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Complex, high-risk but Indicated Percutaneous Coronary Interventions (CHiP) types, trends, and clinical outcomes

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Publications

Publications arising directly from this thesis:

1- Shamkhani W, Kinnaird T, Ludman P, Rashid M, Mamas MA. Sex differences in high-risk but indicated coronary interventions (CHiP): national report from British Cardiovascular Intervention Society Registry. Catheter Cardiovasc Interv. 2022;99:447-456.doi:10.1002/ccd.30081456

2- Shamkhani W, Kinnaird T, Wijeysundera HC, Ludman P, Rashid M, Mamas MA. Ethnicity in Complex High-Risk but Indicated Percutaneous Coronary Intervention Types and Outcomes. The American Journal of Cardiology 2022;175:26-37

3- Complex, High-risk but Indicated Percutaneous Coronary Interventions (CHiP) Types and Outcomes Among different Age Groups. An Insight From a National Registry . Warkaa Shamkhani, Muhammad Rashid, Mamas Mamas. Catheter Cardiovasc Interv. 2022 ; 100: 711-720 . doi.10.1002/ccd.30366.

4- Warkaa Shamkhani, Saadiq Moledina, Muhammad Rashid, Mamas A. Mamas. Complex High-risk Percutaneous Coronary Intervention Types, Trends, and Outcomes According to Vascular Access. Catheter Cardiovasc Interv. 2023 Nov;102(5):803-813.doi: 10.1002/ccd.30846.

5- Warkaa Shamkhani, Muhammad Rashid, Saadiq Moledina, Peter Ludman, Nick Curzen, Harindra C. Wijeysundera, Cindy L. Grines, Mamas A. Mamas. Complex High-risk Percutaneous Coronary Intervention Types, Trends, and Outcomes in

Non-surgical Centres. Canadian Journal of Cardiology (2024), doi: https://doi.org/10.1016/ j.cjca.2024.01.003.

Other publications

In addition to the above publications, there are other publications which I have led or contributed during the course of my MD:

1- Trends of sex differences in clinical outcomes after myocardial infarction in the United States. Andrija Matetic, Warkaa Shamkhani, Muhammad Rashid, Annabelle Santos Volgman, Harriette GC Van Spall, Thais Coutinho, Laxmi S. Mehta, Garima Sharma, Purvi Parwani , Mohamed Osama Mohamed, Mamas A. Mamas. CJC Open, 2021. 3(12, Supplement): p. S19-S27.

Presentations

1- Sex differences in High Risk but indicated Coronary Interventions (CHiP): national report from British Cardiovascular Intervention Society Registry. Warkaa Shamkhani, Tim Kinnard, Peter Ludman, Muhammad Rashid, Mamas A. Mamas. **Presented as moderated poster presentation at the ACC conference April 2022**; JACC

2- Is There Racial Differences in Complex High-risk but Indicated PCI (CHiP) Types and Their Outcomes?. Warkaa Shamkhani, Tim Kinnaird, Harindra C. Wijeysundera, Peter Ludman, Muhammad Rashid, Mamas A. Mamas. **Presented as poster presentation at the TCT conference Nov 2021**; TCT-323; JACC. 2021 Nov, 78 (19_Supplement_S) B131–B132

3- Complex, High-risk but Indicated Percutaneous Coronary Interventions (CHiP) Types and Outcomes Among different Age Groups. An Insight From a National Registry . Warkaa Shamkhani, Muhammad Rashid, Mamas Mamas. **Presented as moderated poster presentation at the ACC conference April 2022**; JACC

4- Complex High-risk Percutaneous Coronary Intervention Types, Trends, and Outcomes According to Vascular Access . Warkaa Shamkhani, Saadiq Moledina, Muhammad Rashid, Mamas A. Mamas. **Presented as moderate poster presentation at the ESC conference August 2022**.

5- Complex High-risk Percutaneous Coronary Intervention Types, Trends, and Outcomes in Non-surgical Centres. Warkaa Shamkhani, Muhammad Rashid, Saadiq Moledina, Peter Ludman, Nick Curzen, Harindra C. Wijeysundera, Cindy L. Grines, Mamas A. Mamas. **Presented as moderated poster presentation at the ACC conference March 2023.**

Abstract

Coronary artery disease (CAD) remains the leading cause of death worldwide. Medical therapy and lifestyle modifications are the first line of therapy to minimise symptoms and retard disease progression. An Invasive therapy in the form of percutaneous coronary intervention (PCI) usually offered when medical therapy fails to improve symptoms. [1] Developments in the field of interventional cardiology have introduced advances in stents, equipment, and techniques resulting in complication rates of less than 1% for elective PCI. [2, 3] This has enabled a growing elderly population who have heavier co-morbid burden and more challenging coronary anatomy to benefit from more complex PCI which is referred to as Complex, High-risk PCI (CHiP). Whilst disparities in clinical outcomes and practices in PCI in the general population are known among different groups defined by sex, ethnicity and age, there is little data in the CHiP population. In particular, there are limited data regarding the differences in types of CHiP procedures performed, patient baseline characteristics, risk profiles, and clinical outcomes among special populations, as outlined above, in contemporary practice. Furthermore, limited data is supporting whether there are advantages in utilising certain technological advances/strategies in CHiP such as access site choice or intracoronary imaging.

Consequently, this thesis was designed to determine whether there are differences in the baseline clinical and procedural characteristics, risk profile, trends, and clinical outcomes of CHiP undertaken to treat stable angina 1) among males and females 2) among different age groups and whether patients' age has an effect in receiving invasive therapy 3) among

different ethnic groups and how this has changed over time 4) according to the access approach utilised and what is the optimal access site practice to perform in a CHiP 5) and finally according the availability of on-site surgical support and whether this has a significant effect on clinical outcomes.

This thesis addresses the objectives in three parts. Part 1 pertains to results in Chapters 4, 5, and 6, which systematically examine the type of CHiPs, baseline characteristics, and clinical outcomes based on sex, different age groups, and ethnic background. Chapter 4 demonstrates the existence of a sex paradox, where females have a favourable risk profile and less complex CAD yet experience worse outcomes compared to males. Chapter 5 reveals that despite Black, Asian, and other Ethnic Minorities (BAME) being younger and having a worse cardiometabolic profile, their odds for adverse events post CHiP are similar to those of their white counterparts. Finally, Chapter 6 reveals that the number of CHiP procedures performed in the older age group has gradually increased over time, but age remains an independent risk factor for worse outcomes.

Part 2 pertains to results in Chapter 7, which examines the effect of certain procedural modalities/techniques on the outcomes of CHiPs and details the related differences in baseline characteristics and the changes in access site use over time. It concludes that radial access has become the most common access site used in CHiPs across all types of CHiP and that it is associated with better outcomes compared to CHiP performed via femoral access.

Finally, part 3 of the thesis pertains to results in Chapter 8, which examines CHiPs undertaken according to the type of hospital facility and highlights the important differences in the type of CHiP undertaken based on the presence or absence of on-site

surgical support. It concludes that, in selected cases, it is safe to perform CHiP in non-surgical centres.

Overall, this thesis provides compelling evidence of substantial variations in the types of CHiPs undertaken, as well as in the clinical and procedural characteristics, trends, and outcomes influenced by factors such as sex, ethnic backgrounds, and different age groups. Additionally, the study reveals that radial access has emerged as the prevailing approach in CHiPs, displaying superior outcomes in contrast to femoral access. Notably, performing CHiPs in non-surgical centres, in selected cases, does not exhibit any adverse impact on clinical outcomes as compared to CHiPs undertaken in surgical centres. The clinical implications of these findings, along with potential avenues for further research, are thoroughly examined and discussed.

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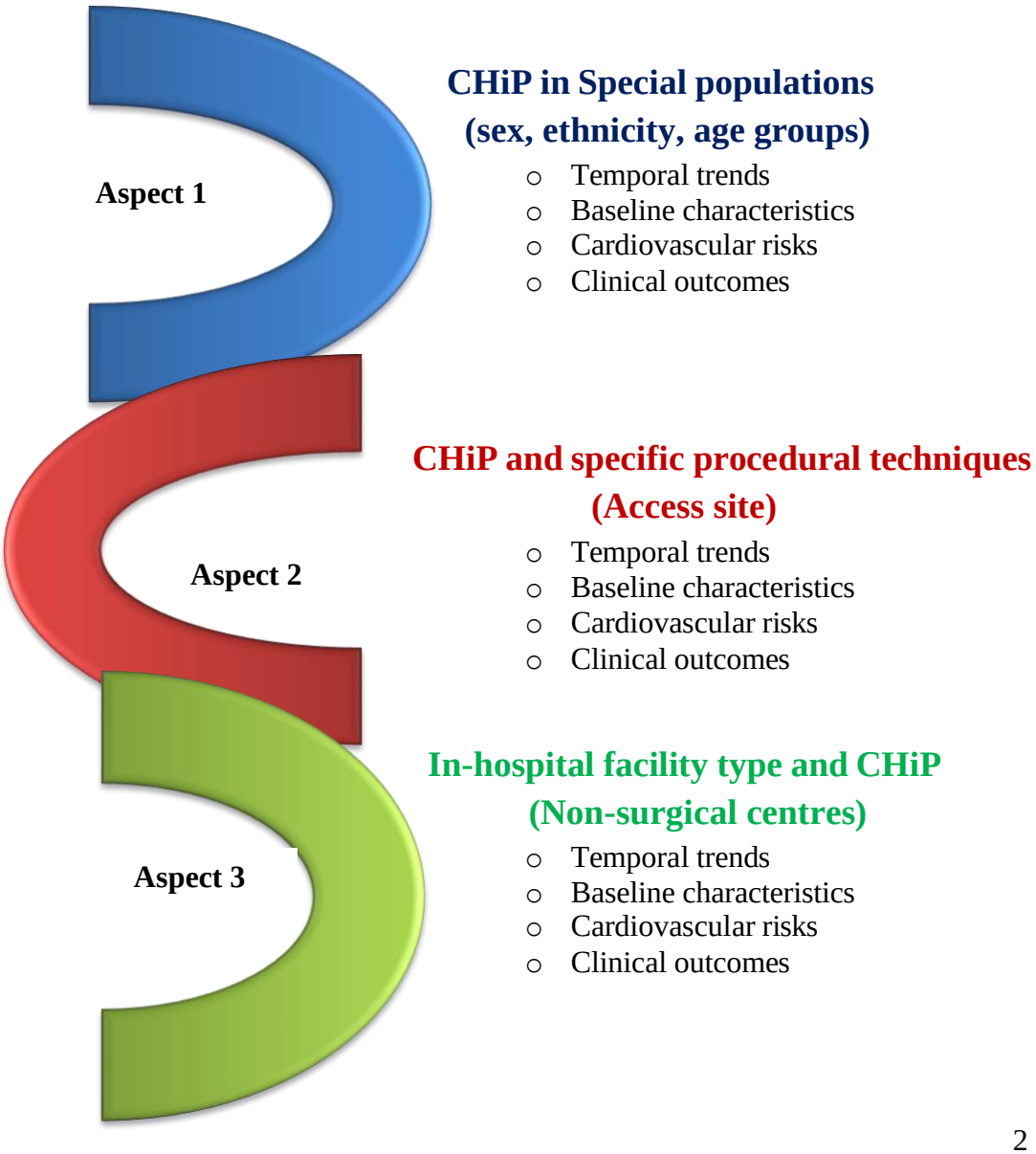
Chapter 1 - Overview of Thesis

This chapter includes the introduction of this thesis and provides a brief outline for each chapter

1.1 Introduction

This thesis focuses on examining Complex, High-Risk PCI (CHiP) types, trends, characteristics, and clinical outcomes among special populations of patients with stable angina, moving onto differences in certain PCI techniques/modalities used in CHiP and its effect on clinical outcomes, to finally looking at safety and trends of CHiP undertaken in non-surgical centres. On the whole, this thesis can be divided into 3 parts, as illustrated in **Figure 1.1.**

Figure 1-1 Pictorial demonstration of the three main aims of the thesis.



1.2 Objectives

The main objective of the thesis were to investigate the following:

1. Investigate the differences in patients' characteristics and risk profiles, types and trends of CHiPs undertaken for stable angina among sexes and its association with clinical outcomes.
2. Investigate the differences in patients' characteristics and cardiovascular risks, types and trends of CHiPs undertaken for stable angina among patients from different ethnic backgrounds and its association with clinical outcomes.
3. Investigate the differences in patients' characteristics and risk profile, types and trends of CHiP undertaken for stable angina among patients of different age groups and its association with clinical outcomes.
4. Investigate trends of access site use in CHiPs undertaken for stable angina and compare CHiPs' types, patients' baseline characteristics and risk factors prevalence among two access approaches (radial and femoral) and explore its association with clinical outcomes.
5. Investigate the effect of hospital characteristics (surgical vs non-surgical centres) on CHiP's outcome and look at CHiP's trends and differences in baseline characteristics and cardiovascular risks.

1.3 Chapter 2

This chapter provides a concise overview of the pathophysiology, clinical presentation, and management strategies for stable angina. It specifically focuses on percutaneous

coronary intervention (PCI) as an option in managing stable angina. Additionally, it introduces the term "CHiP" and conducts a thorough literature review around CHiP to identify existing research gaps in this area.

1.4 Chapter 3

This chapter provides a detailed description of the dataset utilised in this thesis, which is the British Cardiovascular Society (BCIS). It also includes the cohort selection process, the methods used for the descriptive analysis, and the modelling designs employed in this section.

1.5 Chapter 4

This chapter focuses on the first objective of this thesis, which is to examine the differences in CHiPs performed on patients with stable angina according to sex. It offers a comprehensive analysis of the sex-specific disparities in CHiP types and trends, clinical and procedural characteristics, and clinical outcomes of patients who underwent CHiP procedures for stable angina.

1.6 Chapter 5

This chapter addresses the second objective of this thesis. Specifically, it examines the differences in CHiP types and trends, patients' baseline characteristics, and clinical outcomes among different ethnic groups. To do so, the study divides the ethnic groups into two main categories: White and BAME (Black, Asian, and Ethnic Minorities).

1.7 Chapter 6

This chapter addresses the third objective of the thesis, which is to investigate the differences in the most common types of CHiP procedures among three age groups: G1 (<65 years), G2 (65-79 years), and G3 (≥80 years). The study further examines the differences in the baseline characteristics and clinical outcomes among the age groups, as well as the changes in the prevalence of individual CHiP factors over time.

1.8 Chapter 7

This chapter addresses the fourth objective of the thesis, which is to investigate the effect of the access site approach on CHiP clinical outcomes. Specifically, the study examines the differences in CHiP types, baseline characteristics, and risk profile of patients with stable angina between those undertaken via radial and femoral access sites. Additionally, the study investigates how the use of radial access has changed over time.

1.9 Chapter 9

This chapter focuses on the fifth objective of the thesis, which is to investigate the correlation between the type of hospital facility (surgical vs. non-surgical centres) and various aspects related to CHiP undertaken on patients with stable angina. This objective is particularly intriguing, considering the need for clearer recommendations in current guidelines regarding the management of CHiP in non-surgical centres. Consequently, the primary emphasis lies in examining disparities in patient and procedural characteristics, specifically exploring the trends for CHiP procedures conducted in non-surgical centres and their corresponding outcomes.

1.10 Chapter 10

This chapter summarises the overall findings of the thesis as well as the potential clinical implications in directing future research, changes in clinical practice and or guidelines.

Chapter 2

This chapter provides an introduction to chronic stable angina and its invasive management and ends with a detailed overview of Complex, High-Risk but Indicated PCI (CHiP).

2.1 Introduction

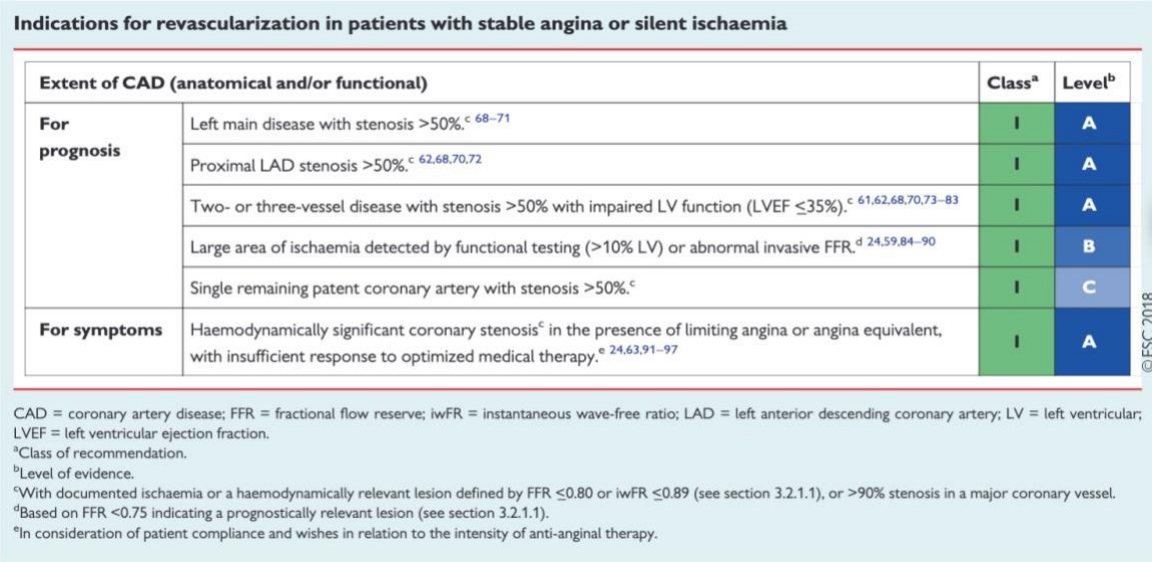
This chapter focuses on the invasive management of chronic stable angina, following a brief introduction to the pathophysiology, definition, and management of stable angina. Specifically, the study examines the management of those subsets of cases with CHiP. The chapter provides a comprehensive overview of the concept of CHiP, its inception, and a literature review of current knowledge. It concludes with an analysis of the current gaps in the literature.

2.1.1 Stable coronary artery disease (sCAD)

Ischaemic heart disease (IHD) remains the leading cause of death worldwide, accounting for 9 million deaths in 2016, according to the World Health Organisation (WHO). [4] Stable angina refers to the syndrome of recurrent, transient episodes of chest pain (tightness) that is typically felt across the chest in response to exertion (or stress) and relieved after a few minutes of rest and or nitrates (vasodilators). It is a result of supply-demand mismatch, that is, angina pectoris[5]. sCAD can be due to flow-limiting obstruction as a result of atherosclerotic (fatty deposits) plaque build-up. Or due to other causes which are not associated with obstruction of the epicardial arteries and are secondary to systemic problems like anaemia or due to microvascular dysfunction. This thesis focuses on the management of the obstructive atherosclerosis disease type.

The management of patients with angina pectoris due to flow-limiting obstruction according to the most recent guidelines[6, 7 8] (Tables 2.1 and 2.2) involves lifestyle changes, optimal medical therapy, and consideration of myocardial revascularisation with either PCI or coronary artery bypass graft surgery (CABG).

