**Sex differences in High Risk but indicated Coronary Interventions (CHiP): national**

**report from British Cardiovascular Intervention Society Registry**

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**Abstract**

**Objective:** To assess sex-based differences in clinical outcomes following complex and high-risk but indicated percutaneous coronary intervention (CHiP).

**Background:** CHiP is increasingly common in contemporary PCI practice. Data on sex differences in the type of CHiP procedures undertaken or their associated clinical outcomes are limited.

**Methods:** Patients with stable coronary artery disease who underwent CHiP between 1st January 2006 and 31st December 2017 were included. All procedures were stratified by sex. Multivariate logistic regression analyses were performed to investigate the sex-specific odds ratios (aOR) of in-hospital outcomes.

**Results:** Out **of 424,290** **PCI procedures, 141,610 (33.37%) were CHiP procedures. Overall,** 32,129 (**23%) of CHiP were undertaken in females. Females were older than males (median 74.8 years vs 69.1 years). Males had a higher prevalence of previous MI (44.6% vs 35.6%) and previous PCI (40% vs 32.5%). The most common variable observed in female patients undergoing CHiP was age >80 (35.4%), followed by prior CABG (24.3%) and severe coronary calcification (22.6%). In contrast, the most common variable in male patients was prior CABG (36%), followed by CTO PCI (34.4%) and severe coronary calcification (22%).** Females had higher odds (aOR) for mortality [ aOR 1.78 95%CI (1.4, 2.2)], bleeding [aOR 1.99 95%CI (1.72, 3.2)], and major adverse cardiovascular and cerebral events [aOR 1.23 95%CI (1.09, 1.38)] compared to males.

**Conclusion:**  In this national analysis of **CHiP procedures over 12 years, there were significant sex differences in the type of CHiP procedures undertaken, with females at increased odds for mortality and in-hospital adverse outcomes.**

Key words (sex, complex PCI, high risk PCI, stable angina)

**Abbreviation list**

**CHiP, complex high-risk but indicated percutaneous coronary interventions**

**CAD, coronary artery disease**

**CABG, coronary artery bypass graft surgery**

**PCI, percutaneous coronary intervention**

**LMS, left main stem**

**BCIS, British Cardiovascular Intervention Society**

**NICOR,** National Institute of Cardiovascular Outcomes and Research

**MACCE,** major adverse cardiovascular and cerebral events

**Introduction**

At its inception, the success rate of percutaneous coronary interventions (PCI) was less than 60%, and at that time, all PCIs were considered high risk, and onsite cardiothoracic support was mandatory [1]. Since then, the evolution of interventional cardiology, with optimization of stent design, adjunct equipment, procedural techniques, and newer antiplatelet agents have led to complication rates lower than 1% for elective PCI[2, 3]. This progress has allowed a growing population of patients that are older and with higher comorbidities and more challenging coronary anatomy to benefit from more complex PCI[4, 5].

The term "complex PCI" may be used to refer to challenging coronary anatomy such as left main stenosis, ostial or calcified lesions, bifurcation disease, chronic total occlusions, and saphenous vein graft disease [6, 7]. 'Complex PCI' may also be used to refer to challenging comorbidities, which increases the risk that patients might develop complications, regardless of coronary anatomical complexity. These factors include advanced age, frailty, poor LV function [8], cancer[9], and renal failure [10]. Finally, the term 'complex PCI' can be used to describe the use of equipment such as haemodynamic support and rotational atherectomy.

Complex, High-risk but indicated PCI (CHiP) is an emerging concept with an evolving definition. The current consensus is that these high-risk PCI patients are defined as those with the combination of complex CAD, hemodynamic compromise ( LV support/ shock / severe LV dysfunction), and/or comorbidities such as advanced age, prior CABG, and chronic renal failure[7].

