V. Bittner, S.F. Kelsey, M. Olson, B.D. Johnson, C.J. Pepine, S. Mankad, B.L. Sharaf, W.J. Rogers, G.M. Pohost, A. Lerman, A.A. Quyyumi, G. Sopko, Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study: part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease, *J. Am. Coll. Cardiol.* 47 (2006) S21–S29.
- [45] E.-S. Shin, C.W. Lee, J.-M. Ahn, P.H. Lee, M. Chang, M.-J. Kim, S.-H. Yoon, D.-W. Park, S.-J. Kang, S.-W. Lee, Y.-H. Kim, S.-W. Park, S.-J. Park, Sex differences in left main coronary artery stenting: different characteristics but similar outcomes for women compared with men, *Int. J. Cardiol.* 253 (2018) 50–54.
- [46] S.M. Madonis, K.A. Skelding, M. Roberts, Management of acute coronary syndromes: special considerations in women, *Heart* 103 (2017) 1638–1646.
- [47] C.J. Pepine, J. Abrams, R.G. Marks, J.J. Morris, S.S. Scheidt, E. Handberg, T.I. The, Characteristics of a contemporary population with angina pectoris, *Am. J. Cardiol.* 74 (1994) 226–231.
- [48] G.S. Aldea, J.M. Gaudiani, O.M. Shapira, A.K. Jacobs, J. Weinberg, A.L. Cupples, H.L. Lazar, R.J. Shemin, Effect of gender on postoperative outcomes and hospital stays after coronary artery bypass grafting, *Ann. Thorac. Surg.* 67 (1999) 1097–1103.
- [49] M.S. Abdallah, K. Wang, E.A. Magnuson, J.A. Spertus, M.E. Farkouh, V. Fuster, D.J. Cohen, Quality of life after PCI vs. CABG among patients with diabetes and multivessel CAD: results from the FREEDOM trial, *JAMA* 310 (2013) 1581–1590.
- [50] M. Cohen, G.F. Gensini, F. Maritz, E.P. Gurfinkel, K. Huber, A. Timmerman, J. Santopinto, G. Corsini, P. Terrosu, F. Joulain, The role of gender and other factors as predictors of not receiving reperfusion therapy and of outcome in ST-segment elevation myocardial infarction, *J. Thromb. Thrombolysis* 19 (2005) 155–161.
- [51] B. Redfors, O. Angeras, T. Ramunddal, P. Petursson, I. Haraldsson, C. Dworeck, J. Odenstedt, D. Ioanescu, A. Ravn-Fischer, P. Wellin, H. Sjolund, L. Tokgozoglu, H. Tygesen, E. Frick, R. Roupe, P. Albertsson, E. Omerovic, Trends in gender differences in cardiac care and outcome after acute myocardial infarction in Western Sweden: a report from the Swedish Web System for Enhancement of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART), *J. Am. Heart Assoc.* 4 (2015).
- [52] I.M. Kronish, S. Ye, Adherence to cardiovascular medications: lessons learned and future directions, *Prog. Cardiovasc. Dis.* 55 (2013) 590–600.
- [53] M.A. Russ, C. Wackerl, U. Zeymer, M. Hochadel, S. Kerber, R. Zahn, B. Zrenner, H. Topp, V. Schächinger, M.A. Weber, for the A-SG, Gender based differences in drug eluting stent implantation - data from the German ALKK registry suggest underuse of DES in elderly women, *BMC Cardiovasc. Disord.* 17 (2017) 68.
- [54] D.N. Feldman, R.V. Swaminathan, L.A. Kaltenbach, D.V. Baklanov, L.K. Kim, S.C. Wong, R.M. Minutello, J.C. Messenger, I. Moussa, K.N. Garratt, R.N. Piana, W.B. Hillegass, M.G. Cohen, I.C. Gilchrist, S.V. Rao, Adoption of radial access and comparison of outcomes to femoral access in percutaneous coronary intervention: an updated report from the national cardiovascular data registry (2007–2012), *Circulation* 127 (2013) 2295–2306.
- [55] T. Kinnaird, J. Cockburn, S. Gallagher, A. Choudhury, A. Sirker, P. Ludman, M. de Belder, S. Copt, M. Mamas, A. de Belder, Temporal changes in radial access use, associates and outcomes in patients undergoing PCI using rotational atherectomy between 2007 and 2014: results from the British Cardiovascular Intervention Society national database, *Am. Heart J.* 198 (2018) 46–54.