Table 2-1: 2018 ESC/EACTS Guidelines[7]



Indications for revascularization in patients with stable angina or silent ischaemia

Extent of CAD (anatomical and/or functional)		Class[a]	Level[b]
For prognosis	Left main disease with stenosis >50%.[c] [68–71]	I	A
	Proximal LAD stenosis >50%.[c] [62,68,70,72]	I	A
	Two- or three-vessel disease with stenosis >50% with impaired LV function (LVEF ≤35%).[c] [61,62,68,70,73–83]	I	A
	Large area of ischaemia detected by functional testing (>10% LV) or abnormal invasive FFR.[d] [24,59,84–90]	I	B
	Single remaining patent coronary artery with stenosis >50%.[c]	I	C
For symptoms	Haemodynamically significant coronary stenosis[c] in the presence of limiting angina or angina equivalent, with insufficient response to optimized medical therapy.[e] [24,63,91–97]	I	A

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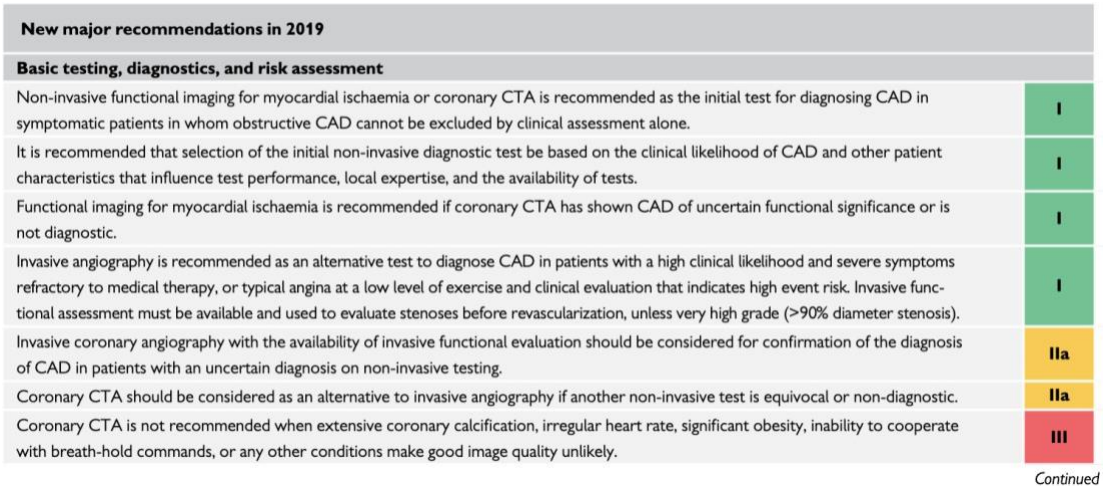
CAD = coronary artery disease; FFR = fractional flow reserve; iwFR = instantaneous wave-free ratio; LAD = left anterior descending coronary artery; LV = left ventricular; LVEF = left ventricular ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]With documented ischaemia or a haemodynamically relevant lesion defined by FFR ≤0.80 or iwFR ≤0.89 (see section 3.2.1.1), or >90% stenosis in a major coronary vessel.
[d]Based on FFR <0.75 indicating a prognostically relevant lesion (see section 3.2.1.1).
[e]In consideration of patient compliance and wishes in relation to the intensity of anti-anginal therapy.

Table adopted from the 2018 ESC/EACTS document for the management of patients with stable angina. European Heart Journal, *Volume 40, Issue 2, 07 January 2019, Pages 87–165, https://doi.org/10.1093/eurheartj/ehy394*.

Table 2-2:What is new in the 2019 Guidelines?[6]



New major recommendations in 2019	
Basic testing, diagnostics, and risk assessment	
Non-invasive functional imaging for myocardial ischaemia or coronary CTA is recommended as the initial test for diagnosing CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone.	I
It is recommended that selection of the initial non-invasive diagnostic test be based on the clinical likelihood of CAD and other patient characteristics that influence test performance, local expertise, and the availability of tests.	I
Functional imaging for myocardial ischaemia is recommended if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic.	I
Invasive angiography is recommended as an alternative test to diagnose CAD in patients with a high clinical likelihood and severe symptoms refractory to medical therapy, or typical angina at a low level of exercise and clinical evaluation that indicates high event risk. Invasive functional assessment must be available and used to evaluate stenoses before revascularization, unless very high grade (>90% diameter stenosis).	I
Invasive coronary angiography with the availability of invasive functional evaluation should be considered for confirmation of the diagnosis of CAD in patients with an uncertain diagnosis on non-invasive testing.	IIa
Coronary CTA should be considered as an alternative to invasive angiography if another non-invasive test is equivocal or non-diagnostic.	IIa
Coronary CTA is not recommended when extensive coronary calcification, irregular heart rate, significant obesity, inability to cooperate with breath-hold commands, or any other conditions make good image quality unlikely.	III

Continued

Picture adopted from the 2019 ESC guidance on the management of patients with stable angina. European Heart Journal, Volume 41, Issue 3, 14 January 2020, Pages 407–477, https://doi.org/10.1093/eurheartj/ehz425.

2.1.2 Conventional and non-conventional risks for sCAD

Ischemic heart disease (IHD) is associated with numerous recognisable risk factors, some of which can be modified, such as smoking, hypertension, hypercholesterolaemia, and a sedentary lifestyle, while others cannot, such as age and sex. Conventional risk factors for IHD include a family history of CAD, a previous history of myocardial infarction (MI), advanced age, hypertension, hypercholesterolaemia, diabetes mellitus, obesity, and smoking. However, recent studies have suggested the presence of non-conventional risk factors for significant CAD, such as the Ankle-Brachial index (ABI), which measures blood pressure at the ankle and in the arm, hs-CRP (high sensitivity C-Reactive Protein), which is a marker of inflammation, and the calcium score on CT, which measures the calcium content of the coronary arteries from CT imaging[5, 9, 10]. Of note, the presence of coronary artery calcification in a CT scan is also a feature of CAD and is associated with adverse outcomes.

2.1.3 Prognosis of patient's with sCAD

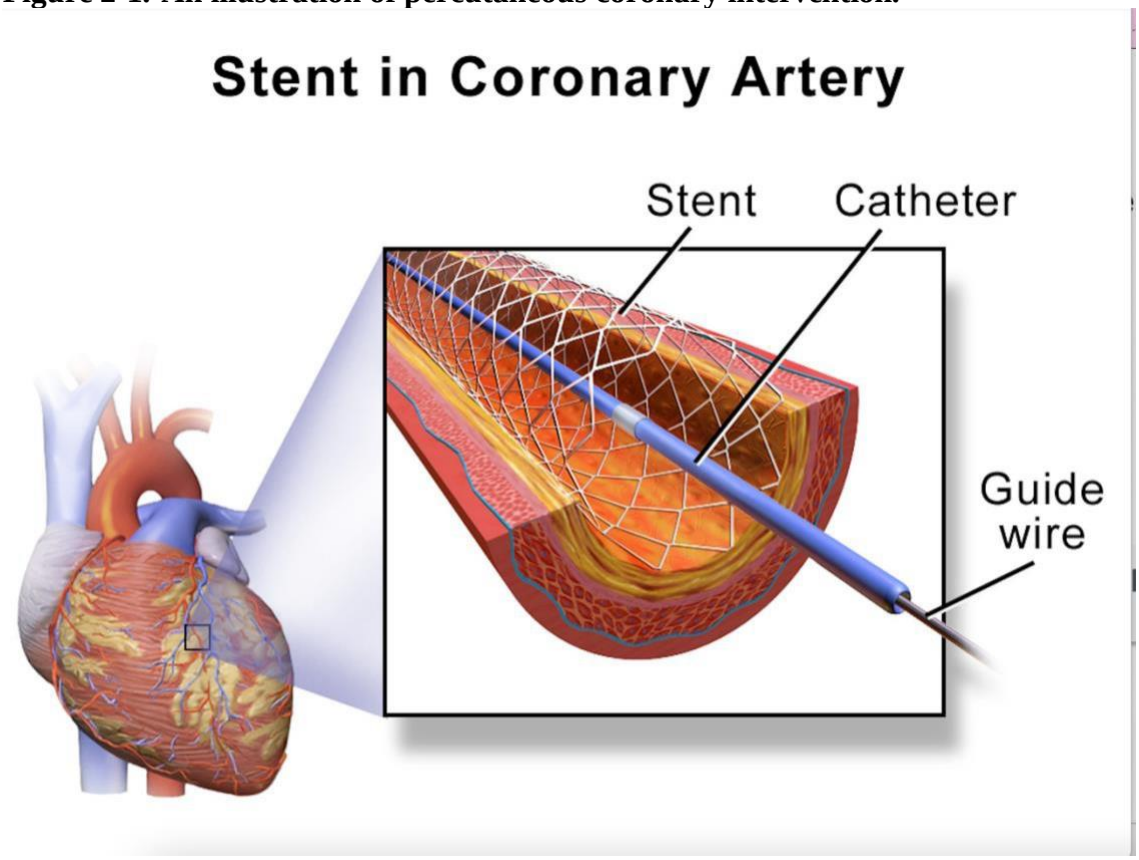
The prognosis for patients with sCAD varies; the annual mortality rate reaches 3.2% [8]. Factors that affect the survival include the left ventricular systolic function (left ventricle of the heart), the complexity and extent of the CAD (e.g. length of the diseased segment, the extent of calcifications, the location of the disease, and number of vessels involved) , the associated co-morbidities (medical conditions of a patient) along with their severity / burden[11, 12].

2.1.4 Invasive management of patients with sCAD

If non-invasive measures fail to control anginal symptoms, revascularisation should be considered. *Percutaneous coronary intervention* is a non-surgical procedure used to treat CAD. During the procedure, a thin, flexible tube called a catheter is inserted into a blood

vessel in the groin (femoral artery) or the arm (radial artery). Fluoroscopy, a special type of X-ray, is used along with a radiographic contrast media that is injected through specific coronary catheters to enable visualisation of the arteries. Various types and shapes of catheters are used to engage both the right and left coronary arteries. Intravenous contrast is introduced into the coronary artery to visualise its anatomy. Pictures of the coronary arteries are taken from different angles to help assess the three-dimensional nature of the narrowing. The blocked segment can then be treated using a balloon to compress the arterial plaque and a metallic tube called a stent to keep the artery open (Figure 2.1). The goal is to improve blood supply to ischemic tissue by relieving coronary artery narrowing or occlusion.

Figure 2-1*: An illustration of percutaneous coronary intervention.*



This image was adopted from Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436.

Contraindications to PCI includes [13]: A) Inability to take dual antiplatelet therapy or failure to comply with the procedure. B) Patients who are at high risk of bleeding due to thrombocytopenia (low platelet count), peptic ulcers, or severe coagulopathy (problems with blood clotting). C) Restenosis following multiple PCIs.

Important equipment in a PCI: The PCI procedure is typically performed in a catheterisation laboratory, where standard sheaths, catheters, and other equipment are routinely used. However, a PCI may also require additional devices such as stents. Stents can be broadly classified into two types: those with drug-eluting properties (DES) that have been shown to reduce the rate of restenosis and revascularisation compared to older-generation bare-metal stents (BMS); and BMS, which can be considered a preferred alternative to DES when dual antiplatelet therapy (DAPT) cannot be administered due to patient intolerance or contraindications. Additionally, vascular scaffolds are stents made from bioresorbable materials (BVS).[14]

PCI procedure technique : Following identification of stenosis or occlusion in the artery, a guidewire is introduced through the catheter and positioned beyond the site of narrowing. A balloon catheter or stent catheter is then threaded over the guidewire and positioned at the site of narrowing to perform either angioplasty or stent placement.

a) Balloon angioplasty involves inflating a balloon in the coronary artery to open the narrowing and disrupt plaque. However, as the ballooned artery tends to narrow again over time, this procedure is no longer the primary intervention and is usually performed nowadays to prepare the area for stent placement.[14]

b) Stent angioplasty involves using a stent catheter where the stent is positioned over a balloon. Once the stent is in the lesion segment, the balloon is inflated to expand the stent and open up the narrowed artery. The catheter is then withdrawn, and multiple images are taken to confirm the proper placement of the stent and the resolution of stenosis.

c) Coronary atherectomy[15] is a procedure that involves physically removing cellular debris or calcified atheroma from coronary arteries by cutting the lesions with a cutter, typically a burr or crown. There are two types of atherectomy: directional coronary atherectomy and laser atherectomy. Balloons and stents are typically placed following atherectomy. However, among the potential complications of atherectomy are arterial dissection, coronary artery perforation, coronary spasms, and particle embolism.

d) The coronary artery wall can be imaged using intravascular (IV) imaging devices such as IV ultrasound (IVUS) or optical coherence tomography (OCT)[16] to delineate plaque morphology and distribution, which can aid in the decision-making process for PCI. This approach overcomes some coronary angiography limitations, as angiography provides a two-dimensional view that may not accurately represent the diameter of the lumen due to limitations in contrast enhancement and angle of view, especially in cases of asymmetric narrowing and complex luminal shapes.

e) Important complications associated with the PCI procedure include significant bleeding events at either the access site or intervention site, acute MI (myocardial infarction/heart attack), acute stroke, and death. Less common complications include acute kidney failure and contrast-induced allergies. The risks in a simple PCI procedure in an elective case are usually less than 1% in most centres. However, the risks increase when the operator is faced with challenging coronary anatomy that may require special skill sets and advanced equipment, such as devices that break down calcium deposition in the wall of the arteries (e.g. rotational atherectomy). Similarly, risks are higher in

patients with challenging medical conditions that would increase procedure risks, regardless of the coronary anatomy[17, 18]. The PCI risks also increase with the use of advanced therapies/devices like devices to support the circulatory system[19]. These PCIs that are of higher risks but with strong indication (such as in patients with high risk anatomy like left main or proximal LAD or in those with severe angina symptoms, despite being on maximum tolerated guideline-directed medical therapy) are usually referred as Complex, High-Risk but Indicated PCI (CHiP)[20].

2.1.5 Complex, high-risk but indicated PCIs (overview)

CHiP is an emerging concept with an evolving definition. Up to the date of submitting this thesis, there is no universal definition or agreed criteria[21]. However, the consensus is that CHiP can be any or the combination of the following (Figure 2.2):

a) **A complex coronary anatomy, this includes:**

- Left main stem disease
- Ostial or bifurcation disease
- Triple vessel disease
- Long segment disease
- Chronic total occlusion
- Heavily calcified artery
- Severe tortuosity
- Graft lesion

b) **A challenging co-morbidity, this includes**:

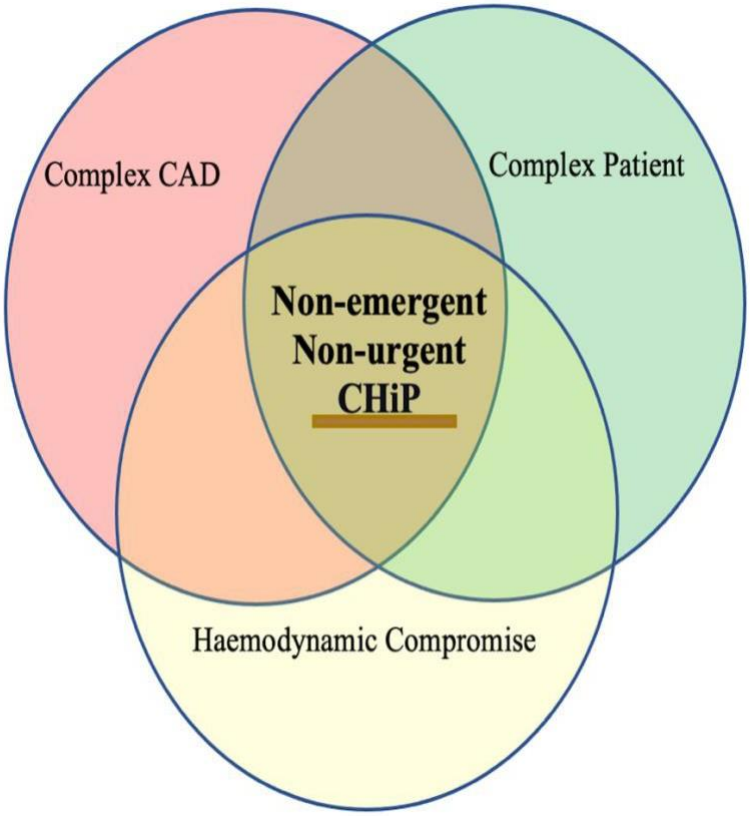
- Old age
- Chronic renal failure
- Cancer (active)

- Severe left ventricular dysfunction

c) The use of procedural devices, like:

- Any calcium modification devices (cutting balloons, shockwaves, rotational atherectomy devices, laser angiography)
- Circulatory support devices (Intra-aortic balloon pump (IABP) and Impella)

Figure 2-2: What is CHiP



In this thesis, CHiP factors were sub-grouped into two as follows:

a) Patient's factors

- **Old age**: Age is an important factor that influences both short and long term outcomes following PCI in both settings, the acute (acute coronary syndromes) [22] and the elective setting (chronic stable angina) [23]. Age was found to be an independent risk factor for death and other major adverse cardiovascular and cerebral events following PCI (MACCE)[24-27]. Elderly patients (≥75 years) tend to have more risk factors for cardiovascular disease (disease of the heart and major blood vessels) and a greater angina burden than younger patients needing PCI. This means that they are also likely to get more potential benefits from PCI. However, they are also more likely to develop higher rates of PCI related complications given their frailty, co-morbidities, and age-related physiological changes (which could augment both the benefits and the risks from PCI [28].
- **Previous history of Coronary artery bypass graft surgery (CABG):** CABG was first introduced more than 50 years ago. The first surgery performed on a human dates back to 1960 [29]; where an arterial or venous graft (conduit) is used to bypass a severe blockage in a coronary artery. Nowadays, patients referred for surgery are usually those with complex disease in their coronary arteries such as chronic total occluded artery (CTO), disease in a long segment, more than two vessels occluded, or occlusion in the main stem artery [30] [31].

  The post CABG patients are unique in their issues mainly related to:

  a) graft failure is inevitable with as much as 3-12% of saphenous vein grafts (SVG) occludes before discharge; 8-25% diseased or occluded at 1

year ; and 40-50% occluded at 10 years[32, 33] b) native vessel disease progression.

Factors that contribute to graft failure could be related to conduit defect, poor anastomosis techniques, poor run-off of the native vessel, and competitive flow (the more severe the stenosis prior to the graft the more likely the graft survives and vice versa [34].

Patients with a prior history of CABG who undergo PCI tend to have a more complex profile, including older age, frailty, and a higher incidence of co-morbidities such as diabetes, severe left ventricular and renal impairments, and a history of major bleeding. Additionally, the disease in both the native vessels and the graft tends to be more complex in these patients. For example, PCI to a diseased graft carries a higher risk for no flow or stroke due to a heavier clot burden. Furthermore, the risk of perforation is higher in a calcified vein graft compared to an arterial graft. Moreover, PCI to a native chronic total occlusion tends to be more complex depending on factors such as the presence of an ambiguous or absent proximal cap, lesion length, amount of calcifications, and the presence of side branches or tortuosity. These factors often require the use of two catheters in both (right and left) coronary arteries. [35]. Hence PCI in patients with previous bypass is considered high risk. Some studies suggested that outcomes of PCI to a native heart artery in a patient with grafts had the highest in-patient, 30-day and 1-year mortality as compared with those patients who had PCI to their grafts[36]. However , many others suggested the contrary [37, 38].