 Over the past few decades, studies looking at sex differences in outcomes following PCI have demonstrated worse outcomes in females than males [9, 11], which persist even at long term follow-up [12]. However, studies looking at whether such sex disparities are observed in CHiP are limited. A recent study that looked at sex-related outcomes in complex-PCI versus non-complex-PCI in a large-volume single tertiary-care center concluded that a sex-paradox exists [13]. Females tend to have less complex coronary artery disease yet paradoxically suffer from higher rates of adverse outcomes following complex PCI. However, this single-centre study's findings may not apply to patients undergoing complex PCI in other centers and cannot inform national practice. Furthermore, the authors did not systematically look at how the case-mix amongst complex PCI is different between sexes and how it has evolved.

We, therefore, study whether there are sex differences in the types of CHiP procedures undertaken in a national cohort of patients undergoing PCI and how these have evolved. We also report whether there are sex-related differences in outcomes following CHiP using data from the British Cardiovascular Intervention Society (BCIS) PCI registry.

**Methods**

*Data source*

Data were obtained and analyzed from the British Cardiovascular Intervention Society (BCIS) registry, which is managed by the National Institute of Cardiovascular Outcomes and Research (NICOR). BCIS registry collects data about clinical characteristics, important cardiovascular comorbidities, Interventional and pharmacological treatments, in-hospital procedural complications and mortality from over 95% PCI procedures undertaken in the National Healthcare System (NHS) in England and Wales. The BCIS registry data are collected prospectively, as part of a NICOR national audit initiative, and encrypted before transfer to central database services. Moreover, all data have section 251 approval of NHS Act 2006, which allows dataset use for audit purposes and medical research without seeking patients consent[14] . Therefore, ethical approval was not required for this study. Data are entered by interventional operators performing the procedures, with almost 100,000 procedures records are added into the BCIS registry every year.[15] The BCIS data entry is mandated as part of the professional revalidation. The BCIS data accuracy and quality has been previously ascertained[16].

*Study design and definitions*

We analyzed all patients who underwent PCI for stable angina in England and Wales between 1st January 2006 to 31st December 2017 in the BCIS database. Based on our previously published work, CHiP was defined as any procedure with at least one clinical high-risk feature, such as (age ≥ 80, previous history of CABG or chronic renal failure, or severely impaired left ventricular function) and/or one procedural (anatomical) high-risk factor such as (left main PCI, severe vessel calcification, chronic total occlusion PCI, or the need of LV support) [5, 17, 18]. All CHiP procedures were then stratified by sex into male or female groups.

Chronic renal failure was defined as chronic creatinine elevation of more than 200 umol/l, renal transplant history, or chronic dialysis, where all of which were predefined in the dataset. Severe LV impairment was defined as LV function with an estimated ejection fraction of 30% or less. Severe vessel calcification was defined as any PCI that required the use of any of the calcium modification devices (cutting balloon, rotational, or laser atherectomy devices). The need for LV support was defined as the use of IABP or Impella.

*Study endpoints*

 The primary outcome of interest was in-hospital all-cause mortality. The secondary outcomes included a) in-hospital MACCE defined as the cumulative incidence of in-hospital death, periprocedural MI or stroke b) and In-hospital major bleeding complication defined as clinically evident gastrointestinal bleeding, radiological evidence of intracranial bleed, retroperitoneal bleed/hematoma, any transfusion of blood or blood products, access site bleeding requiring intervention, or any access site complications requiring intervention or surgery. Periprocedural MI was defined as a composite of Q-wave myocardial infarction, non-Q-wave myocardial infarction, reinfarction, and reintervention (emergency PCI or CABG) defined within the BCIS registry. Access site complications defined as a composite of a false aneurysm, retroperitoneal hematoma, hemorrhage without hematoma, arterial dissection, which has been utilized in the previous studies from the BCIS registry[19] [20].