- [56] J.A. Valle, L.A. Kaltenbach, S.M. Bradley, R.W. Yeh, S.V. Rao, H.S. Gurm, E.J. Armstrong, J.C. Messenger, S.W. Waldo, Variation in the adoption of transradial access for ST-segment elevation myocardial infarction: insights from the NCDR CathPCI Registry, *J. Am. Coll. Cardiol. Interv.* 10 (2017) 2242–2254.
- [57] G. Gargiulo, S. Ariotti, P. Vranckx, S. Leonardi, E. Frigoli, N. Ciociano, C. Tumscitz, F. Tomassini, P. Calabro, S. Garducci, G. Crimi, G. Ando, M. Ferrario, U. Limbruno, B. Cortese, P. Sganzerla, A. Lupi, F. Russo, R. Garbo, A. Ausiello, D. Zavalloni, G. Sardella, G. Esposito, A. Santarelli, S. Tresoldi, M.S. Nazzaro, A. Zingarelli, A.S. Petronio, S. Windecker, B.R. da Costa, M. Valgimigli, impact of sex on comparative outcomes of radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: data from the randomized MATRIX-access trial, *J. Am. Coll. Cardiol. Interv.* 11 (2018) 36–50.
- [58] P. Gukop, A. Momin, Early saphenous vein graft disease following coronary artery bypass grafting, *Surgery (Oxford)* 36 (2018) 83–85.
- [59] J.F. Sabik 3rd, B.W. Lytle, E.H. Blackstone, M. Khan, P.L. Houghtaling, D.M. Cosgrove, Does competitive flow reduce internal thoracic artery graft patency? *Ann. Thorac. Surg.* 76 (2003) 1490–1496 (discussion 1497).
- [60] J. Tatoulis, Total arterial coronary revascularization—patient selection, stenoses, conduits, targets, *Ann. Cardiothorac. Surg.* 2 (2013) 499–506.
- [61] N.R. Aggarwal, H.N. Patel, L.S. Mehta, R.M. Sanghani, G.P. Lundberg, S.J. Lewis, M.A. Mendelson, M.J. Wood, A.S. Volgman, J.H. Mieres, Sex differences in ischemic heart disease: advances, obstacles, and next steps, *Circ. Cardiovasc. Qual. Outcomes* 11 (2018), e004437.
- [62] A. Yip, J. Saw, Spontaneous coronary artery dissection—a review, *Cardiovasc. Diagn. Ther.* 5 (2015) 37–48.
- [63] D. Corcoran, R. Young, D. Adlam, A. McConnachie, K. Mangion, D. Ripley, D. Cairns, J. Brown, C. Bucciarelli-Ducci, A. Baumbach, R. Kharbanda, K.G. Oldroyd, G.P. McCann, J.P. Greenwood, C. Berry, Coronary microvascular dysfunction in patients with stable coronary artery disease: the CE-MARC 2 coronary physiology sub-study, *Int. J. Cardiol.* 266 (2018) 7–14.
- [64] T.L. Sedlak, A. Pu, E. Aymong, M. Gao, N. Khan, H. Quan, K.H. Humphries, Sex differences in coronary catheterization and revascularization following acute myocardial infarction: time trends from 1994 to 2003 in British Columbia, *Can. J. Cardiol.* 26 (2010) 360–364.
- [65] H. Jabagi, D.T. Tran, R. Hessian, D. Glineur, F.D. Rubens, Impact of gender on arterial revascularization strategies for coronary artery bypass grafting, *Ann. Thorac. Surg.* 105 (2018) 62–68.
- [66] A.H. Dougherty, Gender balance in cardiovascular research: importance to women's health, *Tex. Heart Inst. J.* 38 (2011) 148–150.
- [67] C.S. Kwok, S.V. Rao, J.E. Potts, E. Kontopantelis, M. Rashid, T. Kinnaird, N. Curzen, J. Nolan, R. Bagur, M.A. Mamas, Burden of 30-day readmissions after percutaneous coronary intervention in 833,344 patients in the United States: predictors, causes, and costs: insights from the Nationwide Readmission Database, *J. Am. Coll. Cardiol. Interv.* 11 (2018) 665–674.
- [68] A. Tripathi, J.D. Abbott, G.C. Fonarow, A.R. Khan, NGT Barry, S. Ikram, R. Coram, V. Mathew, A.J. Kirtane, B.K. Nallamothu, G.A. Hirsch, D.L. Bhatt, Thirty-day readmission rate and costs after percutaneous coronary intervention in the United States: a National Readmission Database analysis, *Circ. Cardiovasc. Interv.* 10 (2017).
