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Sex-related survival outcomes after unprotected left main percutaneous coronary intervention: evidence from the BIA-LM registry

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What's new?

Despite multiple randomized trials comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting in left main coronary artery (LMCA) disease, the impact of sex on long-term PCI outcomes appears to be insufficiently defined. In this single-center registry of LMCA PCI, men had significantly worse long-term survival than women after adjustment for clinical and procedural confounders. Higher mortality in men was particularly evident in subgroups with heart failure, multivessel disease, or those undergoing rotational atherectomy. These observations emphasize the need to consider sex-specific differences in risk stratification and management of LMCA disease and call for prospective studies to clarify the underlying biological and procedural mechanisms.

Abstract

Introduction: Sex-related differences in outcomes after left main coronary artery (LMCA) percutaneous coronary intervention (PCI) remain incompletely understood, particularly in real-world settings.

Objectives: This study evaluated the impact of sex assigned at birth on long-term clinical outcomes after LMCA PCI in the largest single-center registry in Poland.

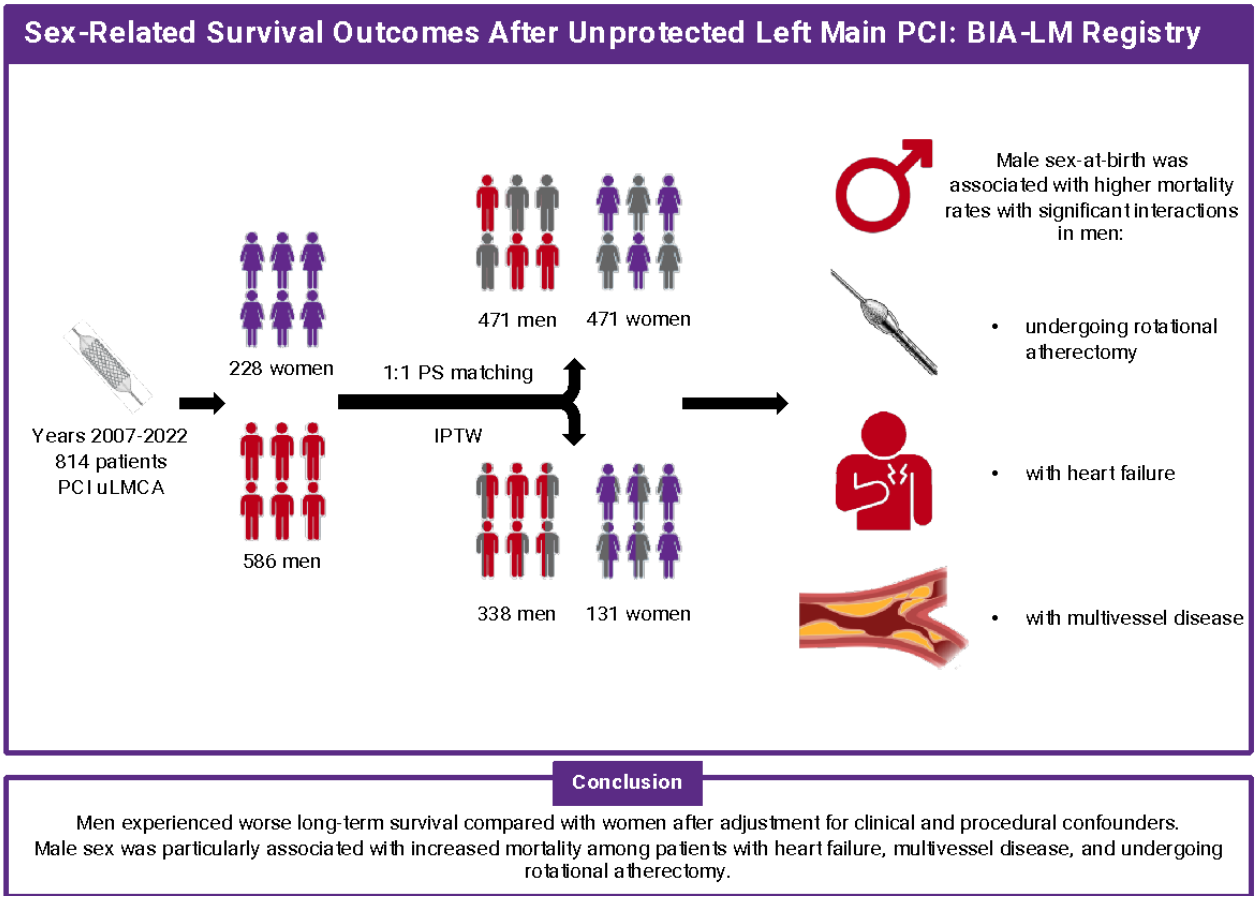
Patients and methods: We retrospectively analyzed 998 patients who underwent LMCA PCI between 2007 and 2022. The endpoint was 5-year all-cause mortality. Survival analyses were performed in the overall cohort and after propensity score matching (PSM) and inverse probability of treatment weighting (IPTW).

Results: The final cohort included 814 patients, of whom 228 (28%) were women. In the overall population, there was no difference in 5-year mortality between men and women (HR 1.31, 95% CI 0.99–1.73; $P = 0.06$). PSM resulted in 471 pairs, and IPTW generated a weighted cohort of 469 patients (131 [28%] women). After PSM, men had significantly higher mortality (HR 1.64, 95% CI 1.28–2.11; $P <0.001$), consistent with IPTW analysis (HR 1.71, 95% CI 1.04–2.83; $P = 0.04$). Exploratory subgroup analyses demonstrated higher mortality among men with heart failure (HR 2.25, 95% CI 1.66–3.04; $P = 0.002$), undergoing rotational atherectomy (HR 4.15, 95% CI 2.25–7.65; $P <0.001$), and treated for ≥2 lesions (HR 2.02, 95% CI 1.44–2.83; $P <0.001$).

Conclusions: Men experienced worse long-term survival than women after adjustment for clinical and procedural confounders. Mortality risk was higher among men with heart failure, multivessel disease, and those undergoing rotational atherectomy, highlighting the importance of considering sex-based differences in LMCA management.