*Statistical analysis*

Data were expressed as median (interquartile range) for continuous data and whole numbers (percentages) for categorical data. Differences between the male CHiP and female CHiP groups were assessed using Pearson's Chi-squared test for categorical variables and the Kruskal Wallis test for continuous data. The information about missing data for each variable included in the study is reported in Supplementary Table 1. Multiple imputations with chained equations were used to impute missing data to create ten datasets, assuming that data were missing at random. Logistic regression for binary variables, multinomial for nominal variables, ordinal logistic regression for ordered and linear regression for continuous variables were used in the multiple imputation framework. The variables included in the model were age, BMI, history of dyslipidaemia, smoking history, previous acute myocardial infarction, previous CABG, previous ischaemic heart disease, previous percutaneous coronary intervention, previous cerebrovascular accident, diabetes mellitus, hypertension, renal failure, peripheral vascular disease, family history of coronary artery disease, clopidogrel, vascular access, left main PCI, Intra-aortic balloon support, number of treated lesions, rotational atherectomy, and number of stents used. All the subsequent analyses were performed on the imputed dataset, and results were pooled using Rubin's rule[21]. Finally, multivariable logistic regression analyses were used to determine the adjusted odds ratios (aOR [95% confidence interval]) of outcomes between male and female CHiP groups. For cases where event rates were low, findings from the multivariate analysis were interpreted after evaluating the assumptions implied by the model against both data and prior information obtained from literature search [22]. Variables with extensive missing observations (>20% missing), for example the LV function variable, were also included in the multiple imputation models; it has been shown that multiple imputation frameworks are robust even when levels of missingness are extremely high, although they can offer some protection when data are missing not at random. [23][24, 25]. All models included the same variables as used in the multiple imputation framework.

**Results**

*Study Cohort*

**The final study cohort consisted of 141,610 (33.37%) CHiP procedures performed in England and Wales from January 2006 to December 2017 out of 424,290** PCI procedures undertaken for Stable CAD**. The process of patients' inclusion and exclusion for this analysis is presented in Figure 1. Figure 2 shows the absolute number of each CHiP factors stratified by sex. Temporal changes in CHiP cases prevalence are illustrated in Figure 3, where CHiP increased from 7,525 in 2006 to 13,722 in 2017. Overall,** 109,481 (77.3%) **CHiP cases were performed in males, and** 32,129 (22.7%) **were performed in females. Figure 3 also shows the percent changes over time in CHiP procedures in males and females per study year, with the percentage of CHiP procedures remaining stable in females throughout the study years.**

***Clinical characteristics***

 **Table1 details the sex-stratified CHiP risk factors, cardiovascular risk factors, pharmacology, and procedural characteristics of the cohort. The median age of the total cohort was 70.5 years of age (IQR 61.9 -79.6), and 26% of patients had diabetes. Higher percentage of females had weight below 60 (males:1.4% vs. females: 14.1%) and lower BMI readings (males: 28 (25.4-31.34); females: 27 (24.7-32). The three most common CHiP factors included prior history of CABG (33.4%), CTO PCI (33%), and age above 80 (23%).**

**Females were on average 5.7 years older than males (median age: females 74.8, males 69.1; P<0.001).** Among cardiovascular risk factors, hypertension was more prevalent in females than males (69 vs 64.4 % respectively, p<0.001) and females were more likely to be non-smokers (56 vs 37 % respectively, p<0.001). Males, compared to females, had a higher prevalence of previous history of myocardial infarction (MI) (44.6 vs 35.6 % respectively, P<0.001) and PCI (40 vs 32.5 % respectively, p<0.001) and had higher rates of moderately impaired (21.4 vs 17 % respectively, p<0.001) and severely impaired (10 vs 7 % respectively, p<0.001) LV function.