Factors contributing to native vessel disease progression include: pre-existing high disease burden and low flow with reduced sheer stress which results in accelerated atherosclerosis proximal to the anastomosis and formation of CTO [39] at a post-operative rate of 14-21% after 1 year [40] .

- **Severe left ventricular (LV) impairment:** Severe LV impairment is a common problem in patients undergoing PCI, affecting an estimated 10-30% of patients.[41]. Typically, patients with heart failure have extended non-viable heart muscle and a cardiac reserve that is too low to respond to a temporary decrease in blood flow (perfusion) that occurs during balloon inflation and/or stent deployment in a PCI procedure. This can result in hemodynamic instability, including a profound drop in blood pressure due to acute heart failure, which can lead to a decrease in the flow of blood to multiple organs like the brain, liver, and kidney (cardiogenic shock), or even death. In high-risk cases, temporary percutaneous LV/circulatory support devices (such as the Intra-Aortic Balloon Bump (IABP) or the Impella device are advised[42]. IABP devices are employed to enhance diastolic blood pressure, thereby improving coronary perfusion with a modest yet significant impact on cardiac output. On the other hand, the Impella serves as an assist device by pumping blood from the LV into the ascending aorta, thereby sustaining systemic circulation within the range of 2.5 to 5.0 L/min. Overall, these devices are used temporarily to prevent catastrophic hemodynamic decompensation and enhance heart function and PCI outcomes.

  Patients with severe LV dysfunction are often excluded from clinical trials [43] and they tend to be older, have high co-morbid burden and have more extensive coronary artery disease than those with preserved heart function. Thus, PCI in patients with severe LV systolic dysfunction is associated with increased mortality risk [44] [45] and MACCE [46, 47] both at short- [48] and long-terms [49].

- **Chronic renal failure (CRF):** A prominent cause of mortality among patients with advanced kidney disease or failure is attributed to cardiovascular disease (CVD)[50, 51]. Notably, the incidence of CVD-related mortality is 10-20 times higher in patients with advanced kidney disease or those undergoing dialysis compared to individuals with normal kidney function [52]. Research evidence indicates that cardiovascular disease manifests at an early age in these patients and follows an accelerated course[53]. Furthermore, it is important to note that CAD in this population is typically not attributed to progressive atherosclerosis (accumulation of lipid plaque in arterial walls) but rather to dysregulation of calcium phosphate homeostasis and the development of vascular calcifications[54]. Comparative studies investigating outcomes of PCI or CABG in patients with stable angina have suggested higher risks of mortality, stroke, and major bleeding events among those with renal failure as compared to individuals with normal renal function[55].

b) Procedural's factors

- **Left main stem (LMS) PCI:** The LMS originates above the left aortic cusp from the aorta and provides more than 80% of the blood supply to the left side of the heart muscles through its branches. Data suggests a gradual increase in LM PCI procedures[56]. Obstruction of the LMS has the greatest impact on morbidity and mortality related to CAD compared to obstructions in other coronary arteries. Unprotected LMS obstruction (unprotected referring to the absence of a bypass graft into the LMS) carries a significantly poor prognosis with a low survival rate[57]. Bypass grafting has traditionally been considered the standard of care [58] due to the complexity of LMS lesions, while PCI serves as an alternative when

surgical risk is deemed high[59] However, more recently, PCI has expanded to lower and intermediate risk cases, emerging as a viable alternative to surgery [60].

- **Chronic total occlusion (OCT):** The first reports of CTO PCIs were published in 1985, thanks to the pioneering efforts of Japanese practitioners who applied techniques developed in the field of percutaneous revascularisation of chronic femoropopliteal occlusions to coronary interventions. Initially, an antegrade approach achieved successful treatment in approximately 60% of cases. However, the observation that penetrating a distal cap is comparatively easier than a proximal cap led to the exploration of a retrograde approach, resulting in an impressive 85% success rate [61].

  CTO is characterised by the deposition of cholesterol, fat, and calcium plaque within the artery, leading to complete occlusion. To be classified as a true CTO, the occlusion must persist for at least 3 months[62]. Studies conducted by the National Cardiovascular Data Registry (NCDR) revealed a CTO prevalence of 5.5% among all diagnostic angiograms, accounting for 10-20% of identified lesions in patients with CAD[63] [64]. CTO PCI is widely recognised as one of the most challenging interventions due to its high technical complexity, potential for major complications, and lower procedural success rates [65].

  Contemporary CTO PCI practice incorporates various techniques and strategies. For instance, wire escalation techniques involve using different wires to gradually cross the occluded segment, starting with the least stiff/safest wire and progressing to the stiffest wire. Another technique involves subintimal dissection or controlled antegrade and retrograde

vessel tracking. However, it is essential to note that these techniques carry inherent risks, such as vessel perforation, bleeding into the pericardial space, and even mortality.[61]

- **Use of calcium modification devices**: the presence of calcium in coronary arteries can adversely affect the outcomes of PCI through various mechanisms. It can impede the deployment of devices that are inserted into the artery to break down or modify the calcific disease in the coronary arteries. Additionally, calcium can limit stent expansion and cause damage to the stent platform [66]. These factors increase the risk of stent failure and subsequent adverse events[67]. Numerous studies have demonstrated that target vessel calcification is an independent risk factor for poorer outcomes, including MACCE and mortality following PCI[9, 68, 69]. Calcific lesions tend to be longer and more commonly found at segments with bifurcation disease, while thrombotic lesions are less frequent. Several factors have been identified as independent predictors of severe vessel calcifications, including age, LMS disease, Caucasian ethnicity, disease in the left anterior descending (LAD) artery (one of the coronary arteries originating from the LMS), renal dysfunction, prior myocardial infarction (MI), and peripheral vascular disease (PVD)[70].

- **The use of percutaneous LV support devices:** Severe left ventricular impairment in patients with significant coronary artery disease poses a significant risk for PCI. This risk primarily stems from the myocardium's limited reserve capacity, rendering it vulnerable to transient ischemia (temporary blood flow loss) when the coronary artery is dilated using balloons. Nonetheless, recent advances in PCI techniques have facilitated

the management of progressively complex and high-risk cases, particularly those where bypass surgery was unsuitable due to coexisting conditions like severe LV dysfunction. In such scenarios, PCI has emerged as a recommended revascularisation strategy.

Incorporating prophylactic circulatory support devices during these procedures not only enhances procedural safety but also holds the potential to improve outcomes [71, 72]. These percutaneously inserted circulatory support devices operate by reducing the heart's afterload, thereby alleviating its workload. Additionally, they augment blood flow to the coronary arteries and, in certain devices, alleviate the ventricles' burden while enhancing cardiac output. For example, the Impella device [73]and the intra-aortic balloon pump (IABP) are widely employed for left ventricular mechanical assistance. These devices can provide support ranging from a few hours to several weeks. Comparative studies comparing the Impella and IABP have demonstrated favourable outcomes for the Impella device[74].

2.1.6 Evidence around CHiP

CHiP procedures continue to pose significant challenges. Several observational and prospective randomised trials have aimed to provide insights into the safety and efficacy of these procedures. This chapter focuses on the most relevant studies conducted on CHiP and their respective findings.

One notable study, derived from the British Cardiovascular Intervention Society (BCIS) dataset[13], examined a large cohort to define complex PCI and associated risks. The study

identified 13 CHiP factors (7 patient-related factors and 6 procedural factors) that were found to be linked to worse clinical outcomes. It is worth noting that these factors align with the ones examined in the current thesis.

Another analysis based on the same dataset investigated the influence of operator volume on CHiP outcomes found that one-year survival was not associated with higher operator volume. [75] Similarly, an analysis conducted using the Veteran Affairs Clinical Assessment, Reporting, and Tracking Program indicated that high-risk PCIs performed by multiple operators yielded similar outcomes to those performed by a single operator, although procedures involving left main stem (LMS) or chronic total occlusion (CTO) vessels were primarily carried out by multiple operators. [76]However, a subsequent survival analysis using the BCIS dataset demonstrated a significant improvement in survival for unprotected LMS procedures performed by high-volume operators, both in terms of in-hospital survival and at 12 months of follow-up. [77]

Regarding post-procedure medical management, a pooled analysis of data from six randomised controlled trials examined the optimal timing for dual antiplatelet therapy (DAPT) following PCI. The analysis concluded that for more complex PCI procedures, longer-term DAPT (>12 months) provided greater benefits (adjusted hazard ratio: 1.01 [95% CI: 0.75 to 1.35]; p-interaction = 0.01)[57]. Lastly, a large observational study utilising the Alberta Ministry database compared the short- and long-term clinical benefits of revascularisation (PCI or CABG) versus medical therapy alone in patients with complex CAD and stable angina. [78] The study demonstrated that revascularisation in complex CAD was associated with improved all-cause mortality (inversed probability weighted hazard ratio [IPW-HR]: 0.61; 95% CI: 0.57-0.66; $p < 0.001$) and longer survival (IPW-HR: 0.57; 95% CI: 0.53-0.61; $p < 0.001$). [78]

Evidence from RCT around CHiP

One of the most significant randomised controlled trials RCTs focusing on individual CHiP factors is the REVIVED[79] (percutaneous Revascularisation for Ischaemic Left Ventricular Dysfunction) trial. This prospective, randomised, multi-centre open-label trial investigated the outcomes of PCI in patients with poor left ventricular function compared to guideline-directed medical therapy. The study findings suggested no significant difference between the two groups in terms of their primary outcomes, which encompassed all-cause mortality or hospitalisation for heart failure over a median follow-up period of 3.4 years. However, there were notable differences in unplanned revascularisation events, favouring the PCI group (hazard ratio [HR] 0.27, 95% confidence interval [CI] 0.31-0.53).

2.1.7 CHiP score; do we need one?

The CHiP field is expanding rapidly, underscoring the urgent need for a robust definition of CHiP. In response, numerous efforts have been made to establish reliable, reproducible, and internationally applicable risk stratification models. Such models serve a dual purpose, assisting both patient counselling and decision-making regarding the optimal management strategy. The SYNTAX[80] (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) randomised controlled trial played a pivotal role in the development of the SYNTAX score I, which effectively stratifies the risks associated with PCI versus CABG. However, it is essential to note that this score primarily relies on angiographic and anatomical parameters, overlooking crucial clinical factors. To address this limitation and provide better guidance for revascularisation decisions, the SYNTAX II score was subsequently introduced, taking into account important clinical parameters. Recently, the SYNTAX score II underwent further refinement and validation, resulting in the creation of the SYNTAX II 2020 score.

This updated scoring system enables personalised decision-making by predicting 10-year mortality and 5-year major adverse cardiac and cerebrovascular events (MACCE).[81].

In a recent study by Sorin et al. (2021), a novel risk score was proposed to predict one-year mortality in patients undergoing CHiP procedures. The authors compared clinical outcomes among 4,478 patients from the National Cardiovascular Data Registry (NCDR). While this analysis excluded certain variables that are relevant to CHiP identification (e.g., the use of rotational atherectomy), it revealed higher mortality rates among CHiP patients compared to non-CHiP patients. Specifically, four CHiP criteria—age over 80, chronic renal failure, left ventricular ejection fraction below 30%, and treatment of more than one lesion—were independently associated with higher event rates.[82]

Furthermore, Protty et al. undertook a more comprehensive approach to develop risk stratification models. [13] Their study utilised a large dataset of 313,054 patient records from the British Cardiovascular Intervention Society registry. Through retrospective analysis, they identified seven patient-related factors (age over 80, history of stroke, female sex, history of myocardial infarction, peripheral vascular disease, ejection fraction at or below 30%, and chronic renal failure) and six procedural factors (use of calcium modification devices, left main PCIs, three-vessel disease, multiple accesses, use of LV mechanical support devices, and coronary lesions longer than 60mm) that were associated with worse clinical outcomes. This investigation provides a robust foundation for future research to build upon in the pursuit of enhanced risk stratification models.

To sum up, these studies collectively contribute to the ongoing advancement of risk stratification models in CHiP procedures, fostering improved patient care and informed decision-making.

2.1.8 Gap in evidence and rational for this thesis

As previously discussed, the field of complex, high-risk percutaneous coronary interventions (CHiP) has experienced significant growth in contemporary practice, owing to advancements in PCI techniques and the continuous evolution of PCI technologies and mechanical support systems. While there is a substantial body of evidence-based knowledge available on various aspects of CHiP, several gaps in the existing literature remain. In this section, we will summarise these gaps for a comprehensive understanding of the current state of research in CHiP.

1. Despite compelling evidence regarding worse clinical outcomes in females compared to males following PCIs in general, there is a dearth of research specifically focusing on CHiP and how these gender/sex disparities have evolved over time. Therefore, it is crucial to examine whether there have been any systematic biases in the allocation of CHiP based on sex. Most of the existing evidence on sex differences in outcomes following CHiP is derived from studies that investigated individual components or types of CHiPs or from small-scale single-centre studies that did not systematically explored CHiP differences and trends according to sex. Consequently, this thesis aims to investigate the disparities in baseline clinical and procedural characteristics, clinical outcomes, and trends in CHiP procedures performed on patients with stable ischaemic heart disease (angina) with respect to their sex.
2. The population of Black, Asian, and other ethnic minorities is steadily growing in developed countries such as the United Kingdom and Europe. Despite the expanding body of literature on ethnic disparities in outcomes following PCI,

there is a scarcity of research specifically focusing on CHiP and its association with ethnicity. Most of the existing studies on ethnicity and CHiP are based on highly selective cohorts or suffer from limited generalisability. Therefore, this thesis aims to fill this research gap by investigating whether there are any variations in the types of CHiP procedures, as well as the clinical and procedural characteristics and clinical outcomes, among different ethnic groups. Furthermore, this research will provide insights into how these differences have evolved over time, thereby contributing to a more comprehensive understanding of ethnic disparities in the context of CHiP.

3. Age has long been recognised as a significant indicator of worse clinical outcomes following PCI, and extensive evidence supports this association. However, to date, there have been no dedicated investigations focusing on the differences in types of CHiP and their corresponding clinical outcomes based on age. This knowledge gap is of utmost importance as it holds the potential to provide interventionists with valuable insights into the risks involved in performing and counselling patients prior to CHiP procedures. In light of this, the present thesis aims to conduct an in-depth analysis of changes in baseline clinical and procedural characteristics, the variety of CHiP procedures performed, and the associated trends based on age. By addressing this research gap, the study seeks to contribute crucial information that can enhance the understanding of age-related considerations in the context of CHiP and further inform clinical practice.
4. Extensive research has been conducted in the field of PCI to investigate the optimal access site for achieving successful outcomes. Among the various access sites, radial access has emerged as a superior option in terms of safety and comparable success rates compared to femoral access. However, there is a significant dearth of data specifically focused on CHiP and its association with

access site selection. The available evidence primarily consists of studies conducted on highly selective cohorts, small-scale investigations with limited geographical representation, or international surveys. Consequently, the question of whether radial access remains superior to femoral access in the context of CHiP procedures remains unresolved. To address this critical knowledge gap, the present thesis will comprehensively examine the differences in CHiP procedures performed via radial and femoral accesses. This analysis will encompass an evaluation of variations in baseline characteristics, trends, and clinical outcomes associated with each access site. By shedding light on these important aspects, this study aims to provide valuable insights into the ongoing debate surrounding the choice of access sites in CHiP procedures.

5. The safety of PCI procedures performed in non-surgical centres has been extensively investigated and supported by a wealth of evidence from large observational studies and randomised controlled trials. However, the applicability of these findings to CHiP remains uncertain. It is noteworthy that previous studies have specifically excluded cases involving complex CAD or high-risk procedures. Moreover, the existing observational studies in this area have been limited in scope, characterised by small sample sizes, generalisation challenges, and high selectivity. Consequently, there is a critical knowledge gap surrounding CHiP procedures performed in non-surgical centres, warranting further investigation. This thesis addresses the research gap by examining different CHiP procedures and their clinical outcomes in relation to the type of hospital facility, focusing on CHiP cases in non-surgical centres; it provides unique insights into their safety and efficacy. Through a comprehensive analysis of clinical data, including patient characteristics and clinical outcomes, this study enhances our

understanding of the implications of CHiP in non-surgical centres, enabling more informed decision-making in this setting.

Chapter 3

Datasets description and general methodology

3.1 Introduction

This chapter describes the dataset utilised to study the different aspects around CHiP in patients with stable angina. A brief description is provided regarding the source of the dataset, how information is collected, dataset codes, and its strengths and limitations. The methodology used in this thesis is then detailed, along with a description of the statistical methods employed for the study analyses. Full details of the methods used for each objective will be further discussed in the relevant section of the related chapter.

3.2 Study dataset

This thesis data was obtained from the British Cardiovascular Intervention Society (BCIS)[83] dataset.

The BCIS registry aims to improve the quality of cardiovascular interventions and care in the UK by collecting data from all hospitals offering PCI services. Its objectives include assessing service availability, evaluating care against national standards, examining procedure-related complications and their impact on patient outcomes, and utilising the data for national audits and research.

Setting: the BCIS registry collects comprehensive data on almost all PCI procedures performed in the national health service (NHS) hospitals across the country, with some contributions from private hospitals. Notably, out of the 118 PCI centres in the UK, only six did not provide data to the registry during the 2017-18 period, demonstrating a high level of participation and capturing around 95% of PCI activity nationwide[83].

Baseline Data: The dataset comprises 113 variables that gather information on various aspects, including patients' demographics, cardiovascular risk factors, previous cardiovascular interventions or surgeries, indication for PCI, pharmacology, access site,

types of angioplasty catheters or devices used, and peri-procedural complications such as access site complications, death, major bleeding, stroke, myocardial infarction, and others. The dataset contains records of over a million PCI procedures conducted in the United Kingdom. The participation of all NHS hospitals nationwide contributes to the dataset's comprehensive representation, reinforcing the significance of the BCIS as a valuable resource for understanding cardiovascular interventions[14].

Data quality: To enhance data quality in the BCIS dataset, the audit committee employs various methods. Participating hospitals receive a comprehensive data dictionary and regular updates, ensuring clear definitions. A dedicated help team provides technical support, while complex clinical queries are addressed by the BCIS audit clinical committee. During data uploads, rigorous checks are performed, including range checks and internal consistency checks. If issues arise, the data set is returned for further cleaning and verification. These measures ensure the completeness, consistency, and accuracy of the BCIS dataset. The BCIS dataset has been used for research and national audit purposes, and its quality and accuracy have been previously ascertained[84.]

Patient Identification and population consent: All data have section 251 approval of NHS Act 2006, allowing use for audit and research matters without the formal need for individual patient's consent[85]. Detailed information about data protection and security can be found on https://www.nicor.org.uk/for-researchers/.

Data capture and storage : Each patient's record in the BCIS dataset is identified by a unique 10-digit NHS registration number, except for patients in Scotland who are tracked using their full name and date of birth. Additional information collected includes the patient's postcode, hospital number, and present and past geographical location. However, to ensure data privacy, patient identifier information is encrypted before being transmitted

to the central database. National Institute for Cardiovascular Outcome Research (NICOR) has access to identifiable patient information for audit and research purposes, but researchers do not have access to these specific data fields.