Key words

coronary artery disease, left main, percutaneous coronary intervention, registry, special populations



Graphical abstract

Introduction

Ischemic heart disease (IHD) constitutes a major cause of death worldwide and remains the leading determinant of mortality among women [1,2]. Clinical manifestation of IHD typically occurs approximately a decade later in women than in men, a delay partly linked to hormonal factors and the potentially protective effects of estrogen, though evidence remains inconclusive. Conversely, the marked increase in cardiovascular risk observed after menopause is well established. Women are also exposed to sex-specific cardiovascular risk factors, including early

menarche, preterm delivery, pre-eclampsia, and gestational diabetes mellitus [1,3]. Furthermore, they more often present with atypical features such as dyspnea or fatigue, potentially contributing to diagnostic delays [1,3-5]. Although biological mechanisms have long been emphasized in explaining sex-based disparities in cardiovascular care, growing evidence highlights the role of sociocultural determinants, including communication dynamics, psychosocial stress, and the patient-physician relationship [1,3].

The left main coronary artery (LMCA) represents one of the most critical anatomical sites in coronary artery disease (CAD). Historically, coronary artery bypass grafting (CABG) has been the gold standard for the treatment of LMCA disease, offering durable clinical outcomes. However, advances in percutaneous coronary intervention (PCI) have positioned PCI as a viable alternative in appropriately selected patients [2,6].

The anatomical and physiological differences associated with sex introduce further complexity to the decision on revascularization treatment [3]. This observation aligns with the growing emphasis in contemporary cardiovascular medicine on personalized clinical management, in which sex is increasingly recognized as an important determinant of therapeutic decision-making [7,8]. Notably, being a woman has been identified as an independent predictor of long-term mortality following PCI and has subsequently been incorporated into the SYNTAX II score, a validated clinical tool to guide revascularization strategies [9]. However, follow-up of landmark randomized trials, including EXCEL, FREEDOM, and BEST demonstrated that the treatment effect of PCI versus CABG on mortality over 3 to 8 years did not significantly differ between women and men [10], raising questions regarding the validity of sex as a prognostic determinant within the SYNTAX II model and the potential need for its reassessment.

Despite several randomized trials comparing PCI and CABG in patients with LMCA disease, the influence of sex on long-term outcomes after PCI remains insufficiently characterized. Furthermore, numerous studies have shown that women with CAD often experience worse

clinical outcomes than men. It is uncertain if similar disparities also apply to patients undergoing LMCA PCI. To address this important knowledge gap, we aimed to analyse data from the largest single-center registry of LMCA percutaneous revascularization procedures in Poland, focusing particularly on whether women experience an unfavourable long-term prognosis following PCI.

Patients and methods

Study population The design and study population of the BIA-LM Registry was described before [2,11]. In brief, out of the 998 patients undergoing LMCA PCI from December 27, 2007 to February 21, 2022, 814 patients with unprotected (i. e., with no prior history of CABG) LMCA stenosis were included. The study's flowchart is presented in Figure 1.

The BIA-LM Registry was approved by the Bioethics Committee of the Medical University of Białystok, Poland (approval no. APK.002.78.2022 obtained on 10.02.2022) and adheres to Helsinki Declaration as revised in 2013. The study is reported in accordance with the STROBE guidelines (Supplementary Table 1).

Definitions and outcome The diagnosis of co-morbidities was based on the anamnesis, previous reports, and ECGs performed during the hospitalization, as well as on concomitant treatment and laboratory tests for selected disease. Angiographic lesion characteristics were derived from procedural reports prepared by the interventional cardiologist performing the PCI. LM lesion location was categorized as ostial/shaft or distal bifurcation. Distal lesions were defined as those involving the bifurcation into the left anterior descending (LAD) and/or left circumflex (LCx) artery, including all Medina bifurcation patterns. In cases of uncertain lesion localization, angiograms were additionally reviewed by two investigators (E.J.D. and K.G.), which was required in 136 cases. List of all ICD-10 diagnostic codes and electronic health records search strategy is provided in Supplementary Methods.

All-cause mortality data was obtained for all of the patients from Center for Information Technology, Minister of Digital Affairs, Poland and is valid as for 13.06.2022. For statistical analysis, five-year observation time was selected. No imputation methods were used for missing values for baseline variables.

Statistical analysis Categorical baseline characteristics are presented as numbers (N) and percentages (%). Continuous variables were assessed for normality using Shapiro-Wilk test and reported as mean with standard deviation (SD) or median with interquartile range (IQR). Comparisons between groups were conducted using chi square test, Rao-Scott corrected chi square test, Fisher's test, Student's t-test or Wilcoxon rank-sum test when appropriate based on the data distribution. Interactions following principal component analysis (PCA) were assessed using Wald test.

To ensure reduction of bias and confounding, mortality analysis was performed in the overall population and following implementation of propensity score matching (PSM), inverse probability of treatment weighting (IPTW) and PCA. In the first step of PSM, out of the baseline and angiographical variables, we determined mortality predictors with LASSO Cox regression using 10-fold cross-validation with 100 lambda values. The optimal penalty parameter was selected based on the minimum mean cross-validated deviance. LASSO cross-validation plot is presented in Supplementary Figure 1. Secondly, multivariable Cox proportional hazard regression was performed and significant variables were included in the final model of one-to-one nearest neighbor matching with replacement (caliper of 0.2). As for IPTW, propensity scores were calculated using multiple logistic regression analysis using the variables provided in Supplementary Table 2. Weights were truncated on 1st and 99th centiles to avoid an over-dispersion and stabilized to reduce variability. The mean stabilized weight was 1.0 (0.36–5.57), indicating absence of extreme weights. Then, analysis included survival assessment using weighted univariate Cox proportional hazard regression model in the overall, PSM and IPTW

cohorts. Additional moderation effects and subgroup differences were examined in cohorts adjusted with PSM and IPTW. The proportional hazards assumption was formally tested using Schoenfeld residuals, while log-log survival plots were used as a complementary graphical assessment. Findings from LASSO cross-validation, along with graphical displays of Schoenfeld residuals and log–log survival plots, are shown in Supplementary Figures 1–8.