*CHiP Factors*

 **The three most common CHiP factors in females were age > 80 (35.4%), prior CABG (24.3%), and severe coronary calcification (21.6%). Whilst in males, they were prior CABG (36%), CTO PCI (34.4%) and severe coronary calcification (22%) (Table 1, Figure 3). M**ore females than males were 80 years of age or older (35.4 vs 19.2 % respectively, p<0.001); In contrast, males had a higher prevalence of prior CABG (36 vs 24.3% respectively, p<0.001), renal failure (11.7 vs 9% respectively, p<0.001), poor LV function (10 vs 7.3% respectively, p<0.001), and CTO-PCI (34.4 vs 21.1% respectively, p<0.001). Similar rates of LMS PCI and use of LV support were observed in the two groups**.**

Supplementary figure 2 shows temporal trends in each CHiP factor stratified by sex. Overall, there was a gradual increase in the absolute number of CHiP in patients aged 80 and above, previous CABG, severe vascular calcifications, chronic renal failure, and LMS PCI among females and males. However, the percentage of females in almost all CHiP procedures remain unchanged with the except of those cases with LMS PCI and CTO PCI. There was a gradual increase in percentage of females undergoing LMS PCI (2006: 10% vs. 2017: 15%; and a gradual decrease in percentage of cases undergoing PCI to a CTO vessel (2006: 42% vs. 2017; 29%.

*Procedural characteristics*

Differences in procedural characteristics were observed between the sexes. Females, compared to males, had higher rates of LAD PCI (44 vs 40 % respectively, p<0.001) and RCA PCI (38 % vs 35% respectively, p<0.001). Males, on the other hand, had higher rates of LCX (27 vs 22 % respectively, p<0.001) and graft PCI (10.4 vs 7 % respectively, p<0.001). There were no significant sex differences in LMS revascularisation rates (males, 11.7% vs females, 11.6%, p=0.694).

Moreover, females had less extensive coronary disease treated compared to males. More females had one lesion treated (65.9 vs 63.8 % respectively; p<0.001). In contrast, more males had two or more (35.6% vs 36.1% respectively) lesions treated (p<0.001). A greater proportion of females were treated with one stent used (44 vs 39.6 % respectively, p<0.001). Higher rates of rotational atherectomy therapy were utilized in females compared to males (10 vs 9 %, respectively; p<0.001), suggestive of more calcific lesions. The rates of laser atherectomy and cutting balloons did not differ between the sexes. Females, compared to males, had lower radial access rates (43 vs 46% respectively, p<0.001) and lower dual access site use (8 vs 9 %, p<0.001) during CHiP procedures. Finally, slightly higher IABP use rates in females were observed (0.6 vs 0.5 % respectively, p=0.027), although there was no statistical difference regarding Impella use between sexes.

*Clinical Outcomes*

 Table 2 shows the crude outcomes stratified by sex. Crude in-patient mortality, bleeding and MACCE were higher in females compared to males [Mortality: 0.45% vs. 0.25%, Bleeding: 1.42% vs. 0.63%, MACCE: 1.76% vs. 1.4% respectively; p>0.001 for all]. Following adjustments for differences in baseline characteristics, female sex was independently associated with higher risk of death (aOR 1.78 (1.4-2.2); p<0.001), bleeding (aOR 1.99 (1.72-2.30); p<0.001), and MACCE (aOR 1.23 (1.09-1.38); p<0.001) (Table 3). Age stratification of outcomes according to sex suggested again worse outcomes in females (Supplementary Table 2).

 Table 4 shows trends of crude outcomes amongst sexes according to study year (Group 1, 2006-2009; Group2, 2010-2013; Group3, 2014-2017). Interestingly, mortality trends for males have not changed over time and remained consistently lower than females, whereas in females’ trends show a gradual increase in mortality rates (males: 0.3 to 0.3% vs females: 0.4 to 0.5% (Group 1 to Group 3 respectively for both; p<0.001 for both). Bleeding rates, however, have declined in both sexes, with females consistently showing higher rates (males: 0.6 to 0.5% vs females:1.76% to 1.3% (Group 1 to Group3 respectively for both); p<0.001 for both). Also, a decreasing trend was observed among sexes in incident rates of MACCE rates (males: 1.7 to 2.1 % vs females:2.1% to 1.6% (Group 1 to Group3 respectively for both); p<0.001 for both