Funding and organisation: the audit project is funded by the Department of Health (DoH) in the central government, and it is managed by NICOR. The BCIS audit lead oversees a team of support staff, including analysts and statisticians from NICOR. Additionally, a project manager is responsible for supervising logistic support, data monitoring, and analysis.

Strength and weaknesses of the dataset: The BCIS dataset aims to gather information on every PCI procedure performed in the UK, with participation from NHS hospitals nationwide, ensuring comprehensive representation. The BCIS dataset includes a wide range of patients, from stable CAD cases to those with haemodynamic instability. With nearly a million PCI records, researchers can study rare complications and compare treatments/strategies across different patient cohorts, which may not be feasible in randomised control trials. Public reporting of adjusted outcome analysis enables performance comparison against national benchmarks. However, limitations include limited data collection from the private sector (constituting <5% of PCI activity), unavailability of cause of death information, potential under-reporting of complications, and the lack of post-discharge data for assessing outcomes.

In conclusion: the BCIS dataset provides an excellent opportunity for researchers to study patients baseline characteristics, cardiovascular risks, procedural characteristics, access site practice, clinical outcomes and even hospital characteristics from a national

perspective and represents whole national practice rather than highly selected cohorts in trials (Table 3.1).

Table 3-1: The British Interventional Cardiovascular Society minimum data standard fields

Table I **Minimum data standard fields requiring over 95% completion for successful data uploads**

Variable field	Description	Reason
1.03	NHS number (England and Wales)	For linkage to ONS and HES
1.06	Date of birth	For age calculation required for risk-adjusted outcome calculation
1.07	Sex	For risk-adjusted outcome calculation
2.03	Procedural urgency	For risk-adjusted outcome calculation
2.04	Pre-admission cardiogenic shock	For risk-adjusted outcome calculation
2.07	Date/time of symptoms onset	For delays to treatment calculations
2.08	Date/time of arrival at first hospital	For delays to treatment calculations
2.13	Prior myocardial infarction	For risk-adjusted outcome calculation
2.16	Diabetes	For risk-adjusted outcome calculation
2.18	Weight	For risk-adjusted outcome calculation
3.02	Consultant responsible for procedure (name)	Used to assign procedures to the operator for the operator outcomes reporting
3.09	Number of vessels attempted	For risk-adjusted outcome calculation
3.26	Date/time of first balloon inflation	For delays to treatment calculations
4.01	In-hospital PCI outcome	To identify in-hospital complications
4.03	Status at discharge	For in-hospital mortality
4.04	Discharge date	For length of stay
5.05	History of CVA	For risk-adjusted outcome calculation
5.06	History of renal disease	For risk-adjusted outcome calculation
5.26	Date/time of arrival at PCI hospital	For delays to treatment calculations
5.27	Date/time of call for help	For delays to treatment calculations
5.30	Location of patient at onset of STEMI	For delays to treatment calculations
5.31	Consultant responsible for procedure (GMC number)	Used to assign procedures to the operator for the operator outcomes reporting
5.35	Creatinine	For risk-adjusted outcome calculation

NHS, National Health Service; ONS, Office of National Statistics; HES, Hospital Episode Statistics; GMC, General Medical Council; CVA, cerebrovascular accident.

This table was adopted from European Heart Journal - Quality of Care and Clinical Outcomes (2019)5, 292 doi:10.1093/ehjqcco/qcz023

3.3 Statistical methods

This chapter describes the general methodology used and details the statistical analyses used to examine differences between specific groups as mentioned in the study objectives section.

3.3.1 Data cleaning

The dataset was examined to identify its limitations and scope, focusing on completeness, errors, and consistency. The variables necessary for the analyses were identified, and erroneous observations were removed. Observations with unknown sex or ambiguous hospital codes were excluded. Descriptive statistics were evaluated for each variable, and upper and lower outliers beyond the acceptable range were checked. Exclusions were made for the age variable with values below 18 or above 100, as well as the weight variable with values below 35 kg or above 450 kg. Additionally, new variables were created, such as the Body Mass Index (BMI) using registered weight and height variables. Some observations in specific variables, such as the number of stents used, were rearranged. For example, cases with three or more stents were grouped together, resulting in a new variable categorising the number of stents used into three categories: 1 stent, 2 stents, and 3 or more stents.

3.3.2 Methodology

After completing the data cleaning and initial exploratory analysis, cases admitted for stable angina (elective admission) were isolated.

3.3.2.1 CHiP factors selection

As mentioned earlier, CHiP is an emerging concept with an evolving definition. The selection of CHiP factors for this thesis was based on consensus from international society position statements, conclusions drawn from high-quality studies (as detailed in Chapter 2 (Section 2.1.5: Complex, high-risk but indicated PCIs - Overview)), and guidance from the supervisory team. Unfortunately, Certain factors that are believed to increase the

procedure's risks, such as active cancer, were not included in the CHiP cohort due to unavailability of the variable in the BCIS dataset.

The following CHiP factors were selected to be included in the CHiP cohort, these are:

a) Patients' factors :

   Age >= 80 years

   Previous CABG

   CRF

   Poor LV function

b) Procedural factors

   LMS PCI

   CTO PCI

   Use of LV support devices

   Presence of severe vascular calcifications

3.3.2.2 Definitions:

CHiP factors were defined as follows:

High-risk age was defined as any patient aged 80 years and above; *Chronic Renal Failure* was defined as chronic creatinine elevation of =>200 umol/L, dialysis dependant, or previous history of renal transplant. P*oor LV function* was defined as and LV with an ejection fraction of =< 30%. *Use of LV support devices* was defined as the use of IABP or Impella devices. *LMS or CTO PCI* as any procedure involves the revasularisation of the LMS or CTO respectively. Finally *severe vascular calcifications* was defined as any PCI procedure that required the use of any of the following calcium modification devices: cutting balloons, rotational atherectomy, and laser therapies.

3.3.2.3 Descriptive analyses:

The distribution of continuous data was assessed using distribution curves and quantile-quantile (QQ) plots. Normally distributed data were presented as mean (with standard deviation), while not normally distributed data were presented as median (interquartile range). Categorical and ordinal variables were presented as frequencies (percentages). To compare two means for normally distributed data with equal variance, the Student's t-test was used. If the data were not normally distributed or had unequal variance, the Wilcoxon Rank Sum or Mann-Whitney test was employed. For comparisons involving more than two groups, the Kruskal-Wallis test (for not normally distributed data) or the one-way analysis of variance (ANOVA) test (for normally distributed data) was used.

Categorical variables were compared using Pearson's chi-squared test. Given the large sample size, the focus was on both clinically important effects or associations in addition to statistically significant p-values.

3.3.3 Dealing with missing data

The missing data were reported in the relevant section of each chapter, indicating the number of observations (percentage of missingness), with consideration given to any significant variations with respect to outcome variables. To address the missing data, multiple imputations with chained equations (MICE) were performed. All variables of interest, including outcome variables, were included in the imputation models. Missing information in sex, age, outcome variables, and treatment (exposure) variables was removed and then included in the MICE process. Multiple imputation techniques were employed to account for missingness in the data and mitigate biases resulting from missing data.[86] The assumption made for handling the missing data was that they were missing at random (MAR).[87] Data distribution curves for each variable were examined to assess missingness. In the imputation models, variables with a high level of missingness

were included, as studies have shown that multiple imputation frameworks are robust even with high levels of missingness. This approach provides some protection against missing data not at random (MNAR).[88, 89] The missing observations in each variable were replaced with predictions obtained from the multiple imputation model, along with a random error derived from the multivariate regression models. Linear regression was used for continuous variables, logistic regression for binary variables, and multinomial or ordinal logistic regression for ordinal variables. Sensitivity analysis, such as complete case analysis, was also performed where applicable, particularly in cases where missingness was low.

Further details about the methodology and variables included in each model per relevant objective were discussed in the relevant chapter.

3.3.4 Modelling strategy

As the study outcomes were binary, multivariable logistic regression models were utilised to assess the association between the treatment (exposure) variables and the binary study outcomes. The selection of covariates model was based on prior clinical knowledge, data quality (including distribution and level of missingness), and the prognostic relevance of each chosen variable. Following the recommendation and common practices observed in large epidemiological studies, all variables were included in the models to account for potential unmeasured confounders to the greatest extent possible.

Sensitivity analyses were conducted using a backward stepwise approach to identify non-significant variables in the model. The final results were compared with the initial full model. Goodness of fit for each model was assessed using the likelihood ratio test and the area under the curve.[90]To examine multicollinearity among the variables, Variance

Inflation Factors were employed. [91]If multicollinearity was detected, efforts were made to remove the variable causing the issue while maintaining the overall quality of the regression model. The results were reported as adjusted odds ratios (aOR), along with their corresponding 95% confidence intervals (CI) and p-values. A more comprehensive description of the methodology and statistical analysis can be found in the dedicated chapter specifically addressing these aspects.

Chapter 4

CHiP Types, Trends, Characteristics, and Clinical Outcomes According to Sex

4.1 Introduction

This chapter focuses on addressing the first research question outlined in part 1 of the thesis. The objective was to examine the disparities in CHiP types, as well as differences in baseline clinical and procedural characteristics and clinical outcomes between males and females. Furthermore, the investigation explored how these differences have evolved over time. The analysis and findings presented in this chapter were shared at the American College of Cardiology (ACC) April 2022 conference and an abstract of the study was published in the Journal of America College of Cardiology. Additionally, the findings of this study have been published in the Catheterisation and Cardiovascular Intervention Journal. [92].

Worse outcomes following PCI have been consistently associated with female sex in previous studie[93, 94], and this association has been observed even in long-term follow-ups[95]. However, our understanding of sex-specific outcomes in CHiP procedures remains limited. The current evidence on outcomes for females compared to males in CHiP procedures is primarily derived from studies that focused on specific CHiP factors[93, 96, 97]. A recent study conducted at a large tertiary centre examined outcomes in complex-PCI versus non-complex-PCI procedures stratified by sex and identified a sex paradox. This paradox suggests that females undergoing complex PCI tend to have a lower burden of co-morbidities but experience worse outcomes following PCI compared to males[98]. It is important to note that this study's findings are limited in terms of generalisability and cannot provide comprehensive insights into national practice. Furthermore, the authors did not systematically address the differences in case mix among sexes for patients undergoing complex PCI and how these differences have evolved over time.

To address the first question posed in this thesis, as outlined in part 1, it is crucial to examine the risk profile and co-morbidities of patients stratified by sex and explore how these factors have evolved over time in a real-world setting.

4.2 Objectives

The main objectives of this Chapter was to: a) Investigate the differences in CHiP types among sexes and how this has evolved over time. b) Study the differences in baseline clinical and procedural characteristics between CHiP patients stratified by males and females. c) Investigate whether female sex is an independent predictor of worse clinical outcomes in CHiP.

4.3 Methods

The BCIS dataset was utilised for the purposes of this study. A comprehensive description of the dataset can be found in Chapter 3, where all pertinent details are provided.

4.3.1 Study design

This is a retrospective study of prospectively collected cohort from the BCIS dataset.

4.3.2 Study definitions

CHiP was defined in this study as any case that met at least one of the following patients' characteristics: age ≥ 80, chronic renal failure (CRF), poor left ventricular (LV) function, or history of previous coronary artery bypass graft (CABG). Additionally, it included cases that met any one of the following procedural characteristics: left main (LMS) PCI, chronic total occlusion (CTO) PCI, use of LV support devices, or treatment for severe vascular calcifications.

The criteria for poor LV function were based on an ejection fraction of ≤ 30%. The use of LV support devices was determined if a case required the implementation of Impella or IABP. CRF was defined as a chronic elevation of creatinine levels ≥ 200 umol/l, history

of renal transplant, or dependence on renal dialysis (as pre-defined in the BCIS dataset). Severe vascular calcifications were identified if a case required the utilisation of cutting balloons, rotational atherectomy, and/or laser atherectomy.

4.3.3 Study population

The study included all patients who underwent a CHiP procedure, as defined earlier, for stable angina between January 1st, 2006, and December 31st, 2017, based on the BCIS dataset. The cohort comprised all cases with an "elective" indication in the BCIS dataset, specifically for stable coronary artery disease (angina). Cases where the indication of admission was related to any acute coronary syndrome (ST-elevation MI, non-ST elevation MI, and unstable angina) were excluded. Subsequently, the cohort was stratified into two groups: males and females (Figure 4.1).

4.3.4 Study endpoints

The primary outcome of interest for this study was in-patient all-cause mortality. The secondary outcomes of interest included: a) In-hospital major bleeding events. b) Major cardiovascular and cerebral events (MACCE)

Major bleeding events were defined according to the Bleeding Academic Research Consortium's definition for Bleeding Type 2 and above (Table 1)[99]. This encompassed access site bleeding complications such as hematoma, false aneurysm, and retroperitoneal bleeding, as well as the need for blood or blood product transfusion, radiological evidence of intracranial bleed, gastrointestinal bleeding, and access site bleeding requiring intervention or surgery.

MACCE was defined as the composite of Q-wave and non-Q-wave myocardial infarction, re-infarction, and re-intervention (urgent or emergent PCI or CABG). The definitions used in this study were based on a comprehensive literature search of previous studies from the BCIS registry.[3, 100, 101]

Table 1: Bleeding Academic Research Consortium Definition for Bleeding[99]

Type 0: no bleeding
Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3
Type 3a
Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
Any transfusion with overt bleeding
Type 3b
Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
Cardiac tamponade
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
Bleeding requiring intravenous vasoactive agents
Type 3c
Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
Subcategories confirmed by autopsy or imaging or lumbar puncture
Intraocular bleed compromising vision
Type 4: CABG-related bleeding
Perioperative intracranial bleeding within 48 h
Reoperation after closure of sternotomy for the purpose of controlling bleeding
Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
Chest tube output ≥2L within a 24-h period
Type 5: fatal bleeding
Type 5a
Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b
Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).

†Cell saver products are not counted.

This table was adopted from "Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. " Circulation.2011Jun14;123(23):2736-47. doi:10.1161/CIRCULATIONAHA.110.009449. PMID: 21670242

4.3.5 Study covariates

The study covariates were identified using the procedure codes utilised in the BCIS dataset. Relevant data regarding patients' baseline demographics were collected, including age, sex, ethnicity, year of admission, and cardiovascular risks such as family history of CAD, previous MI or PCI, smoking status, history of stroke, history of PVD, diabetes mellitus, hypertension, hypercholesterolaemia, and impaired LV function.

Additionally, important pharmacological therapies were documented, including the use of clopidogrel, ticagrelor, aspirin, prasugrel, warfarin, and glycoprotein IIIbIIa inhibitors. Furthermore, data related to significant procedural characteristics were collected, such as the vascular access site, number of vessels and lesions treated, number of stents used, and the utilisation of procedural devices such as Impella, intra-aortic balloon pump (IABP), cutting balloons, laser atherectomy, and rotational atherectomy devices.

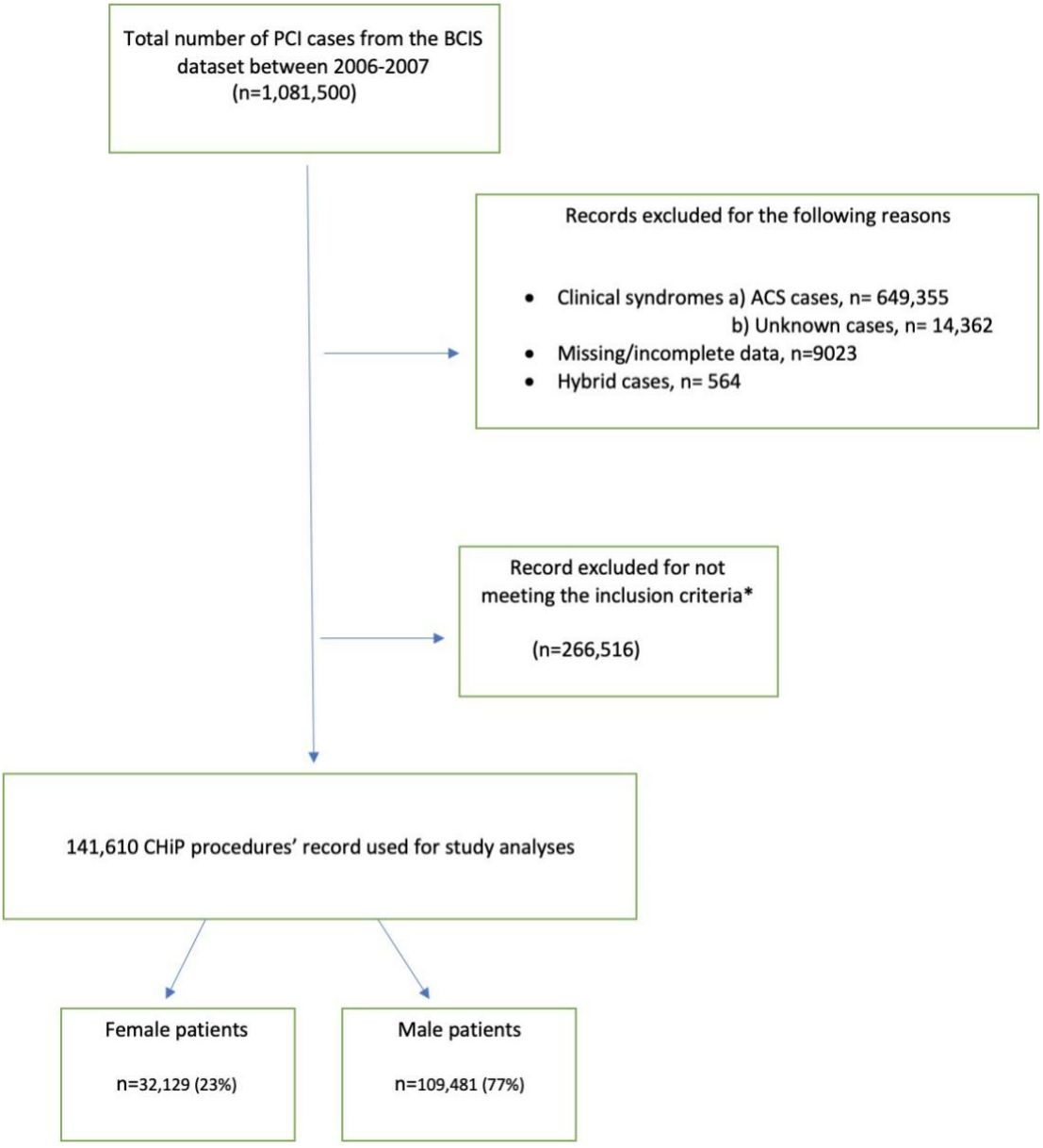
4.3.6 Statistical analysis

The statistical software Stata 14.1 (College Station, Texas, USA) was utilised for all study analyses. In the analysis, any cases with missing data in the sex and outcome variables were excluded (Supplemental Table 4.1). As mentioned in Chapter 3, section 3.3.3, multiple imputations with chained equations were employed to impute the dataset. The following variables were included in the imputation model: age, weight and weight below 60, history of hypertension, hypercholesterolaemia, previous PCI or MI, smoking history, previous CABG, previous stroke, diabetes mellitus, chronic renal failure, PVD, family history of CAD, clopidogrel usage, vascular access, left main PCI, IABP utilisation, number of treated lesions, treatment for severe vascular calcifications, and number of stents used.