PCA was performed as an exploratory complementary analysis to summarize multiple correlated clinical variables into a small number of components reflecting overall clinical risk patterns. PCA was performed on 17 baseline and angiographical variables. Continuous and binary variables were standardised to z-scores prior to analysis. PCA was performed on the correlation matrix using unrotated principal components extraction. Eigenvalues, proportion of explained variance, and component loadings were examined to guide component retention. Based on Kaiser's criterion (eigenvalue >1.0) and clinical interpretability, the first three principal components (PC1–PC3) were retained a priori for further analyses. Component scores were calculated for each patient as linear combinations of the standardised original variables. The derived component scores were subsequently entered as continuous covariates into Cox proportional hazards models to evaluate their association with 5-year all-cause mortality, both independently and in conjunction with sex. Additional models included sex-component interaction terms, and sex-stratified Cox models were fitted as exploratory analyses.

Results are reported as hazard ratios (HR) with corresponding 95% confidence intervals (CI). For all analyses, the level of statistical significance was set at $P < 0.05$. All statistical analysis was performed using StataNow/SE versions 18.5 and 19.5 for Mac (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC.).

Results

Baseline characteristics The final unmatched cohort included 814 patients, of which 228 (28%) were women. Primary indication for PCI in both groups was chronic coronary syndrome (70.1%). In the overall population, women were significantly older (74 vs. 70 years old), more commonly suffered from hypertension, chronic kidney disease (CKD), while men had lower left ventricular ejection fraction, peripheral arterial disease (PAD), and history of previous stroke. Angiographical analysis showed that men had more severe LM stenosis, larger mean diameter of implanted stents and more often performed PCI of LM-LAD.

PSM resulted in 471 pairs, with median age of 70 and 72 years old in men and women, respectively. There was a reduction of imbalances in most of the baseline characteristics, although significant differences, defined as standardized mean difference (SMD) ≥0.2, regarding higher prevalence of PAD, COPD, and history of previous stroke remained. Angiographical data analysis showed higher rates of distal LM stenosis, more severe LM stenosis, two-stent PCI technique and LM-LAD stenting in men.

IPTW resulted in a weighted pseudo-population of 469 patients, of whom 131 (28%) were women. The reported IPTW sample size reflects the effective sample size (sum of stabilized weights), rounded to the nearest whole number. Baseline characteristics analysis showed excellent reduction in disparities with differences regarding only higher rates of PAD and previous stroke in men. As for angiographical data, there were no differences in distal LM narrowing between two groups, but men more frequently had more severe LM stenosis and underwent two-stent technique PCI and LM-LAD stenting.

After restricting to complete cases for the PCA variables, 459 patients remained, including 123 women (27%). Seventeen standardized variables entered the PCA. The first three principal components (PC) explained 14.86%, 9.85% and 8.09% of the variance, respectively (cumulative variance explained by PC1–PC3=32.80%; scree plot, full loadings and eigenvalues

are available in Supplementary Figure 9 and Supplementary Tables 3-6). PC1 represented a global clinical-risk phenotype combining age, multimorbidity and reduced EF, PC2 reflected a metabolic risk profile, and PC3 included anatomical and procedural characteristics.

Detailed information regarding baseline and procedural characteristics in overall and adjusted subgroups are available in Table 1 and Supplementary Table 7.

Mortality analysis In 5-years mortality analysis of the overall population, there was no significant difference in mortality between men and women (HR 1.31, 95% Cl 0.99-1.73, P = 0.06). After adjusting for baseline confounders using PSM, we found significantly higher mortality rates among men (HR 1.64, 95% Cl 1.28-2.11, P <0.001). Survival analysis following IPTW confirmed significantly worse outcomes in men (HR=1.71, 95% Cl 1.04-2.83, P = 0.04). In both PSM and IPTW populations 30-days mortality was higher in women, but the difference was not statistically significant (P = 0.36 and P = 0.47, respectively) based on Cox models restricted to the 30-day follow-up. A crossover of survival curves was observed at approximately 45 days. Cox proportional hazard assumption was not violated for all analyses (P = 0.30 for overall population, P = 0.51 for PSM, P = 0.38 for IPTW). Mortality curves and outcomes for all analyses are presented in Figure 2. Inclusion of distal LM location as a covariate in the outcome models showed results consistent with the primary analysis with higher 5-year mortality in men (Supplementary Figure 10).

Cox regression after PCA revealed significant influence of PC1 (HR 1.57 per 1-SD increase, 95% CI 1.39–1.76, P <0.001), whereas PC2 and PC3 were not independently associated with mortality. After model adjustment for PC1-PC3, the effect of sex remained not statistically significant (HR 1.57, 95% CI 0.99–2.48, P = 0.06. Interaction testing demonstrated no significant PC-by-sex interaction (P = 0.75), indicating similar prognostic patterns in women and men. When analyzed separately, PC1 remained a strong predictor of mortality in both subgroups. Among women, PC1 was associated with a 53% increase in mortality per 1-SD

increment (HR 1.53, 95% CI 1.14–2.06, $P = 0.004$), and among men, PC1 showed a comparable effect (HR 1.57, 95% CI 1.38–1.79, $P < 0.001$). Neither PC2 nor PC3 predicted mortality in either sex. Detailed results are presented in Supplementary Table 5.

Subgroup and interaction analyses Subgroup analyses performed in the PSM and IPTW cohorts showed consistent directional effects favouring women across most subgroups (Figure 3).

Formal interaction testing demonstrated a significant sex-by-heart failure interaction in both cohorts ($P_{interaction}=0.002$ in PSM and $P_{interaction}=0.01$ in IPTW). In the PSM cohort, additional significant interactions were observed for rotational atherectomy ($P_{interaction}=0.007$) and treatment of ≥2 lesions ($P_{interaction}=0.02$), indicating a differential effect of sex on mortality across these subgroups.

Forest plots showing outcomes in selected subgroups after PSM and IPTW are presented in Figure 3. In additional interaction analyses, significant sex interactions with distal lesion location and stenosis severity were observed in the PSM-adjusted model but not in the unadjusted and IPTW-weighted analysis (Supplementary Table 11).