- [69] C. McNeely, S. Markwell, C.M. Vassileva, Readmission after inpatient percutaneous coronary intervention in the Medicare population from 2000 to 2012, *Am. Heart J.* 179 (2016) 195–203.
- [70] A. Grodzinsky, M. Kosiborod, F. Tang, P.G. Jones, D.K. McGuire, J.A. Spertus, J.F. Beltrame, J.-S. Jang, A. Goyal, N.M. Butala, R.W. Yeh, S.V. Arnold, Residual angina after elective percutaneous coronary intervention in patients with diabetes mellitus, *Circ. Cardiovasc. Qual. Outcomes* 10 (2017).
- [71] J.H. Wasfy, J.B. Strom, C. O'Brien, A.H. Zai, J. Luttrell, K.F. Kennedy, J.A. Spertus, K. Zelevinsky, S.-L.T. Normand, L. Mauri, R.W. Yeh, Causes of short-term readmission after percutaneous coronary intervention, *Circ. Cardiovasc. Interv.* 7 (2014) 97–103.
- [72] G.W. Yost, S.L. Puher, J. Graham, T.D. Scott, K.A. Skelding, P.B. Berger, J.C. Blankenship, Readmission in the 30 days after percutaneous coronary intervention, *J. Am. Coll. Cardiol. Interv.* 6 (2013) 237–244.
- [73] E.L. Hannan, Y. Zhong, H. Krumholz, G. Walford, D.R. Holmes, N.J. Stamato, A.K. Jacobs, F.J. Venditti, S. Sharma, S.B. King, 30-day readmission for patients undergoing percutaneous coronary interventions in New York state, *J. Am. Coll. Cardiol. Interv.* 4 (2011) 1335–1342.
- [74] D.J. Cohen, B. Van Hout, P.W. Serruys, F.W. Mohr, C. Macaya, P. Den Heijer, M. Vrakking, K. Wang, E.M. Mahoney, S. Audi, Quality of life after PCI with drug-eluting stents or coronary-artery bypass surgery, *N. Engl. J. Med.* 364 (2011) 1016–1026.
- [75] E.S. Meadows, J.P. Bae, A. Zagar, T. Sugihara, K. Ramaswamy, R. McCracken, D. Heiselman, Rehospitalization following percutaneous coronary intervention for commercially insured patients with acute coronary syndrome: a retrospective analysis, *BMC. Res. Notes* 5 (2012) 342.
- [76] J.P. Curtis, G. Schreiner, Y. Wang, J. Chen, J.A. Spertus, J.S. Rumsfeld, R.G. Brindis, H.M. Krumholz, All-cause readmission and repeat revascularization after percutaneous coronary intervention in a cohort of Medicare patients, *J. Am. Coll. Cardiol.* 54 (2009) 903–907.
- [77] R. Lancey, P. Kurlansky, M. Argenziano, M. Coady, R. Dunton, J. Greelesh, E. Nast, S.G. Robbins, M. Scribani, J. Tingley, Uniform standards do not apply to readmission following coronary artery bypass surgery: a multi-institutional study, *J. Thorac. Cardiovasc. Surg.* 149 (2015) 850–857. e1.
- [78] J.D. Price, J.L. Romeiser, J.M. Gnerre, A.L.W. Shroyer, T.K. Rosengart, Risk analysis for readmission after coronary artery bypass surgery: developing a strategy to reduce readmissions, *J. Am. Coll. Surg.* 216 (2013) 412–419.
- [79] Z. Li, E.J. Armstrong, J.P. Parker, B. Danielsen, P.S. Romano, Hospital variation in readmission after coronary artery bypass surgery in California, *Circ. Cardiovasc. Qual. Outcomes* 5 (2012) 729–737.
- [80] J.P. Fox, L.G. Suter, K. Wang, Y. Wang, H.M. Krumholz, J.S. Ross, Hospital-based, acute care use among patients within 30 days of discharge after coronary artery bypass surgery, *Ann. Thorac. Surg.* 96 (2013) 96–104.
- [81] E.L. Hannan, Y. Zhong, S.J. Lahey, A.T. Culliford, J.P. Gold, C.R. Smith, R.S. Higgins, D. Jordan, A. Wechsler, 30-day readmissions after coronary artery bypass graft surgery in New York State, *J. Am. Coll. Cardiol. Interv.* 4 (2011) 569–576.
- [82] Y. Sandoval, E.S. Briklakis, S. Garcia, Completeness of revascularization in multivessel coronary artery disease, *J. Thorac. Dis.* 8 (2016) E1493–E1496.