Subsequent analyses were performed on the imputed dataset, and the results were pooled using Rubin's rule [102]. Finally, multivariate logistic regression analyses were conducted

to determine the adjusted odds ratios, p-values, and 95% confidence intervals for adverse clinical outcomes. All models included the same variables used in the multiple imputation models.

Figure 4-1: Flow diagram illustrating the process of patients' inclusion and exclusion for the CHiP analysis.



Abbreviations: CHiP, complex, high-risk, but indicated percutaneous coronary intervention; BCIS, British Cardiovascular Intervention Society; PCI, percutaneous coronary interventions.

**Inclusion criteria: left main PCI, PCT to chronic total occlusion vessel, chronic renal failure, poor left ventricle function, severe vessel calcifications, previous coronary artery bypass graft, age => 80 years.*

Descriptive statistics were employed to compare the differences between the groups in baseline demographics, cardiovascular risks, co-morbidities, and procedural characteristics. Chi-square tests and t-tests/Kruskal-Wallis tests were utilised to determine the statistical significance of the differences in baseline characteristics between males and females for categorical and continuous variables, respectively.

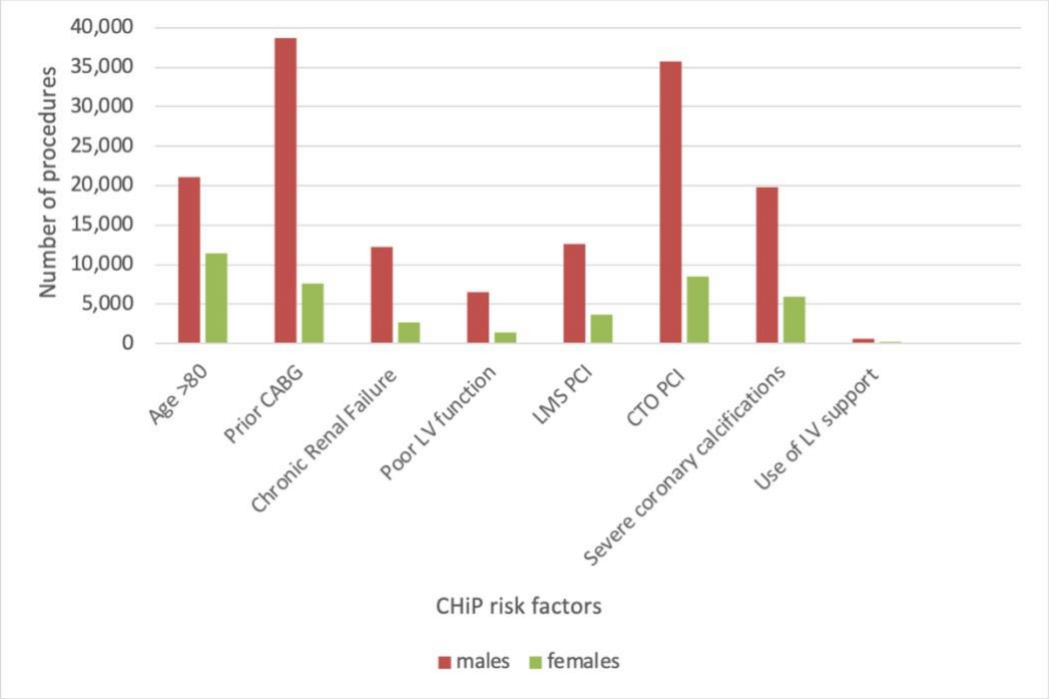
To investigate the association between clinical outcomes and sex (males and females), multivariable logistic regression analyses were conducted. Logistic regression models were fitted using maximum likelihood estimation and were adjusted for all measured and potential confounders, including age, weight, ethnicity, all measured cardiovascular risks, and procedural characteristics.

4.4 Results

4.4.1 Study cohort

The CHiP cohort included a total of 141,610 procedure records conducted in England and Wales between January 2006 and December 2017. This represents approximately 33% of the total 424,290 elective PCI procedures performed during that period. Figure 4.2 displays the absolute number of CHiP factors stratified by sex.

Figure 4-2: Prevalence of CHiP factors in patients with stable angina, stratified by sex.



Abbreviation: CHiP, complex high risk but indicated percutaneous coronary interventions; CABG, coronary artery bypass graft; CTO, chronic total occlusion; LV, left ventricle; LMS, left main stem; PCI, percutaneous coronary intervention.

4.4.2 CHiP factors (Types)

Among females, the most common CHiP types were age >=80 (35.4%), prior CABG (24.3%), and severe vascular calcifications (21.6%). On the other hand, in males, the most prevalent CHiP factors were prior CABG (36%), CTO PCI (34.4%), and severe coronary calcification (22%). The rates of LMS PCI and LV support device use were similar between the two groups. Table 4.1 and Figure 4.2 provide detailed information on these findings.

Table 4-1: Baseline clinical and procedural characteristics of patients with stable angina undergoing CHiP, stratified by sex.

	Total, n	Males, n (%)	Females, n (%)	P-value
Number of participants	141,610	109,481 (77)	32,129 (23)	
Age Median, (IQR)	70.5 (61.9 -79.6)	69.1 (60.7 - 77.5)	75.1 (65.8 - 81.8)	< 0.001
Weight (kg.)		85 (76-95)	70 (62-81.1)	< 0.001
Weight<60 kg) n, (%)		1,580 (1.4%)	4,515 (14.1%)	< 0.001
CHiP risk factors				
a) Patients' factors				
• **Age >80**	32,427 (23)	21,030 (19.2)	11,397 (35.4)	< 0.001
• **Prior CABG**	46,299 (33.4)	38,716 (36)	7,583 (24.3)	< 0.001
• **Chronic Renal Failure**	14,895 (11)	12,234 (11.7)	2,661 (9)	< 0.001
• **Poor LV function**	7,837 (9.4)	6,472(10)	1,365 (7.3)	< 0.001
b) Procedural factors				
• **LMS PCI**	16,220 (12.4)	12,561(11,7)	3,659(11.6)	0.694
• **CTO PCI**	44,184 (33)	35,735 (34.4)	8,449 (21.1)	< 0.001
• **Severe coronary calcifications**	25,743 (22.2)	19,779 (22)	5,964 (22.6)	0.035
• **Use of LV support**	768 (0.57)	573 (0.55)	195 (0.64)	0.064
Cardiovascular risk factors				
• **Hypertension**	87,128 (65.5)	66,206 (64.4)	20,922 (69)	< 0.001
• **Dyslipidaemia**	85,949 (64.6)	66,547 (64.7)	19,402 (64)	0.081
• **Diabetes**	35,091 (26)	27,409 (26.3)	7,682 (25)	< 0.001
• **Smoking**				< 0.001
Never	51,224 (41.6)	35,492 (37)	15,732 (56)	
Ex-smokers	60,046 (48.8)	50,254 (52.8)	9,792 (35)	
Current smokers	11,833 (9.6)	9,401 (9.9)	2,432 (8.7)	
• **Family history of CAD**	52,183 (46.7)	43,784(46.6)	13,040 (47.2)	0.054
• **History of MI**	56,294 (42.6)	45,602 (44.6)	10,692 (35.6)	< 0.001
• **Previous PCI**	48,763 (38.2)	39,201 (40)	9,562 (32.5)	< 0.001
• **Previous stroke**	6,300 (4.7)	4,820 (4.7)	1,480 (4.9)	0.135
• **History of PVD**	9,175 (6.9)	7,244 (7)	1,931 (6.4)	< 0.001
• **LV systolic function**				< 0.001
Normal (EF>50)	58,589(70.2)	44,366 (68.6)	14,223 (76)	
Impaired (EF 30-50)	17,050 (20.4)	13,845 (21.4)	3,205 (17)	
Severe (EF<30)	7,837 (9.4)	6,472 (10)	1,365 (7)	
Pharmacology				
• **Warfarin**	2,742 (2.2)	2,201 (2.3)	541 (1.9)	< 0.001
• **GPIIbIIIa inhibitors**	9,935 (7.8)	9,935 (8)	2,014 (7)	< 0.001
• **Prasugrel**	1,144 (0.9)	929 (0.9)	215 (0.7)	0.002
• **Ticagrelor**	4,488(3.5)	3,548 (3.6)	940 (3.3)	0.005

Vascular access				< 0.001
• **Radial**	61,825 (45)	48,525 (46)	13,300 (43)	
• **Femoral**	63,837 (46)	48,261 (45)	15,576 (49)	
• **Multiple accesses**	12,123 (9)	9,754 (9)	2,369 (8)	
Circulatory support				
• **No support**	134,281 (99.43)	103,953 (99.46)	30,328 (99.37)	0.564
• **IABP**	714 (0.53)	528 (0.5)	186 (0.6)	0.027
• **Impella**	57 (0.04)	47 (0.04)	10 (0.03)	0.361
Number of treated lesions				<0.001
• **One**	90,039 (64.4)	69,167 (63.8)	20,872 (65.9)	
• **Two**	35,136 (25)	27,387 (25.3)	7,749 (24.5)	
• **Three**	14,808 (10.6)	11,760 (10.9)	3,048 (9.6)	
Procedural devices				
• **None**	90,520 (77.2)	69,947 (77)	20,357 (76.1)	0.034
• **Cutting Balloon**	15,268 (13)	11,889 (13.2)	3,379 (13.2)	0.082
• **Rotational atherectomy**	10,542 (9)	7,937 (9)	2,605 (10)	<0.001
• **Laser atherectomy**	86 8 (0.8)	692 (0.8)	176 (0.7)	0.089
Number of stents used				< 0.001
• **None**	19,842 (14)	15,677(14)	4,165 (13)	
• **One stent**	56,884 (40.5)	42,947 (39)	13,937 (44.5)	
• **Two stents**	35,736 (25.5)	27,721 (25)	8,015 (24.5)	
• **Three or more stents**	27,895 (20)	22,180 (22)	5,715 (18)	
Target Vessel PCI				
• **Left main stem (LMS)**	16,220 (12.4)	12,561(11,7)	3,659(11.6)	0.694
• **LAD**	56,879(41)	42,996 (40)	13,883 (44)	< 0.001
• **LCX**	35,588 (26)	28,655 (27)	6,933 (22)	< 0.001
• **RCA**	49,570 (35)	37,660 (35)	11,910 (38)	< 0.001
• **Graft**	13,415 (9.6)	11,178 (10.4)	2,237 (7)	< 0.001
Number of target vessel PCI				< 0.001
• **One**	102,583 (75)	79,075 (74.3)	23,508 (75.7)	
• **Two**	27,582 (20)	21,583 (20.3)	5,999 (19.3)	
• **Three**	7,203 (5)	5,680 (5.4)	1,523 (5)	

Abbreviations: CHiP, complex high risk percutaneous coronary intervention; CABG, coronary artery bypass graft; CTO, chronic total occlusion; CAD, coronary artery disease; GPIIbIIIa, glycoprotein IIaIIIb; LV, left ventricle; LMS, left main stem; LCX, left circumflex; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery.

4.4.3 Baseline characteristics

Table 4.1 provides detailed information on the baseline demographics, cardiovascular risks, procedural characteristics, and pharmacology according to sex. The overall median age of the cohort was 70.5 years (interquartile range [IQR] 61.9 - 79.6), and approximately 26% of the patients had diabetes mellitus.

When stratified by sex, the data showed that 14.1% of females were below 60 kilograms (kg) compared to only 1.4% of males. Females were, on average, 5.7 years older than their male counterparts (median age: females 74.8 vs males 69.1; $p<0.001$).

In terms of cardiovascular risk factors, hypertension was more prevalent among females (69% vs 64.4% in males; $p<0.001$), and the percentage of non-smokers was higher among females (56% vs 37% in males; $p<0.001$). On the other hand, males had a higher prevalence of previous MI (44.6% vs 35.6% in females; $p<0.001$), previous PCI (40% vs 32.5% in females; $p<0.001$), and moderately impaired (21.4% vs 17% in females; $p<0.001$) and severely impaired (10% vs 7% in females; $p<0.001$) LV function.

4.4.4 Procedural characteristics

Females, compared to males, had higher rates of PCI into the left anterior descending artery (LAD) (44% vs 40% respectively; $p<0.001$) and the right coronary artery (RCA) (38% vs 35% respectively; $p<0.001$). Conversely, males had higher rates of PCI into the left circumflex artery (LCX) (27% vs 22% respectively; $p<0.001$) and graft PCI (10.4% vs 7% respectively; $p<0.001$). The rates of LMS PCI were similar between the sexes ($p=0.694$).

Overall, females had less extensive CAD than males. A higher percentage of females had only one lesion treated (65.9% vs 63.8% respectively; $p<0.001$) and required one stent only (44% vs 39.6% respectively; $p<0.001$). While the rates of laser atherectomy and

cutting balloons did not differ between the groups, females had higher rates of calcium modification using rotational atherectomy devices (10% vs 9% respectively; p<0.001).

In terms of procedural access, CHiP procedures undertaken via radial access were less common among females compared to males (43% vs 46% respectively; p<0.001), as was the use of dual access (8% vs 9% respectively; p<0.001). Furthermore, the use of intra-aortic balloon pump (IABP) was slightly higher among female patients (0.6% vs 0.5% respectively; p=0.027).

4.4.5 Clinical outcomes

The crude in-patient mortality, major bleeding, and MACCE rates were higher in females compared to males. Specifically, the mortality rate was 0.45% in females and 0.25% in males, the major bleeding event rates were 1.42% in females and 0.63% in males, and the MACCE rate was 1.76% in females and 1.4% in males (p<0.001 for all comparisons) (Table 4.2).

After adjusting for differences in baseline clinical and procedural characteristics, female sex was independently associated with worse odds for mortality (aOR 1.78, 95% , CI 1.4-2.2; p<0.001), major bleeding events (aOR 1.99, 95% CI 1.72-2.30; p<0.001), and MACCE (aOR 1.23, 95% CI 1.09-1.38; p<0.001) (Table 4.3).

Table 4-2: Crude outcomes of patients with stable angina undergoing CHiP, stratified by sex.

Variables	n (%)	Males, n (%)	Females, n (%)	P-value
Mortality	421 (0.3)	275 (0.25)	146 (0.45)	<0.001
Major bleeding events	1,140 (0.81)	685 (0.63)	455 (1.42)	<0.001
MACCE	2,101 (1.5)	1,534 (1.4)	567 (1.76)	<0.001

Abbreviation: CHiP, complex high risk percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

Table 4-3: Adjusted odds of adverse outcomes post CHiP in patients with stable angina (reference, males)

	Odd ratio	95% Confidence Interval	P value
Death	1.78	1.4-2.2	0.001
Major bleeding events	1.99	1.72-2.30	0.001
MACCE	1.23	1.09-1.38	0.001

Abbreviation: CHiP, complex high-risk but indicated percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

4.4.6 Temporal trends

Figure 4.3 depicts the changes in the prevalence of CHiP factors among sexes over time. The number of CHiP cases increased from 7,525 in 2006 to 13,722 in 2017. However, the percentage change in females remained stable throughout the years. Figure 4.4 provides a detailed breakdown of the temporal trends in each CHiP factor, categorised by sex. In general, there was a gradual increase in the number of cases involving individuals aged 80 and above, those with a history of chronic renal failure (CRF), and LMS PCI in both males and females. Interestingly, females consistently accounted for approximately 20-24% of the procedures within each CHiP factor category across the study years.

Table 4.4 presents the temporal trends based on three study groups (Group 1: 2006-2009, Group 2: 2010-2013, Group 3: 2014-2017) for the crude outcomes by sex. Mortality trends in males remained unchanged over time and consistently remained lower than those observed in females. Conversely, females mortality rates gradually increased from 0.4% in Group 1 to 0.5% in Group 3 ($p<0.001$ for both). Major bleeding events and MACCE rates showed a declining trend in both males and females, with females consistently experiencing higher rates than males. For major bleeding events, rates decreased from 0.6% to 0.5% in males and from 1.7 % to 1.3% in females (Group 1 to Group 3, respectively; $p<0.001$ for both). Similarly, MACCE rates decreased from 1.7%

to 2.1% in males and from 2.1% to 1.6% in females (Group 1 to Group 3, respectively; p<0.001 for both).

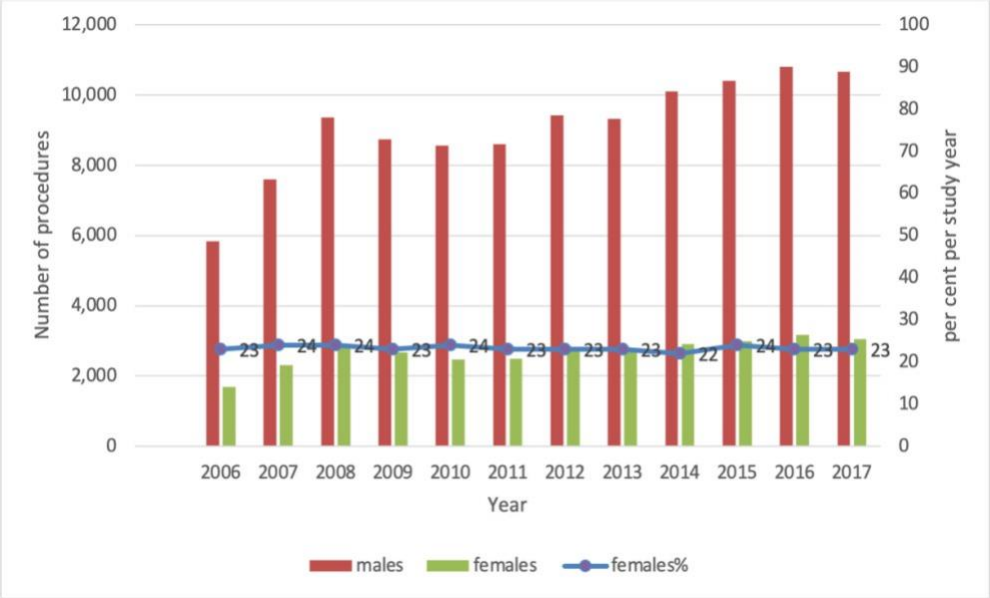
These findings indicate that there have been changes in the prevalence of CHiP factors over time, with an overall increase in cases. However, the percentage distribution of CHiP factors among females remained relatively stable. Additionally, while mortality rates in males remained consistent, there was a gradual increase in mortality rates among females. Major bleeding events and MACCE rates showed a declining trend in both sexes, but females consistently exhibited higher rates compared to males throughout the study period.

Table 4-4: Temporal trends of outcomes of patients with stable CAD undergoing CHiP, stratified by sex.