Discussion

Our study, based on the largest single-center registry of percutaneous revascularization procedures for LMCA disease in Poland, offers novel insights into sex-based and comorbidity-related differences in outcomes following PCI. The key findings of this real-world cohort analysis include: (1) Prior to PSM, there was no difference in 5-year mortality between men and women. Following PSM, mortality was significantly higher in men. After IPTW adjustment, the association remained directionally consistent and was statistically significant. Importantly, the consistency of the sex effect across multiple analytical strategies strengthens the robustness of the observed association between male sex and worse long-term survival. (2)

A crossover in survival curves was observed approximately 45 days post-procedure, reflecting higher early mortality in women, although this difference did not reach statistical significance. (3) Subgroup and moderation analyses showed consistent directional trends toward better prognosis in women. (4) Among patients with HF, those treated with RA and with multivessel disease, men had worse outcomes than women.

While most contemporary therapies for CAD demonstrate efficacy across sexes, the foundational evidence largely originates from studies with underrepresentation of women. These disparities have drawn increasing attention from the cardiovascular community. The European Society of Cardiology (ESC) has emphasized the importance of integrating sex-informed approaches into cardiovascular diagnostics and management. Taken together, there is growing recognition that contemporary medicine must move beyond a "one-size-fits-all" paradigm toward more personalized approaches to care [7].

Sex-based survival differences Before adjustment, all-cause mortality did not differ between the two groups. However, after applying PSM, long-term mortality was significantly higher in men, and this association persisted also following IPTW. These findings contrast with those of the IRIS-MAIN registry, in which all-cause death was similar between women and men during long-term follow-up after PCI for LMCA [12]. In the MITO registry, propensity score adjustment also showed comparable rates of all-cause death between sexes [13]. Furthermore, the PRECOMBAT trial found no sex-related differences in the long-term risk of major adverse cardiac and cerebrovascular events at 10 years after revascularization for LMCA disease [14]. The SYNTAXES study revealed that women had a higher crude rate of all-cause mortality at 10 years following CABG or PCI revascularization compared with men, but being a woman was not an independent predictor of 10-year mortality after adjustment for baseline characteristics [10]. Notably, women comprised only around 25% of enrolled participants, which may have limited the ability to identify sex-related differences in outcomes.

In our cohort, women were older and more frequently presented with hypertension, consistent with previous large-scale trials [10,12]. Although SYNTAX scores were not assessed in our study, both the EXCEL and SYNTAXES trials demonstrated that women generally exhibited lower angiographic complexity compared with men, despite a higher prevalence of conventional cardiovascular risk factors [10,15]. The underlying mechanisms remain incompletely understood, but potential contributors include hormonal and genetic factors, as well as the size of the coronary vessels [10]. In our study, EuroSCORE II remained higher among women even after PSM and a similar pattern was observed in the PRECOMBAT cohort [14]. Conversely, men were more likely to present with PAD and a history of stroke. The higher prevalence of vascular comorbidities among men, likely reflects a greater baseline burden of systemic atherosclerosis and may partially contribute to their increased long-term mortality risk, as also indicated by PCA. Prior stroke has been associated with a higher risk of long-term cerebrovascular and cardiovascular events after PCI [16], while pooled analyses of randomized trials have shown that concomitant PAD is linked to increased adverse cardiovascular outcomes and mortality [17]. Another potential mechanism may relate to the higher prevalence of smoking among men. In a contemporary cohort of patients with ST-segment elevation myocardial infarction treated with primary PCI, smokers were more often male, and although unadjusted analyses suggested more favorable mid-term outcomes, adjustment for baseline characteristics identified smoking as an independent predictor of 36-month mortality [18]. Variation in the use and intensity of guideline-directed medical therapy may also contribute to sex-specific differences in long-term outcomes. Previous studies indicate that women with CAD are less likely to receive optimal pharmacological treatment, including suboptimal dosing of antithrombotic agents, and less frequently achieve target statin therapy despite similar cardiovascular benefit across sexes [3,4,8]. In our registry, no significant sex differences were observed in the use of potent P2Y12 inhibitors; however, detailed data on other medications

were not available, preventing a more comprehensive evaluation of potential treatment disparities.

In addition to clinical differences, we observed anatomical disparities between the sexes. Men more frequently presented with more severe LMCA stenosis, which may reflect a more advanced stage of coronary atherosclerosis. Distal LMCA involvement was the predominant lesion location in our cohort (~87%), consistent with previous LMCA PCI registries, and its distribution was similar between men and women in both the overall and IPTW-adjusted populations.

Taken together, these discrepancies may reflect heterogeneity in anatomical complexity and disease burden across cohorts; importantly, residual or unmeasured confounding cannot be excluded despite the use of multiple statistical adjustment strategies.

Periprocedural outcomes and early mortality Periprocedural mortality was numerically higher in women, although this difference did not reach statistical significance. The early separation of mortality curves followed by a crossover at approximately 45 days suggests that distinct mechanisms may underlie early versus late mortality after LMCA PCI. Although detailed data on procedural complications were not systematically captured in our registry, early competing hazards such as bleeding or vascular complications may contribute to early mortality differences between sexes. Similar trends were reported in the EXCEL trial, where women undergoing PCI experienced higher rates of periprocedural ischemic and bleeding complications [15], and in the BCIS national PCI registry [19], which demonstrated higher in-hospital mortality and major bleeding among women despite less complex coronary artery disease. Beyond baseline differences, the elevated bleeding risk in women may be partly explained by biological factors, including estrogen-mediated modulation. Post-PCI bleeding has been associated with a three- to ten-fold increase in both 30-day and 1-year mortality, as well as higher rates of myocardial infarction and stroke [20]. In our cohort, even after PSM,

stent diameters were larger in men. External studies have demonstrated that women generally present with smaller reference vessel diameters which complicate complex coronary interventions [3]. Importantly, the excess risk of complications in women persisted after adjustment for body surface area and nominal stent diameter, indicating that vessel size alone does not fully explain the observed disparities [20]. Collectively, these findings support the rationale for sex-tailored procedural strategies to optimise stent expansion and mitigate periprocedural risk.