**Discussion**

In the current analysis of a national cohort of **141,610 CHiP procedures**, we show significant differences in the type of CHiP procedures undertaken between males and females, with significant sex differences in both baseline clinical characteristics and the type of coronary artery lesions treated. Females were older with less cardiovascular disease burden than males and were more likely to have PCI to a single lesion or vessel with a greater proportion treated with a single stent. The most common CHiP factor in females was age >80, whereas, in males, it was a history of prior CABG followed by PCI to a CTO lesion. Previous studies have shown evidence suggesting that the outcomes of females following PCI are worse than that of males [11, 12, 26]. As the number of CHiP procedures increases, there is growing interest in studying sex-related outcomes in this challenging cohort and ongoing efforts to develop models that predict high-risk procedures [27]. To the best of our knowledge, this is the first national study that has systematically examined sex differences in both the types of CHiP procedures undertaken in males and females and their outcomes in a real-world setting. Our study suggests the presence of sex paradox where females have favourable risk profile and less extensive coronary disease yet experienced worse mortality, major bleeding and MACCE outcomes that persisted even after adjustments for differences in baseline covariates.

The main CHiP factor in females was age >80, whereas, in males, it was a history of prior CABG or PCI for a CTO lesion. Studies have shown that comorbidity burden increases with age [11]. Moreover, the increased prevalence of risk factors for CAD, like HTN and family history of CAD in females coupled with the less complex coronary disease, has been shown in previous studies and is expected to have a favourable plaque characteristic[28, 29]. Also, females with CTO are more likely to be managed medically[30]. Prior registry data shows that females represent approximately 30% of all patients managed by PCI and 25-28% of stable angina PCI procedures, whereas females in CTO PCI registries range from 14-23%[31] [32, 33]. Older age that is generally accompanied by more comorbid conditions and the perception that females are at an increased risk of procedural complications may prevent some interventional cardiologists from offering CTO PCI in females. Similarly, the proportion of females with a prior history of CABG undergoing PCI is significantly lower than in males (36% vs 24%). This may relate to the fact that females are less likely to be offered CABG for multi-vessel coronary disease [34], which may relate to the fact that females present with CAD at an older age, with more comorbidities and their epicardial vessels, are smaller and may not be suitable for grafting[35]. Furthermore, there may be systemic bias around both offering females CABG[36], but also when they experience angina are more likely to be managed medically. For example, a recent study assessed the management of chest pain in ambulatory care found that although the same proportion of males and females present with cardiac chest pain, males were 2.5 times likely to be referred to a cardiologist (aOR 2.30; 95% CI, 1.30-3.78)[37]. Even after referral to a cardiologist, females remain less likely to be referred for invasive management (OR 0.59; 95% CI, 0.48 to 0.72) [38].

Temporal changes in the prevalence of each CHiP factor suggested a gradual increase in the absolute number of CHiP cases in most of the CHiP types among females and males. Nevertheless, the proportions of females in each CHiP type remained stable over time with the exception of LM PCI and CTO PCI. The observation that the proportion of females undergoing CTO PCI overtime has decreased is of interest, and suggests that females are perhaps more likely to bemanaged medically due to either age, comorbidities, and a higher perception of complications [39] [32]{Guo, 2019 #70}[31]. In contrast, trends of LMS PCI rates in the females showed a gradual increase. This may reflect that female patients are less likely to be offered cardiac surgery than male patients, and so may be more likely to be managed with PCI. Indeed, recent studies have shown similar outcomes following LM PCI between sexes. For example a study on 1026 patients underwent unprotected LMS PCI found that, after propensity score matching that MACCE [ [HR, 1.04 (95% CI, 0.68–1.61; p = 0.85)], all-cause death (HR, 0.96 (95% CI, 0.52–1.77); p = 0.89) or MI [HR, 0.84 (95% CI, 0.21–3.50; p = 0.84)] were not different among males and females[40].