Variables	**Group1**	**(2006-2009)**		**Group2**	**(2010-2013**		**Group3**	**(2014-2017)**	
	Males n (%)	Females n (%)	P value	Males n (%)	Females n (%)	P value	Males n (%)	Females n (%)	P value
Mortality	83 (0.3)	37 (0.4)	P= 0.047	85 (0.2)	46 (0.4)	P= 0.001	107 (0.3)	63 (0.5)	P<0.001
Major Bleeding Events	189 (0.6)	159 (1.7)	P<0.001	270 (0.8	139 (1.3)	P<0.001	226 (0.5)	157 (1.3)	P<0.001
MACCE	539 (1.7)	196 (2.1)	P=0.024	538 (1.5)	183 (1.7)	P=0.071	457 (1.1)	188 (1.6)	P<0.001

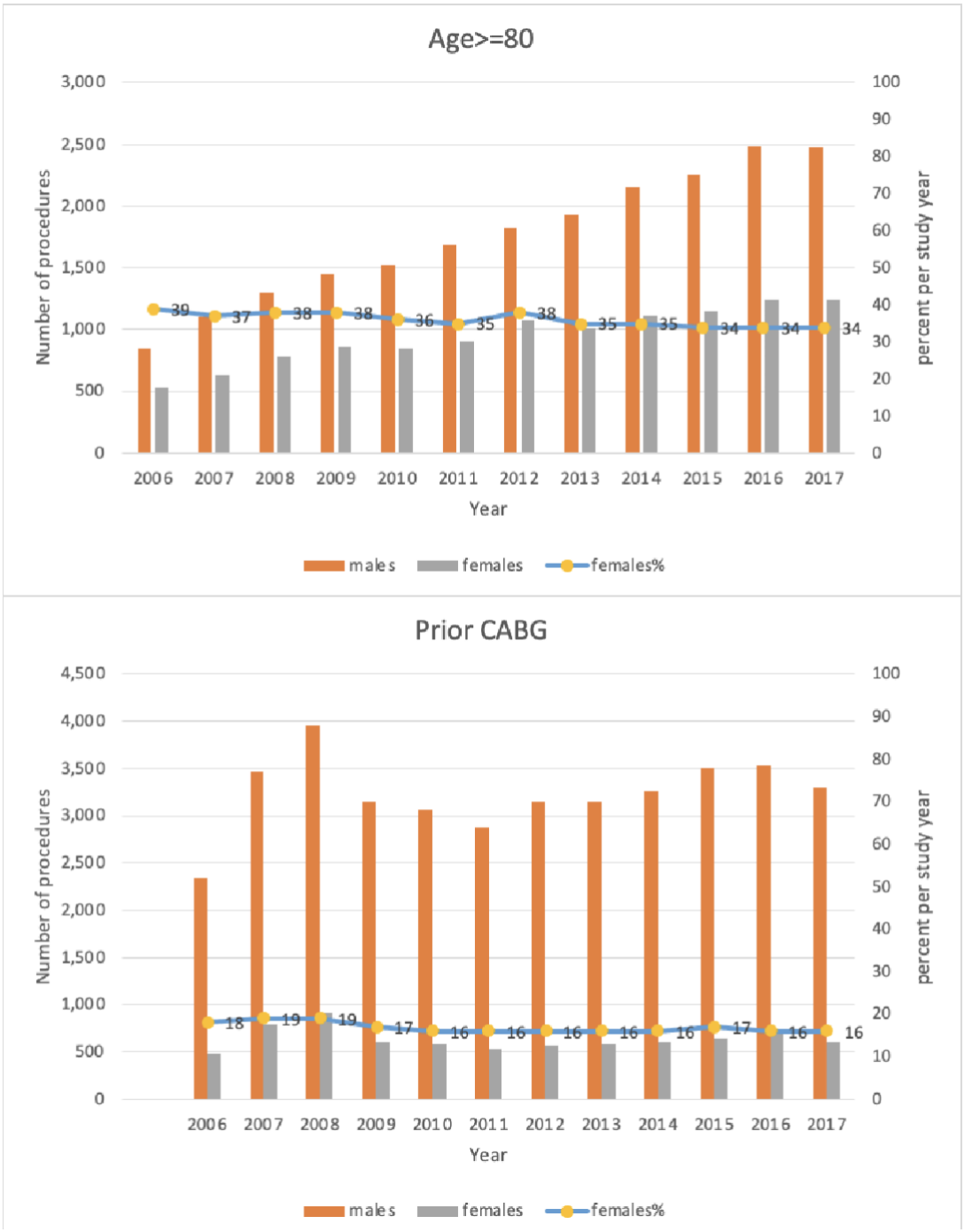
Abbreviation: CAD, coronary artery disease; CHiP, complex high-risk but indicated percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

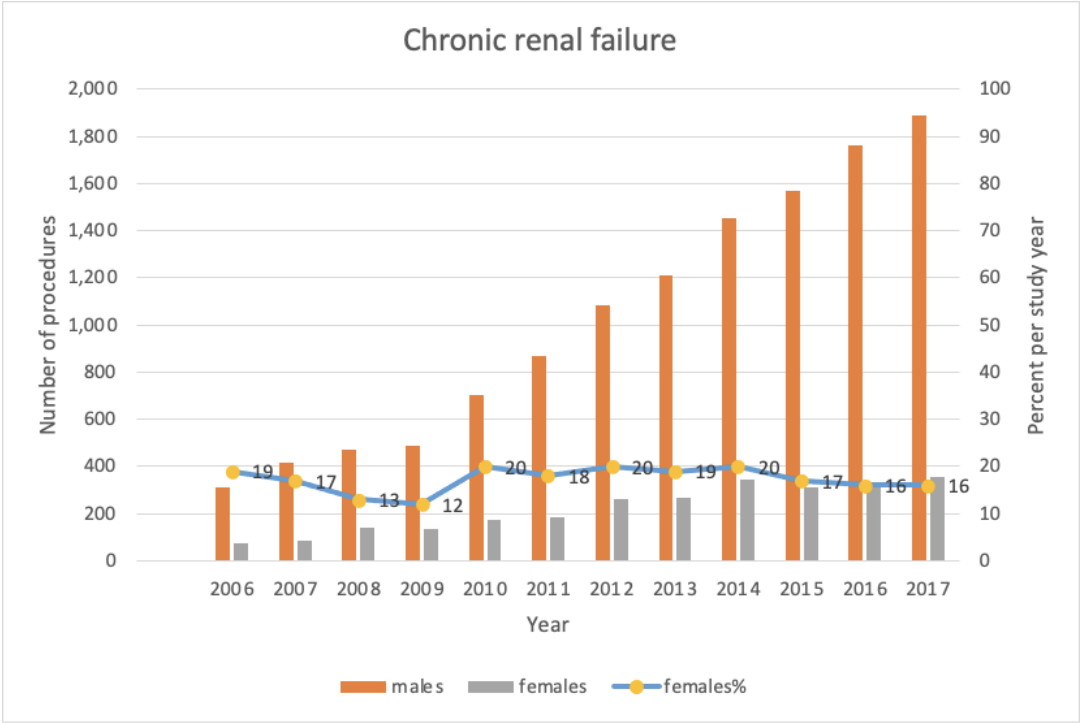
Figure 4-3: Temporal changes in CHiP procedures' prevalence and percent changes over time, stratified by sex.

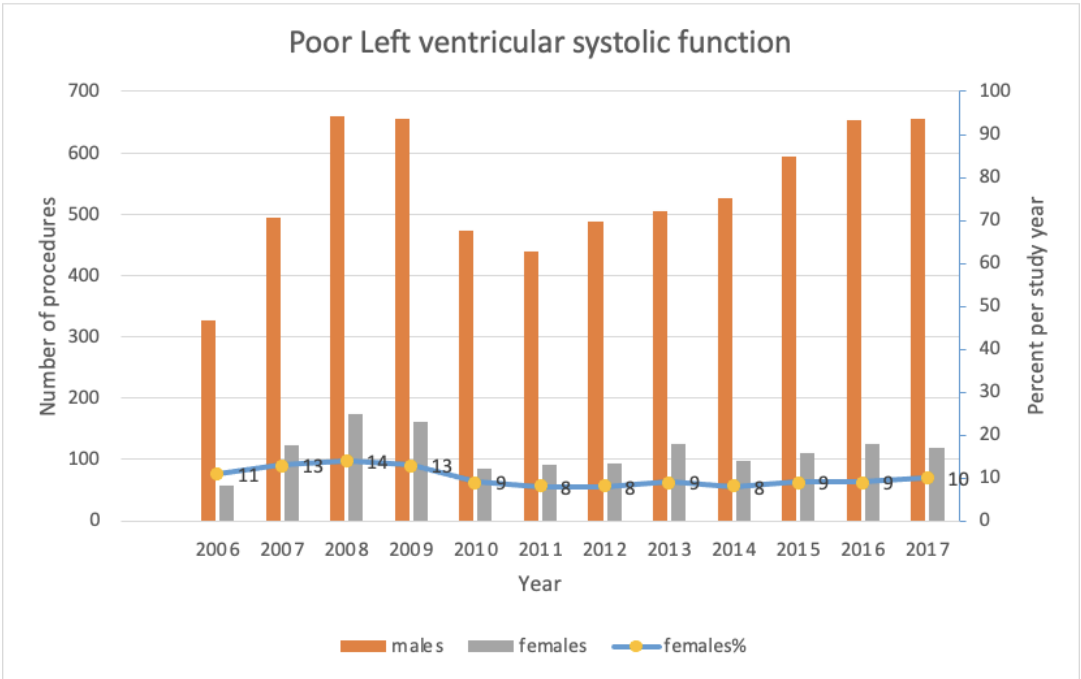


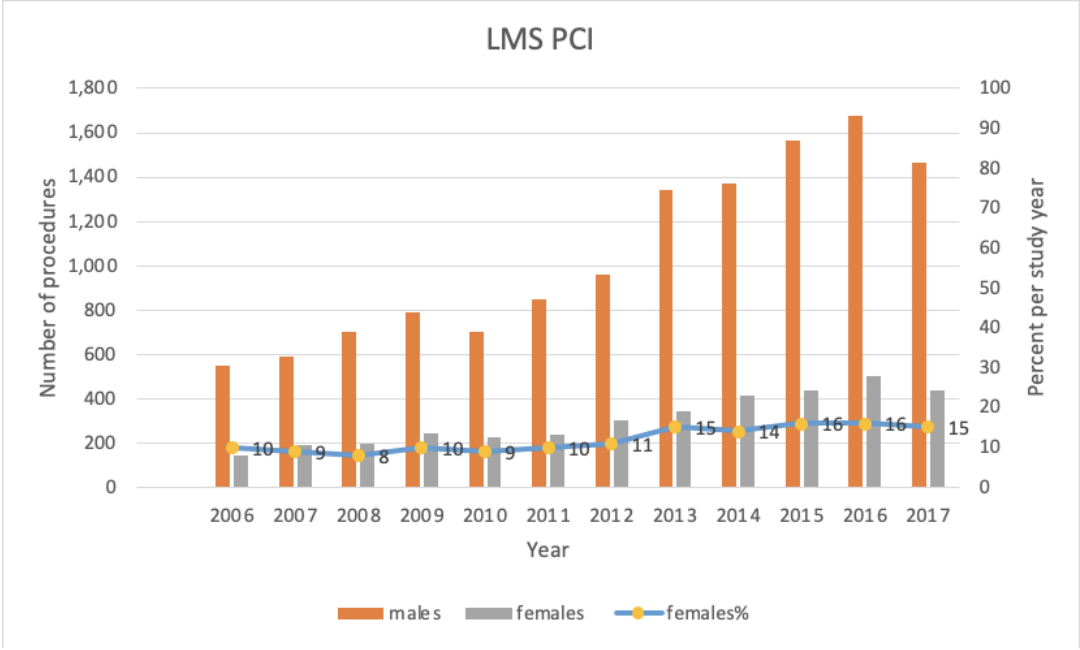
Abbreviation: CHiP, complex high-risk but indicated percutaneous coronary interventions

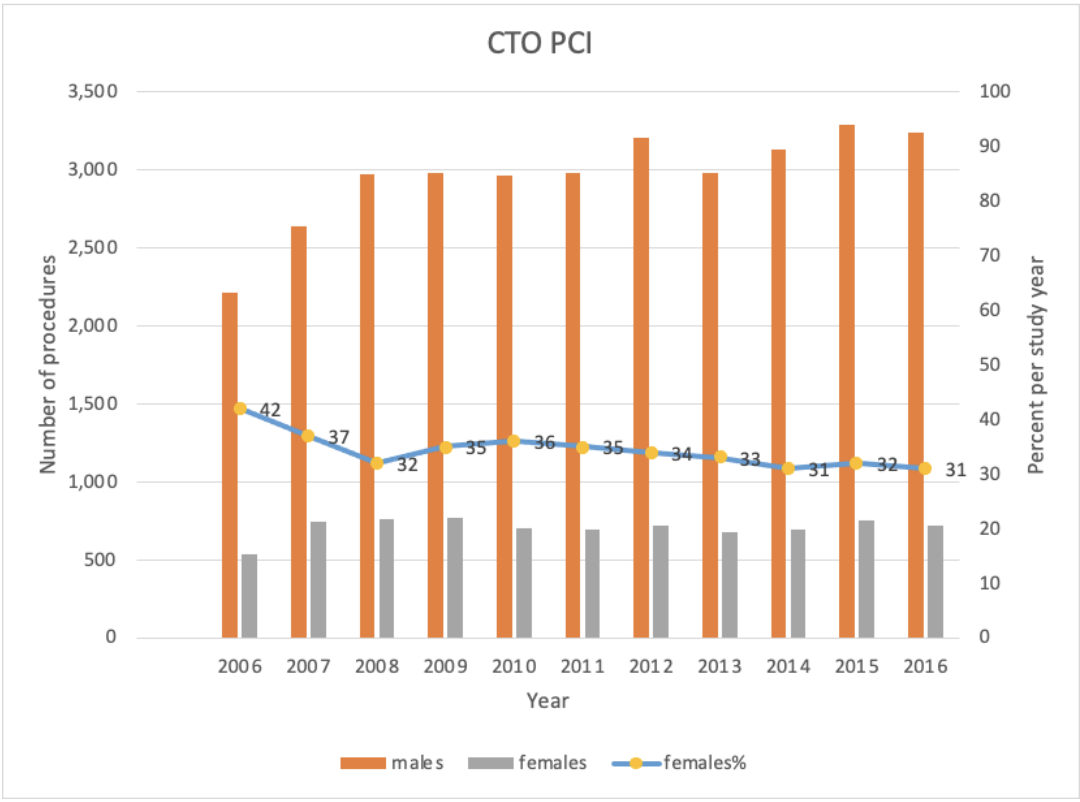
Figure 4-4: Temporal changes in each CHiP factor stratified by sex

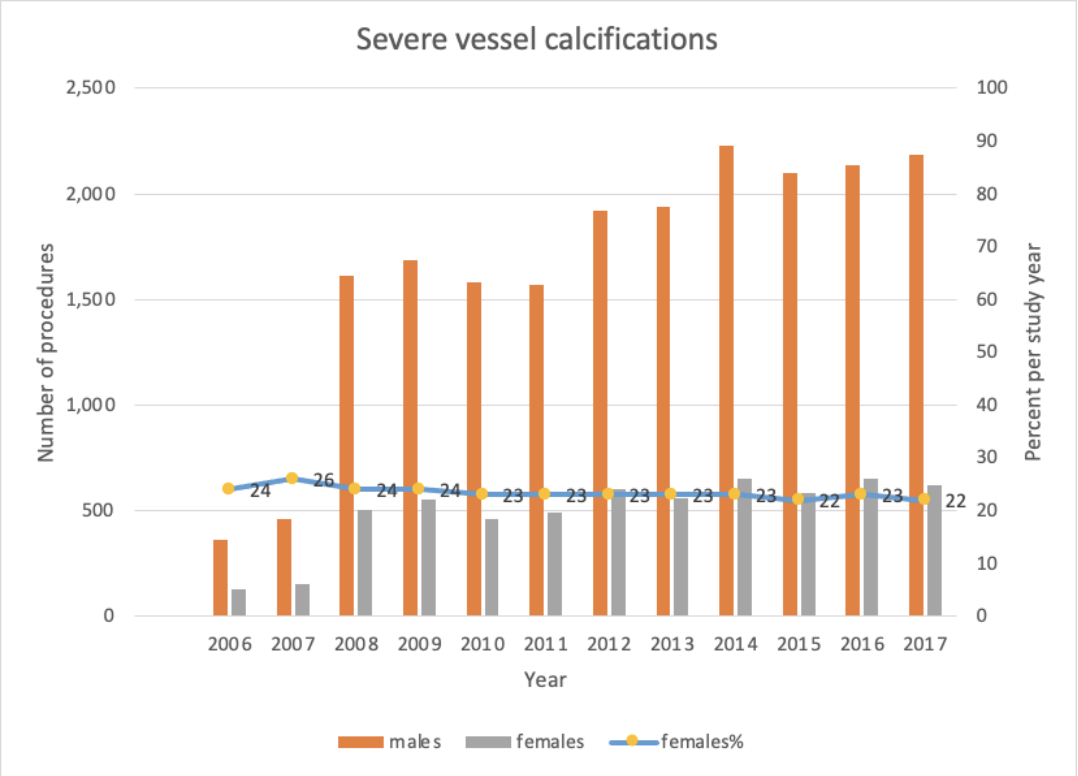


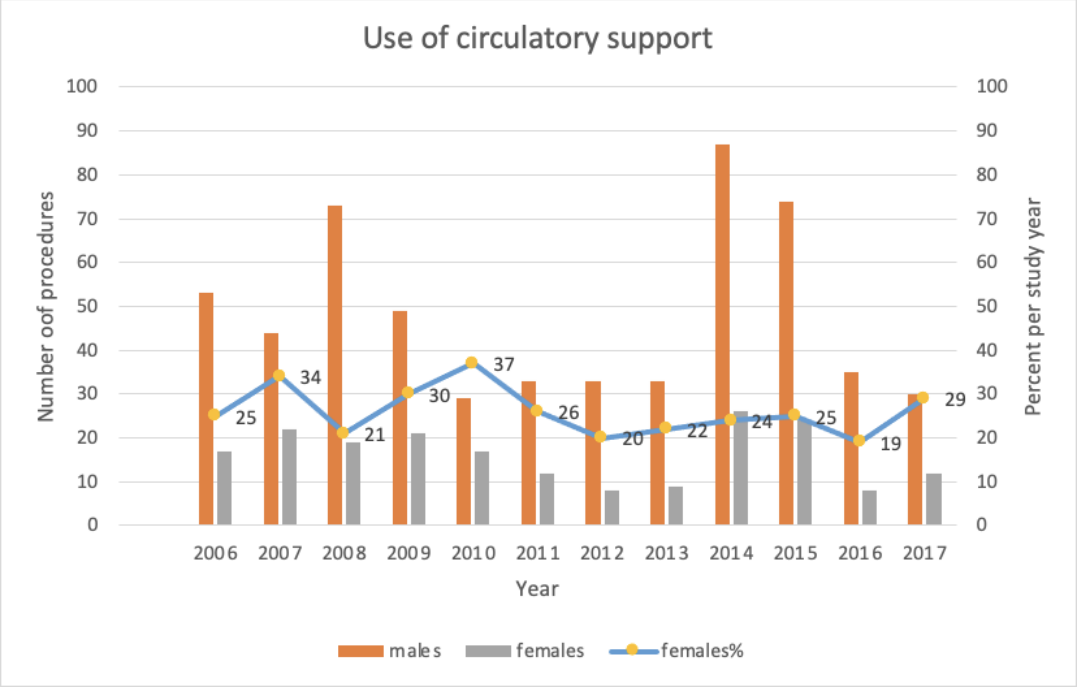

Chronic renal failure
Number of procedures
Percent per study year
Year
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
19 17 13 12 20 18 20 19 20 17 16 16
males
females
females%


Poor Left ventricular systolic function
Number of procedures
Percent per study year
Year
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
11 13 14 13 9 8 8 9 8 9 9 10
males
females
females%


LMS PCI
Number of procedures
Percent per study year
Year
1,800
1,600
1,400
1,200
1,000
800
600
400
200
0
100
90
80
70
60
50
40
30
20
10
0
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
10 9 8 10 9 10 11 15 14 16 16 15
males
females
females%


CTO PCI
Number of procedures
Percent per study year
Year
3,500
3,000
2,500
2,000
1,500
1,000
500
0
100
90
80
70
60
50
40
30
20
10
0
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016
42 37 32 35 36 35 34 33 31 32 31
males
females
females%





Abbreviation: CHiP, complex high-risk but indicated percutaneous coronary interventions, LMS, left main stem, PCI, percutaneous coronary intervention, CABG, coronary artery bypass graft.