Heart failure and rotational atherectomy In our study, among patients with HF and RA, worse outcomes were observed in men. The association between HF and adverse prognosis in men is consistent with prior evidence, including a comprehensive meta-analysis of 94 cohort studies, demonstrating lower rates of all-cause mortality, cardiovascular death, and HF-related hospitalizations in women compared with men [21].

Men are more likely to develop heart failure with reduced ejection fraction (HFrEF), whereas the prevalence of heart failure with preserved ejection fraction (HFpEF) appears higher in women [22]. This distinction may have prognostic implications: a Chinese cohort study found that HFrEF was associated with nearly double the 5-years mortality risk compared with HFpEF [23]. Furthermore, among patients with HFrEF, recent data from the Korean Acute Heart Failure Registry indicated that men had an independently higher risk of cardiovascular death, a pattern not observed in the HFpEF population [24]. Although our analysis did not differentiate between HFrEF and HFpEF, these phenotype-specific considerations may partly explain observed sex-related differences and warrant further investigation. Beyond HF, another domain in which men exhibited poorer outcomes in our cohort was RA. This observation diverges from some previous studies. For example, Ford et al. [25] reported a higher incidence of procedural complications in women undergoing RA, whereas adjusted overall long-term survival free of

major adverse cardiac events was comparable between sexes, underscoring the uncertainty regarding sex-specific prognostic implications in RA.

In our study, the worse outcomes in men may be attributable to greater lesion complexity, particularly a higher calcific burden, as further suggested by the observation of poorer outcomes among men with concomitant multivessel disease. Coronary calcification is more frequently observed in men and increases the technical difficulty of PCI. Extensive calcification can hinder device delivery and optimal stent deployment, potentially contributing to procedural complications [26].

Myocardial infarction and chronic kidney disease In our analysis, we observed similar outcomes in men with MI and those with CKD compared with women. Both subgroups are of significant clinical importance, as previous reports showed sex-based disparities in healthcare. For instance, elements contributing to worse outcomes among women with MI may include more diffuse symptom presentation, lower attribution to cardiac causes, and social responsibilities such as caregiving, which may collectively defer prompt care-seeking and treatment initiation [27].

Our findings align with prior evidence demonstrating that when PCI techniques are applied, sex does not independently predict adverse outcomes. In a cohort of patients with acute coronary syndrome undergoing PCI, unadjusted one-year mortality was higher among women; however, after multivariable adjustment, being a woman was not associated with increased risk of death or major adverse cardiovascular events within one year [28]. By contrast, a large registry-based analysis of MI prognosis has reported worse outcomes among women, both during hospitalization and at long-term follow-up [29]. A potential explanation may be longer delays from symptom onset to reperfusion in women with acute coronary syndromes, including both pre-hospital intervals related to later presentation to medical care, and in hospital waits driven by system-level factors [27,30].

Chronic kidney disease is a well-established cardiovascular risk factor. Despite its high prevalence among patients undergoing coronary angiography, individuals with CKD have been consistently excluded from or markedly under-represented in pivotal trials of revascularization and medical therapy for IHD. Seminal studies such as SYNTAX, which have shaped contemporary practice, exemplify this persistent evidence gap [31].

In our analysis, long-term survival did not differ between men and women with CKD, a finding consistent with prior work. Ndrepepa et al. [32] similarly showed, in a large cohort of patients undergoing PCI with up to 10 years of follow-up, that the adverse prognostic impact of CKD on all-cause mortality was comparable across sexes, with no evidence of a sex-specific interaction. Complementary data from the CAD-REF registry [33] further confirmed that sex was not an independent predictor of long-term mortality in patients with CAD and impaired renal function, with comparable survival observed between women and men across all CKD stages.

PCA interpretation PCA, which was as an exploratory complementary analysis, identified a dominant axis of clinical risk, reflecting multimorbidity and frailty, which was the strongest predictor of 5-year mortality and showed a comparable prognostic effect in women and men. The absence of significant PC-by-sex interactions indicates similar risk gradients across sexes. Importantly, inclusion of PCA components did not attenuate the sex effect observed in PSM and IPTW analyses, suggesting that differences in baseline clinical risk do not explain the residual sex-related mortality difference. This finding implies that other factors - such as anatomical, procedural, or biological sex-specific mechanisms not captured by PCA - may contribute to outcome disparities.

Overall, these supplemental results support the concept that while global clinical risk strongly determines prognosis, it does not fully account for sex-related differences in long-term outcomes following contemporary interventional management.

Strengths and limitations Main limitations of BIA-LM Registry were reported earlier [2,11] and are inherent to the observational design and nature of the study. The first and most important issue is related to the baseline differences between analyzed groups. However, in order to reduce bias, we performed three statistical methods - PSM, IPTW and PCA, which significantly reduced disparities and enhanced the value of our findings. Although these approaches are well-established, we are aware that unmeasured factors may still remain and influence results. It is important to acknowledge that this registry originates from a single, high-volume tertiary center, which supported reliable data, but caution is required when extrapolating the findings or comparing them with other studies. Moreover, the study period spans 2007-2022, during which substantial advancements in PCI techniques, stent technology, adjunctive pharmacotherapy, and intravascular imaging occurred. These temporal changes may have influenced procedural strategies and clinical outcomes and should be considered when interpreting the results. Selection of all-cause mortality as primary endpoint ensures robustness of findings and facilitates comparison with other registries. However, sex-at-birth is known to influence factors beyond mortality, such as vascular complications, which were not available for this analysis.

Moreover, data on certain clinical variables, including SYNTAX score, and medication adherence were unavailable, potentially affecting risk stratification and subgroup interpretation. In addition, although analyses stratified by heart failure, multivessel disease, and rotational atherectomy suggested potentially meaningful trends, these observations should be interpreted with caution as exploratory and hypothesis-generating. The study also did not provide information on the number of patients referred by the Heart Team to CABG, those who declined surgery, or those managed conservatively, including whether these pathways differed between women and men. While such data could provide additional context, the registry was designed

to assess long-term outcomes in patients who underwent PCI, rather than to evaluate sex-related differences in treatment selection.