 Comparing our findings with previous studies that have examined sex differences in outcomes following non-complex PCI, our analysis suggests that the increased risk of death in females (compared to males) was even higher than that seen with non-complex PCIs [26] [11]. Our study findings suggest that female sex is an independent predictor of mortality following CHiP, with an increased risk of in-hospital mortality of 80% even after adjustment for differences in baseline covariates with a 20% increase in the risk of MACCE, and a two-fold increase in the risk of bleeding complications. Several plausible explanations could account for these observed differences. Underutilization of bleeding avoidance strategies such as the radial approach as seen in the current analysis [41] may explain the increased risk of mortality and major bleeding. Despite the obvious benefits of radial access, there remains a lower uptake of this approach in females as evident in current and previously published studies [42, 43].

Previous literature suggests the underutilization of evidence-based medical therapies in females [44]. Females in this study were likely to be at higher risk for coronary perforation post PCI with risk factor such as age over 80 years, heavy coronary calcification and greater use of rotational atherectomy devices more prevalent [45]. Finally, females are more likely to have other comorbidities that are not captured by the BCIS registry and could be attributed to the observed worse outcomes such as frailty, heart failure, chronic obstructive pulmonary disease, connective tissue disorders and poorly controlled diabetes [46] [47] that are known to portend worse outcomes. This highlights the increased need to optimize the management of CHiP cases in females, focusing on strategies to improve early recognition and periprocedural care.

**Study strength and limitations**

This study provides the very first unselected, real-world insight into CHiP outcomes at a national level to the best of our knowledge. The BCIS database has an almost complete record of all cases performed in England and Wales. This study's sample size was large enough to give sufficient statistical power to determine a real difference in outcomes between them.

The study limitations include: first, given the nature of the retrospective analysis and lack of randomization, we cannot exclude possible unmeasured confounders in clinical and procedural characteristics between the groups, such as other potential confounders not recorded in this dataset, including anaemia, frailty, which is likely to be more prevalent in the females who were on average six years older than males. Secondly, there is always the risk of reporting and coding errors representing a potential bias, such as the underreporting of other comorbidities, with complications self-reported and no external validation. Also, although the incident of periprocedural MI is clearly defined in the BCIS dataset, there dataset fails to specify this diagnosis was based on which definition (for example the third or fourth universal MI definitions or SCAI). Finally, although it meets statistical significance due to large number of patients, many variables presented in the result section have small difference. The clinical significance of this small difference is unclear[48]. Furthermore, the study included only in-patients' outcomes; longer follow-ups of outcomes would provide a better and more complete assessment.

**Conclusion**

Our nationwide analysis has demonstrated differences in case-mix in the types of CHiP cases undertaken between Males and Females. Females tend to be older, less comorbid, and have less complex coronary disease treated. We report significant disparities in outcomes following CHiP between sexes, with females at greater risk of mortality, major bleeding episodes and MACCE compared to males. Optimization of periprocedural care, use of advanced technologies and evidence-based therapies could improve the observed outcomes in females.

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**Disclosures**

The authors have nothing to disclose.

Figure Legends

**Figure 1**: Flow diagram illustrating **the process of patients' inclusion and exclusion for the CHiP analysis**

**Figure 2:** Prevalence of CHiP factors in patients with stable angina, stratified by sex.

**Figure 3: Temporal changes in CHiP procedures prevalence in patient with stable angina and percent changes over time, stratified by sex**

Supplementary Figure 2

Temporal changes in prevalence of each CHiP factors among patients with stable angina and per cent change over time, stratified by sex.

**Visual Abstract:** Summary of key findings of the study



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