4.5 Discussion

This large nationwide study analysed the records of 141,610 patients who were admitted electively for invasive management of stable CAD and underwent Complex High-Risk Indicated Procedures. The findings revealed significant disparities in the types of CHiP procedures performed between the two sexes. Additionally, there were notable variations in their baseline characteristics, clinical outcomes, and changes over time. These results provide evidence for the existence of a sex paradox, wherein females who received a CHiP procedure were typically older and had fewer cardiovascular risk factors and less complex CAD than their male counterparts. However, despite lower risk profile, females experienced worse clinical outcomes, and this pattern remained consistent over time. This finding extends our knowledge on PCI outcomes according to sex, where the female sex was found to be associated with worse outcomes following PCI in general[93, 95, 103].

Among females, the most common CHiP factor was age 80 years and over. While it is well-established that co-morbidity burden increases with age[93], our analysis confirmed that females, despite being older on average, had a lower risk profile compared to males. Moreover, existing studies on CAD severity with respect to sex have shown that females tend to have less complex CAD with favourable plaque morphology, along with an increased prevalence of hypertension and a family history of CAD similar to our study findings [104, 105].

The fourth most common CHiP factor in females was PCI to a CTO vessel. Prior registry data reported that the percentage of females undergoing PCI for CTO ranged from 14% to 23%, which is lower than the percentage of females undergoing PCI in general (30%) or PCI for stable angina (25-28%) [96, 106]; Other studies have also confirmed that CTOs in females are often managed medically[97]. Since females with CTO lesions are typically older and more likely to have co-morbidities, they are commonly perceived to be at an

increased risk of peri-procedural complications, which may discourage cardiologists from offering PCI to females with CTO lesions.

Similarly, the proportion of females with a prior history of CABG (the second commonest CHiP factor in females in our study) undergoing PCI was significantly lower compared to males (24% vs. 36%). Research has shown that females are less likely to receive CABG for multivessel disease,[107] possibly due to their older age, higher co-morbidity burden, or the presence of smaller epicardial arteries that are not suitable for grafting [108]. Furthermore, it is crucial to acknowledge the potential systematic bias in the selection or offering of CABG to females [109]. This bias is also evident in the management of angina according to sex, where females presenting with angina symptoms are more likely to receive medical management compared to males. For example, a study examining the management of chest pain in an ambulatory service found that, although the same proportion of males and females presented with cardiac-sounding chest pain, males were 2.5 times more likely to be referred to a cardiologist (aOR 2.30; 95% CI, 1.30-3.78)[110]. Even after referral to a cardiologist, females were less likely to be referred for invasive management (OR 0.59; 95% CI, 0.48 to 0.72)[111] .

Nevertheless, there was a gradual increase in the absolute CHiP number among those with previous CABG, CRF, and LMS PCI in both sexes. Similar trends have been observed in studies focusing on individual CHiP factors and their outcomes[112].

This analysis showed that female sex is independently associated with worse odds for mortality, which was even higher when compared with mortality odds in females from other studies looking at sex outcomes post non-complex PCI[93, 94, 103]. The risk of in-hospital mortality in females in this analysis was 80% higher than that seen in males even after adjustment for differences in baseline covariables. Similarly, major bleeding rates were 2 folds higher, and MACCE rates were 20% higher in females than males.

Looking for plausible explanations from studies that tried to address this issue, we cannot help but recognise the differences in utilising, for example, the bleeding avoidance strategies among sexes,[113] which may explain higher rates of major bleeding and mortality in females. Despite the clear benefits of radial access use, there still lower uptake of this approach in females, as evident in current and preceded studies [114, 115] . But also, the older age in females was associated with higher rates of severe vascular calcifications and hence the use of calcium modification devices which could be attributed to the higher coronary perforation rate and hence MACCE, which is a fact proved by other studies[116].

Moreover, there is growing evidence from studies to back up the underutilisation of evidence-based medical therapies in females [117]. Finally, females are more likely to have co-morbidities that are not captured in this analysis/BCIS registry that could attribute to the observed worse outcomes such as anaemia, frailty, connective tissue disorders, chronic obstructive airway diseases, and poorly controlled diabetes mellitus[94, 117] that are known to portend worse outcomes.

4.6 Study limitations

This study offers valuable real-world insights into Complex High-Risk Indicated Procedures outcomes on a national scale, providing the first comprehensive analysis of unselected cases. The British Cardiovascular Intervention Society database, which captures a nearly complete record of procedures performed in England and Wales, served as the primary data source. With a large sample size, this study was adequately powered to detect significant differences in outcomes between groups.

Several limitations should be acknowledged. Firstly, due to the retrospective nature of the analysis and the absence of randomisation, the possibility of unmeasured confounders in clinical and procedural characteristics cannot be entirely ruled out. It is crucial to consider

the presence of potential confounding factors not recorded in this dataset. Secondly, reporting and coding errors may introduce bias, including the underreporting of co-morbidities and complications that were self-reported without external validation. Additionally, although peri-procedural MI incidence is clearly defined in the BCIS dataset, the specific diagnostic criteria used (such as the third or fourth universal MI definitions or Society for Cardiovascular Angiography and Interventions) are not specified. While statistical significance was achieved by including a large number of patients, the results section indicates minor differences for several variables. The clinical significance of these small differences remains uncertain [118]. Furthermore, it is important to note that this study solely examined in-patient outcomes, and more extended follow-up periods would offer a more comprehensive assessment of outcomes.

4.7 Conclusion

To summarise, this study presents the first nationwide analysis of 141,610 Complex High-Risk Indicated Procedures performed on patients with CAD between January 1, 2006, and December 31, 2017 stratified by sex. The analysis revealed notable differences in case mix between males and females undergoing CHiP procedures. Females tended to be older, had a lower burden of cardiovascular co-morbidities, and exhibited less complex coronary disease. A majority of females received a single stent and had one lesion treated, whereas in males, prior CABG followed by PCI to a CTO vessel were more common CHiP factors. Furthermore, significant disparities in outcomes following CHiP procedures were observed between the sexes. Females exhibited a higher risk of mortality, major bleeding events, and MACCE compared to males.

These findings highlight the importance of optimising peri-procedural care, employing advanced technologies, and implementing evidence-based therapies to improve outcomes for female patients undergoing CHiP procedures.

Chapter 5

CHiP Types, Trends, Characteristics, and Clinical Outcomes According to Ethnicity

5.1 Introduction

This chapter investigates whether the ethnic background is associated with distinct outcomes following Complex High-Risk Indicated Procedures (CHiP) in patients with stable angina. The analysis presented in this chapter was initially shared at the Trans Catheter Therapeutics (TCT) conference Nov 2021 and the abstract has been published in the Journal of the American College of Cardiology. Additionally, the findings from this chapter have been published in the American Journal of Cardiology.

Studies examining the influence of ethnic differences in baseline characteristics and management of patients with coronary artery disease have emerged over the past three decades. [119, 120]. Since then, insights obtained from randomised trials and observational studies have revealed variations in CAD risks and outcomes post-PCI among different ethnic groups[121-125]. While some studies have reported similar outcomes post PCI among different ethnic groups [122, 123], other studies have shown that Black, Asian, and other ethnic minorities (BAME) have worse outcomes [101, 109, 125]. However, limited data are available regarding CHiP outcomes among ethnic groups, and existing studies have often focused on specific CHiP factors in highly selected patient cohorts. For instance, some studies have examined outcomes in patients who underwent CTO PCI procedure [126], addressed outcomes in the last remaining vessel[127], or investigated specific populations such as those with end-stage renal disease[128 129], or were limited to certain geographical areas[128].

Furthermore, the importance of studying CHiP outcomes among the BAME population has increased significantly due to the rising number of CHiP procedures and the growing BAME population. Currently, the BAME population represents 13% of the total population in England and Wales, and it is projected to reach 20% by 2050[130, 131].

5.2 Objectives

The main objectives of this chapter were as follows:

I. To investigate ethnic variations in the types of CHiP procedures performed.

II. To assess differences in cardiovascular risk factors among ethnic groups undergoing CHiP.

III. To examine variations in procedural characteristics of CHiP procedures across ethnic groups.

IV. To compare CHiP outcomes among different ethnic groups.

V. To analyse CHiP trends and assess changes over time.

5.3 Methods

In Chapter 3, a comprehensive description of the methods employed in this study has been provided. Nonetheless, a concise summary of these methods will be presented in this chapter.

5.3.1 Study design and dataset

This is a retrospective study of prospectively collected data from the BSCIS dataset. The BCIS dataset is managed by NICOR, and it collects data from over 95% of PCI centres in England and Wales (112 out of 117 PCI centres). The dataset includes a wide range of important patients demographics, cardiovascular risk factors, pharmacology, procedural characteristics, as well as important clinical outcomes/complications that includes but not limited to success in procedures, immediate complications such as coronary perforation, death, re-intervention, re-infarction, and bleeding complications[14]. As part of NICOR audit initiatives, all data are encrypted after being collected prospectively before then being transferred to the database server. Ethical approval was not needed as all data have

section 251 approval of NHS Act 2006 which allows the data to be used for research and audit purpose without seeking consent from patients.[85]Moreover, the BCIS dataset quality and accuracy have been previously proven.[84]

5.3.2 Study population

The study included all patients who were admitted electively for PCI between 1st January 2006 and 31st December 2017, using the indication for admission variable from the BCIS dataset. Patients were selected based on specific patient characteristics or procedural characteristics. Patient characteristics included age>=80 years, chronic kidney disease (CKD), previous history of CABG, or severe LV dysfunction. Procedural characteristics included left main (LMS) PCI, CTO PCI, severe vascular calcification, or use of LV support devices (Impella or IABP).

Severe LV impairment was defined as LV function with an ejection fraction (EF) <=30%, while CKD was defined as chronic creatinine elevation of 200 umol/l, renal dialysis dependence, or a history of renal transplant, all of which were predefined in the BCIS dataset. Extensive vascular calcifications were defined as the use of calcium modification devices such as cutting balloons and rotational or laser atherectomy devices. A sample size of >13628 was determined to provide a statistical power of 0.8 at an alpha level of $p<0.05$. The collected data was then categorised into two groups: White and BAME (Black, Asian, and minority ethnic) [Figure 5.1].

5.3.3 Study Covariates

Information on baseline demographics, including age, weight, BMI, year of admission, sex, cardiovascular risk factors (hypertension, hypercholesterolaemia, family history of CAD, smoking history, diabetes mellitus), and LV function, was collected. Procedural characteristics were also recorded, such as access site, number of treated vessels and lesions, and size and diameter of stents used. In addition, pharmacology data, including

the use of aspirin, clopidogrel, glycoprotein IIb IIIa inhibitors, and warfarin, were documented. All of these variables were predefined in the BCIS dataset. The BMI variable was calculated based on the weight and height variables.

5.3.4 Study Outcomes

The study outcomes were categorised into primary and secondary outcomes. The primary outcome was in-hospital mortality, while the secondary outcomes included: a) in-hospital major bleeding events and b) in-hospital MACCE (Major Adverse Cardiac and Cerebrovascular Events).

In-hospital mortality data were obtained from the BCIS dataset, specifically from the death variable. Major bleeding events were defined according to the Bleeding Academic Research Consortium's criteria for Bleeding Type 2 and above (Table 1)[132]. This encompassed cases requiring blood transfusion or blood product administration, access site complications (e.g., haematoma, bleeding necessitating intervention or surgery, retroperitoneal bleed, arterial dissection, false aneurysms, or fistulas), as well as radiological evidence of intracranial or gastrointestinal bleeding.

MACCE was defined as the cumulative incidence of death, peri-procedural myocardial infarction (MI), or in-hospital stroke. All of the variables used to measure these clinical outcomes were predefined in the BCIS dataset.

5.3.5 Statistical analysis

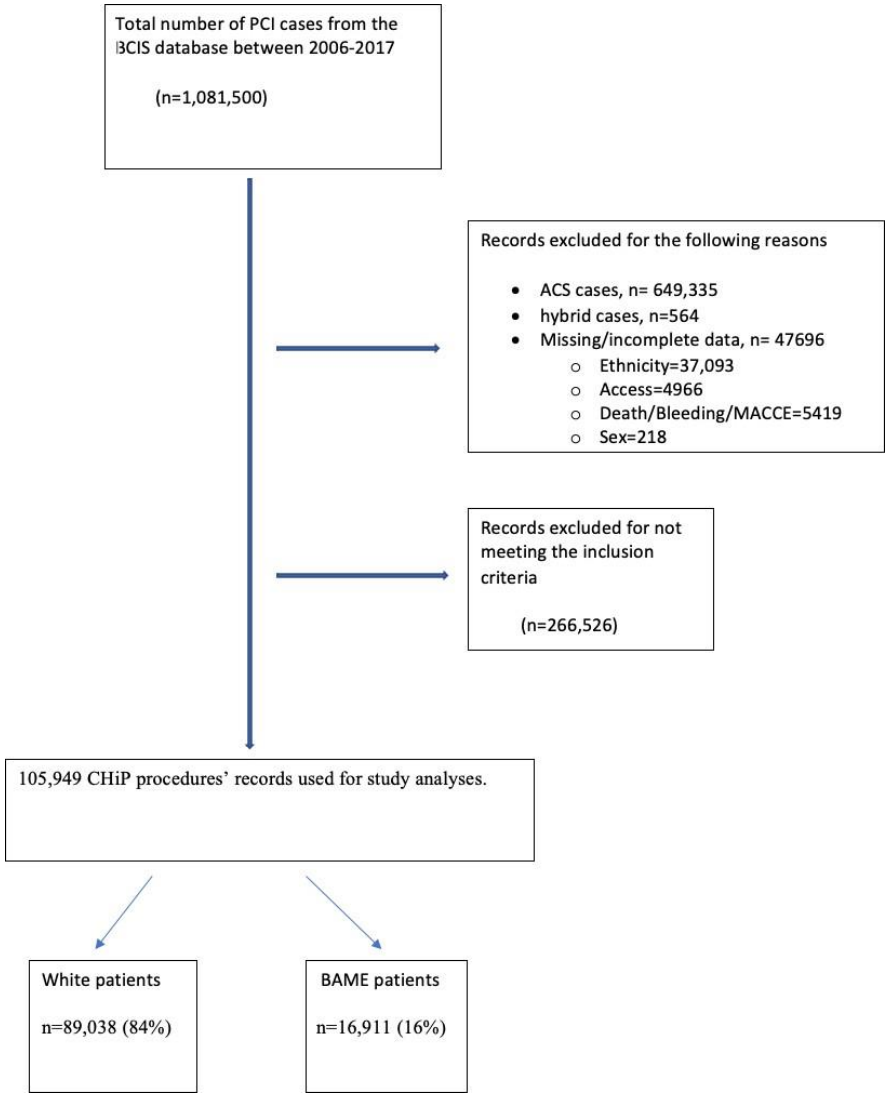
Descriptive statistics were employed to compare the differences between the two groups in terms of baseline demographics, cardiovascular risk factors, procedural characteristics, and outcomes. All missing data in the ethnicity and outcome variables were deleted (Supplemental Table 5.1). Continuous variables were summarised as median with interquartile range, while categorical or ordinal variables were presented as frequencies and percentages. Categorical variables were compared using the chi-square test, and continuous variables were compared using the Kruskal-Wallis test. Missing variables in

ethnicity, sex, and outcome variables were deleted. Missing data were imputed using multiple imputations with chained equations to create 10 dataset, assuming missing data were missing at random (MAR). In our multiple imputation framework, we used logistic regression for binary variables, ordinal logistic regression for ordered, multinomial for nominal, and linear regression for continuous variables . The following variables were included in the imputation model: ethnicity, sex, age, and outcome variables were registered as regular. The following variables were imputed: BMI, history of hypercholesterolaemia, previous PCI, previous CABG, previous MI, previous CVA, diabetes mellitus, hypertension, renal failure, PVD, clopidogrel, family history of CAD, vascular access, LMS PCI, circulatory support, number of treated lesions, and number of stents used. Subsequent analysis was performed on the imputed dataset, and results were pooled using Rubin's rule[102]. We then used Multivariable logistic regression analysis to calculate the adjusted odd ratio, 95% confidence interval, and the p- value for the clinical outcomes between the Whites and BAME groups. To address differences and imbalances in baseline characteristics between the groups, multiple imputations with propensity score matching (PSM) were employed (mi estimate: teffects psmatch). The PMS was used to estimate the average treatment effect (ATE) using all covariates initially used in our main regression analysis model. The ATE coefficients were then converted into odds ratios to better interpret of the results. The robustness of the results was assessed through sensitivity analysis using the non-imputed dataset. Stata version 14.1 (StataCorp, College Station, Texas) was utilised for the analyses. Statistical significance was determined at a type I error rate of 0.05.

5.4 Results

A total of 424,290 PCI procedure records were initially reviewed for patients with stable CAD. After excluding 266,526 cases that did not meet the inclusion criteria, 105,949 cases were identified as CHiP procedures, accounting for 24.9% of the total. Figure 5.1 illustrates the inclusion and exclusion process for this analysis.

Figure 5-1: The process of patients' inclusion and exclusion for the CHiP analysis.