Conclusions The analysis of the largest single-center LMCA PCI registry in Poland showed that after adjustment for confounders, men may have worse prognosis than women. Men were at particularly increased risk of mortality among patients with HF, multivessel disease and undergoing RA. Outcomes of this paper suggest the need for further consideration of sex-at-birth as one of the key factors during personalization of treatment and qualification for invasive treatment. Nevertheless, due to the observational nature of the study all causal inference must be drawn with caution.

Supplementary material Supplementary material is available at www.mp.pl/paim.

Article information

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Conflict of interest None declared.

AI statement Artificial intelligence was not used in preparation of this manuscript.

Data availability The data underlying this article will be shared on reasonable request to the corresponding author.

Consent Each patient hospitalized in The Medical University of Bialystok Clinical Hospital has consented to the use of data for research purposes aimed at evaluating the quality of provided services.

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Table 1 Baseline characteristics before and after propensity score matching and inverse probability of treatment weighting												
	Unmatched				Propensity score matching				Inverse probability of treatment weighting			
Variable	Men (586)	Women (228)	SMD (%)	P *P* value	Men (471)	Women (471)	SMD (%)	*P* value	Men (338)	Women (131)	SMD (%)	*P* value
Age, years	70 (62–79)	74 (66–80)	-31.4	0.001	70 (62–79)	72 (61–80)	-5.4	0.44	71 (62–79)	72 (62–80)	6.5	0.67
BMI, kg/m2	28 (25–31)	28 (25–32)	-15.7	0.09	28 (25–31)	27 (25–31)	5	0.45	28 (25–31)	27 (25–31)	-5.9	0.62
EuroSCORE II, %	1.8 (1.0–3.7)	2.4 (1.4–4.5)	-12.1	0.16	1.8 (1.1–3.8)	2.4 (1.5–4.2)	-13.7	0.046	2 (1–3)	2 (1–4)	-22.9	0.24
Ejection fraction, %	45 (34–55)	52 (40–58)	-48.7	<0.001	45 (33–55)	45 (34–55)	-1.7	0.81	49 (38–55)	48 (36–55)	-5.9	0.68
Myocardial infarction	167 (30.4%)	77 (36%)	-12	0.17	143 (30.4%)	155 (32.9%)	-5.4	0.40	101 (29.9%)	48 (36.5%)	-14	0.17
Hypertension	442 (83.2%)	190 (91.4%)	-24.7	0.009	391 (83.2%)	396 (84.1%)	-3.2	0.66	287 (84.9%)	109 (83.4%)	3.9	0.70
Heart failure	309 (59.6%)	108 (52.6%)	14.1	0.11	280 (59.6%)	299 (63.5%)	-7.9	0.22	189 (55.8%)	75 (57.0%)	-2.4	0.82
Hyperlipidemia	472 (90.9%)	193 (93.7%)	-10.7	0.25	428 (90.9%)	425 (90.2%)	2.4	0.74	308 (91.1%)	119 (90.7%)	1.4	0.89
Atrial fibrillation	133 (26.3%)	47 (21.7%)	10.8	0.23	124 (26.3%)	139 (29.5%)	-7.5	0.28	76 (22.6%)	28 (21.1%)	3.6	0.73
PAD	146 (29.6%)	39 (18.4%)	26.4	0.004	139 (29.6%)	77 (16.3%)	31.1	<0.001	96 (28.5%)	22 (16.9%)	27.8	0.01
COPD	50 (9.6%)	11 (3.4%)	25	0.01	45 (9.6%)	22 (4.7%)	20	0.004	26 (7.7%)	9 (7.2%)	1.8	0.86
CKD	161 (30.6%)	88 (42.3%)	-24.5	0.005	144 (30.6%)	143 (30.4%)	0.4	0.94	106 (31.2%)	45 (34.1%)	-6.2	0.55

Previous PCI	231 (42.8%)	88 (44%)	-2.5	0.78	200 (42.8%)	191 (40.6%)	2.3	0.73	154 (45.6%)	53 (40.3%)	10.7	0.31
Previous MI	235 (45.4%)	72 (38.3%)	14.4	0.11	209 (45.4%)	177 (37.6%)	13.1	0.049	152 (44.9%)	49 (37.1%)	15.8	0.13
Previous stroke	54 (12%)	8 (5.3%)	24.1	0.02	53 (12.0%)	26 (5.5%)	20.5	0.004	39 (11.9%)	4 (3.1%)	33.8	0.01
Isolated LM lesion	65 (12.4%)	27 (14.7%)	-6.8	0.48	48 (12.4%)	59 (12.5%)	-4.4	0.53	40 (11.8%)	16 (11.9%)	-0.5	0.96
Distal LM lesion	514 (87.7%)	199 (87.3%)	10.1	0.24	429 (91.1%)	402 (85.4%)	18.7	0.006	309 (91.3%)	115 (87.4%)	12.8	0.20
1-VD excl. LM	167 (34%)	56 (31.5%)	5.4	0.58	132 (34.0%)	126 (26.8%)	9.3	0.18	118 (34.8%)	44 (33.8%)	2.1	0.84
2-VD excl. LM	150 (32.2%)	69 (35.7%)	-7.3	0.46	125 (32.2%)	160 (34.0%)	-11.4	0.11	110 (32.6%)	46 (35.1%)	-5.2	0.62
3-VD excl. LM	108 (21.4%)	37 (18.2%)	8	0.42	83 (21.4%)	80 (17.0%)	6.4	0.36	70 (20.8%)	25 (19.2%)	4.1	0.70
Rotational atherectomy	74 (14.9%)	37 (19.4%)	-12.1	0.16	70 (14.9%)	92 (19.5%)	-12.4	0.06	40 (11.8%)	19 (14.5%)	-7.9	0.44
Intravascular imaging	235 (42%)	87 (42.3%)	-0.5	0.96	198 (42.0%)	174 (36.9%)	10.3	0.11	141 (41.6%)	50 (38.1%)	7	0.50
IABP	45 (5.1%)	9 (2.9%)	11.5	0.22	24 (5.1%)	23 (4.9%)	1.1	0.88	13 (4.0%)	5 (3.5%)	2.7	0.80
DES	502 (90.8%)	201 (94.9%)	-15.6	0.10	426 (90.8%)	429 (91.1%)	-1	0.89	305 (90.3%)	116 (88.3%)	6.5	0.53
Two-stent technique	109 (19.4%)	44 (17.9%)	3.9	0.66	91 (19.4%)	54 (11.5%)	20.4	0.001	66 (19.7%)	13 (10.2%)	26.9	0.01
Diameter of LM stent, mm	3.81 (0.39)	3.69 (0.43)	21	0.02	3.79 (0.38)	3.71 (0.43)	19.9	0.002	3.82 (0.38)	3.75 (0.43)	17.3	0.18

LM-LAD stenting	452 (80.8%)	147 (67.2%)	31.1	<0.001	378 (80.8%)	318 (67.5%)	30.5	<0.001	267 (79.7%)	85 (64.5%)	34.2	<0.001
FKBI	332 (59.5%)	123 (54.6%)	9.9	0.27	279 (59.5%)	254 (53.9%)	11.2	0.09	207 (61.7%)	73 (55.5%)	12.7	0.22
Treatment of another lesion	210 (37.4%)	76 (33.9%)	7.3	0.42	175 (37.4%)	165 (35.0%)	4.9	0.45	118 (35.1%)	44 (33.2%)	3.9	0.71
Potent P2Y12	84 (17.2%)	38 (20.4%)	-8.2	0.36	76 (17.2%)	80 (17.0%)	-2.4	0.71	61 (18.0%)	24 (18.4%)	-1	0.92
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DES, drug-eluting stent; FKBI, final kissing balloon inflation; IABP, intra-aortic balloon pump; LAD, left anterior descending; LM, left main; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SMD, standardized mean difference; VD, vessel disease												

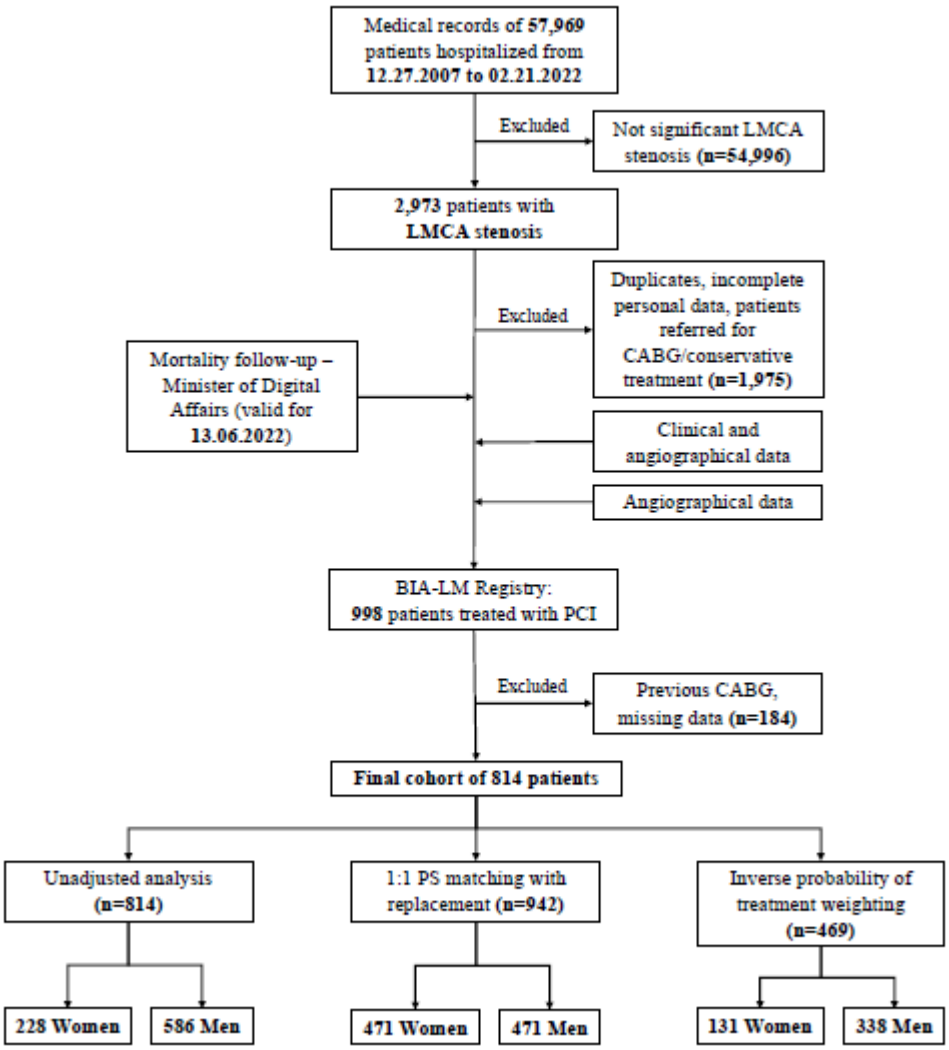


Figure 1 Flowchart of the study. The number of patients presented using inverse probability of treatment weighting reflects the size of the generated pseudo-population, rounded to the nearest whole number

Abbreviations: CABG, coronary artery bypass grafting; DM, diabetes mellitus; LMCA, left main coronary artery; PCI, percutaneous coronary intervention; PS, propensity score

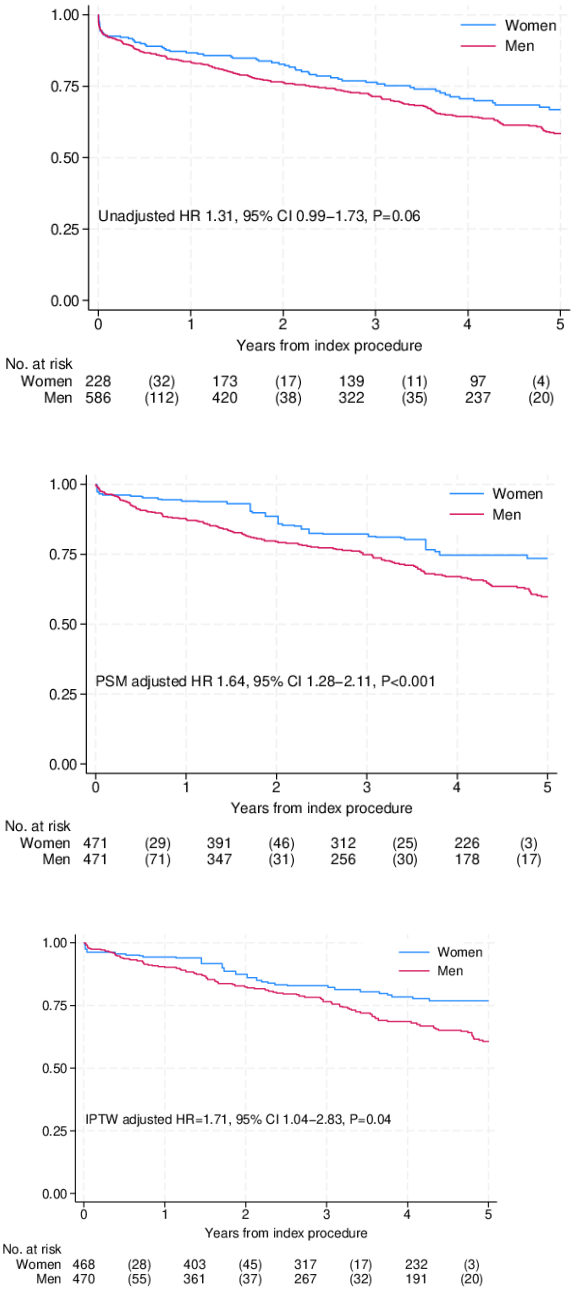
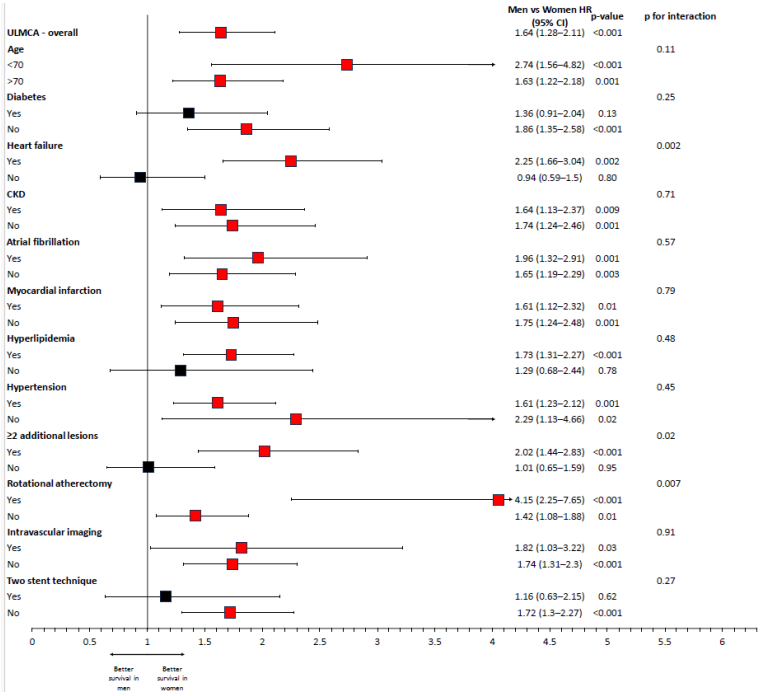


Figure 2 Kaplan-Meier curves showing five-year survival before (A), after propensity score matching (B) and after inverse probability of treatment weighting (C)[a]

a The number of patients reflects the size of the IPTW-generated pseudo-population, rounded to the nearest whole number

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; PSM, propensity score matching.



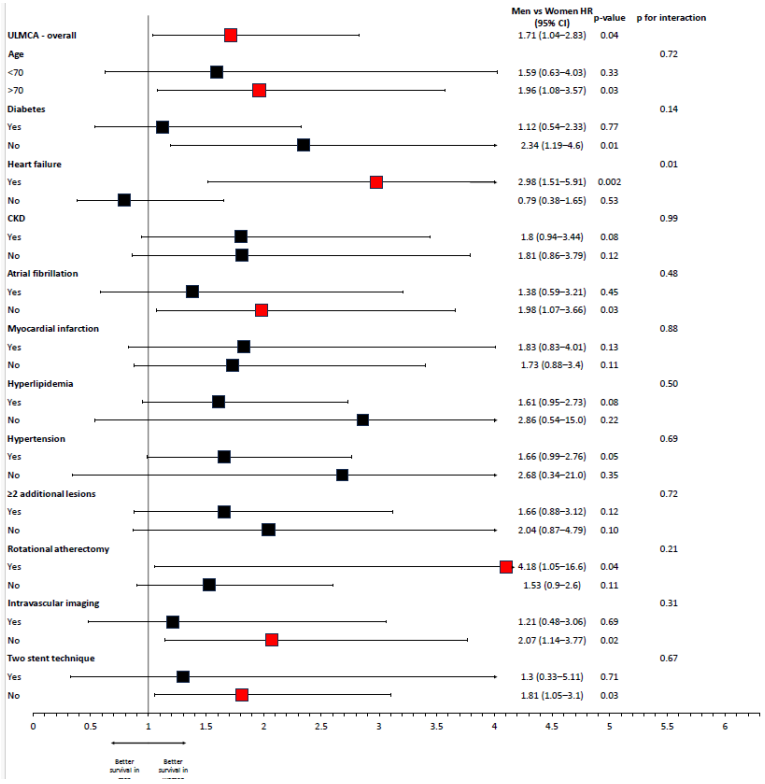


Figure 3 Forrest plot showing selected subgroup analysis after propensity score matching (A) and inverse probability of treatment weighting (B). Hazard ratios represent the effect of male sex compared to female on 5-year all-cause mortality within each subgroup

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; ULMCA, unprotected left main coronary artery

Short title: Sex differences in left main PCI