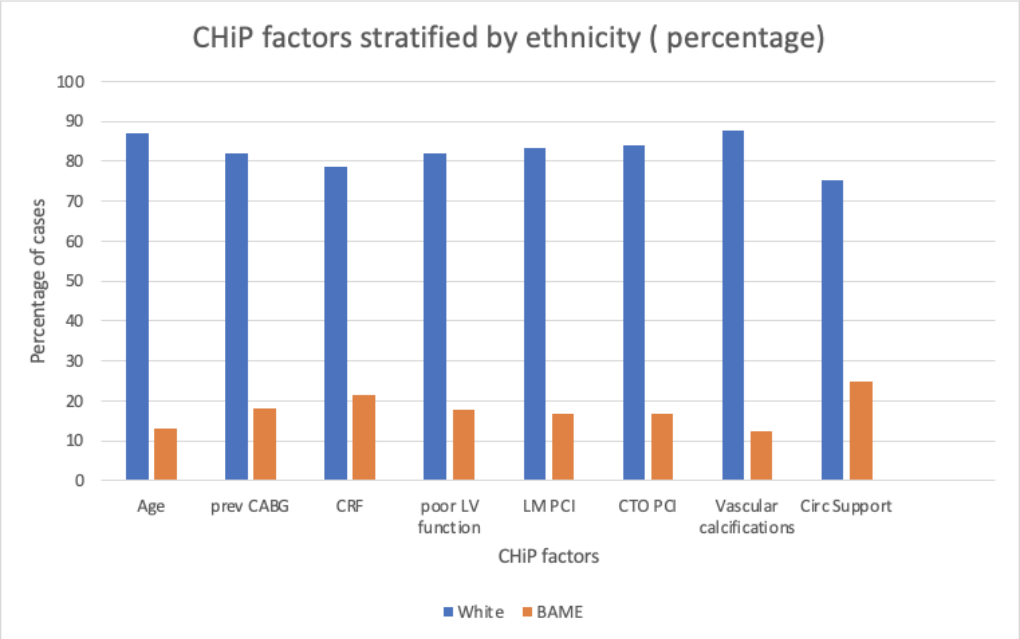
Abbreviations: PCI, percutaneous coronary intervention; CHiP, complex, high-risk, PCI; ACS, acute coronary syndromes; BCIS, British Cardiovascular Intervention Society; MACCE, major acute cardiovascular and cerebral events; BAME, Black, Asian, and other Ethnic Minorities.

5.4.1 CHiP factors (Types) prevalence and trends

Figure 5.2 displays the prevalence of each CHiP factor categorised by ethnicity. In the BAME population, the prevalence of most CHiP factors was below 20%, except for the use of circulatory support and CKD patients, where the prevalence in the BAME group was below 25%.

Figure 5-2: Prevalence of CHiP factors in Patients with stable angina, stratified by ethnicity

Prevalence of CHiP factors in patients with stable angina, stratified by ethnicity (percentage).



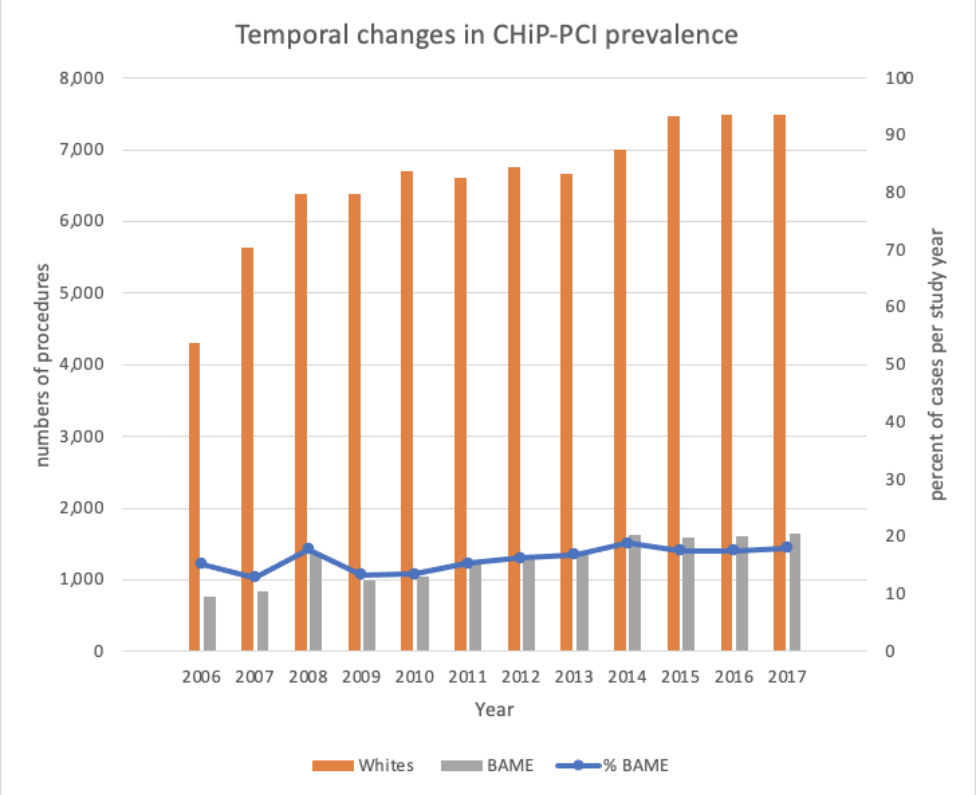
Abbreviation: CHiP, complex high-risk percutaneous coronary interventions; CABG, coronary artery bypass graft; LV, left ventricle; LM , left main stem; PCI, percutaneous coronary intervention; Circ, circulatory.

CHiP types varied between the Whites and BAME patients. The most common CHiP factor in the Whites prior CABG (33.4%), followed by CTO PCI (31.9%), and old age => 80 years (23.6%). Whereas among the BAME, the most common CHiP factors were

previous history of CABG (38.3%), then CTO PCI (32%), and severe vascular calcifications (18.8%).

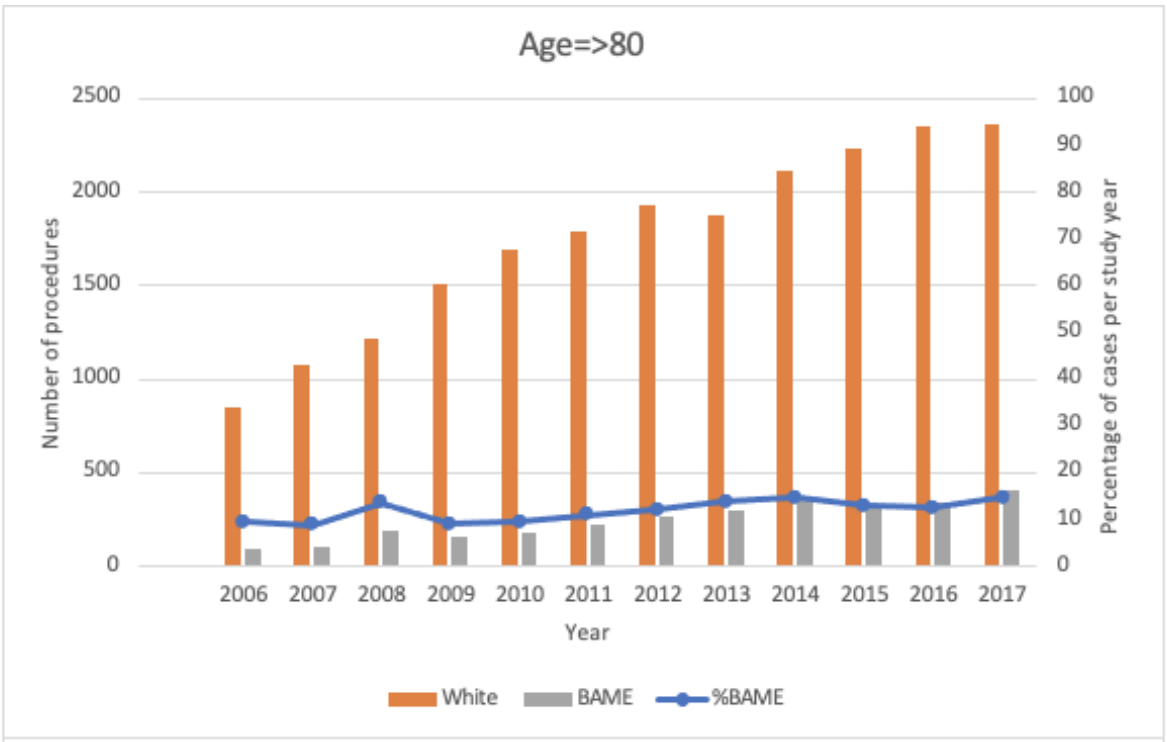
The temporal changes of the prevalence in CHiP types according to ethnicity are illustrated in Figure 5.3, where CHIP procedure numbers increased from 5073 procedures in 2006 to 9131 procedures in 2017. Similar findings in trends were seen among each CHiP factor (Figure 5.4). The proportion of BAME throughout the study years ranged between 13-18%. Of the BAME patients, Asians had the highest rates of previous CABG (47.5%), followed by PCI to a CTO lesion (31.5%).

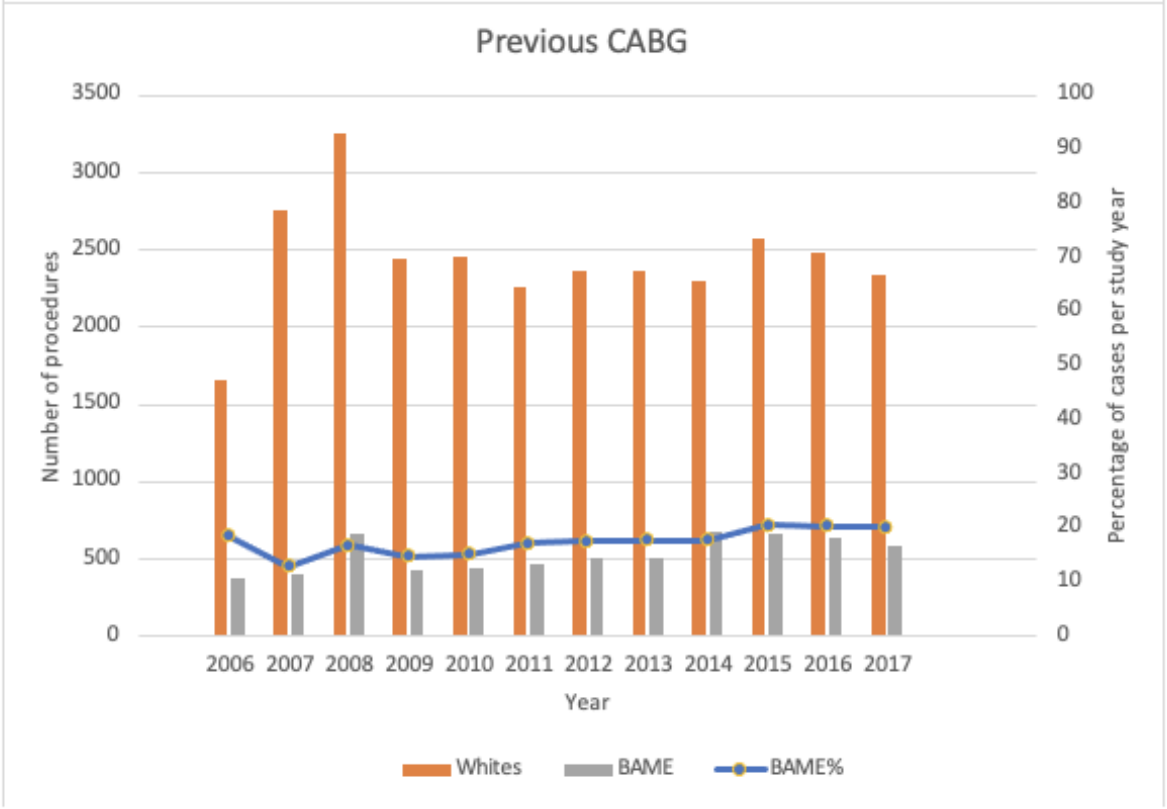
Figure 5-3 Temporal changes in CHiP prevalence in patients with stable angina and per cent change over time, stratified by ethnicity.

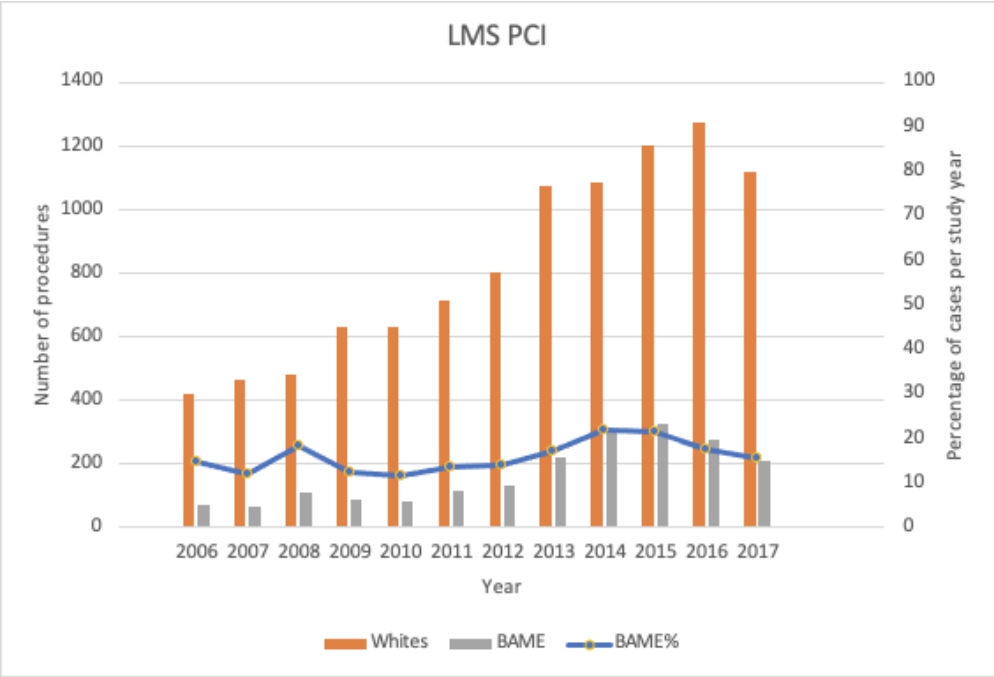


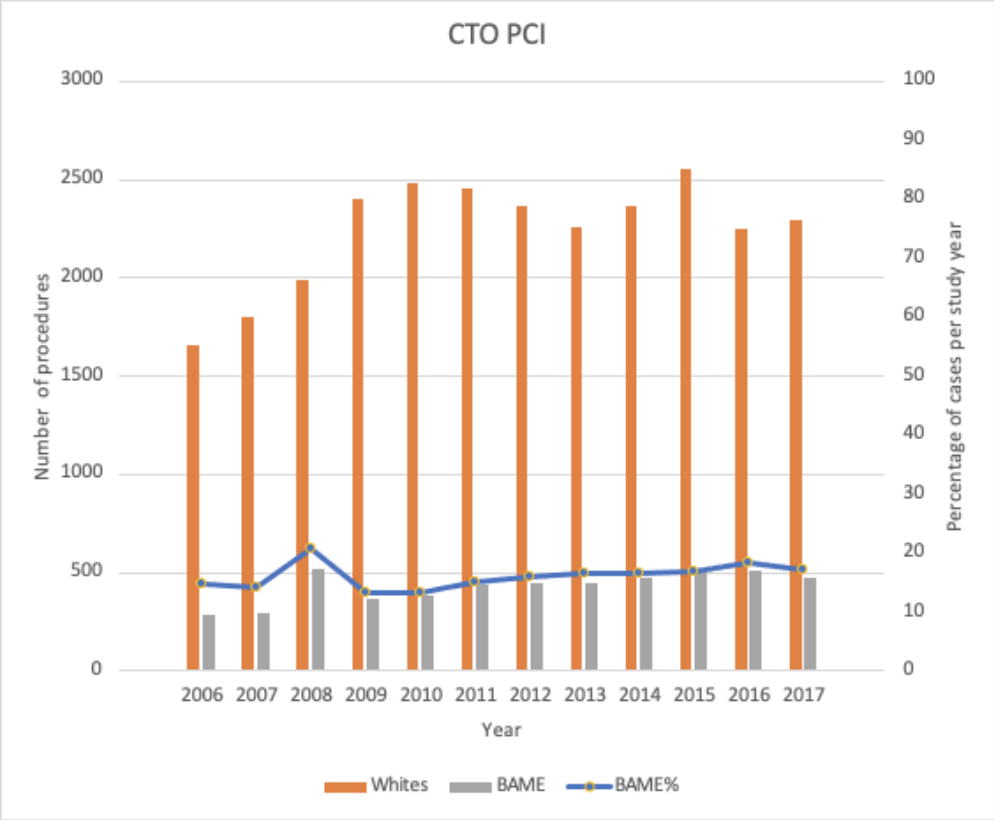
Abbreviations: CHiP, complex, high-risk percutaneous coronary intervention; BAME, Black, Asians, Other Ethnic Minorities.

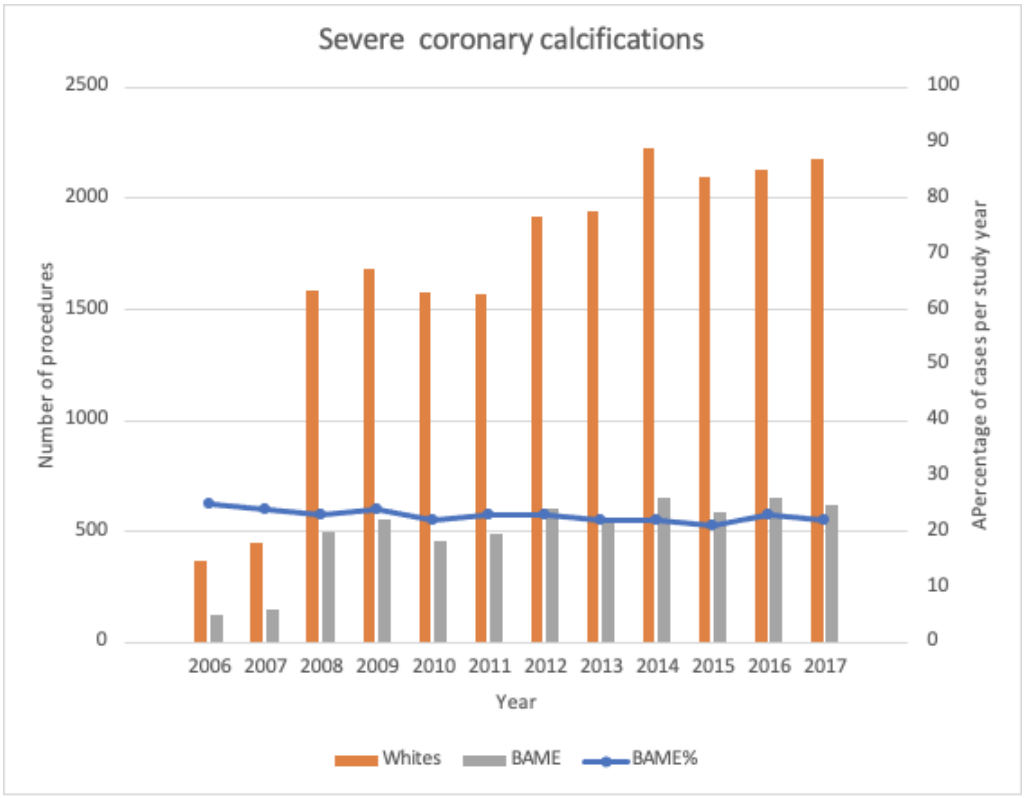
Figure 5-4 ***Temporal changes in prevalence of each CHiP factor among patients with stable angina and per cent change over time, stratified by ethnicity.***

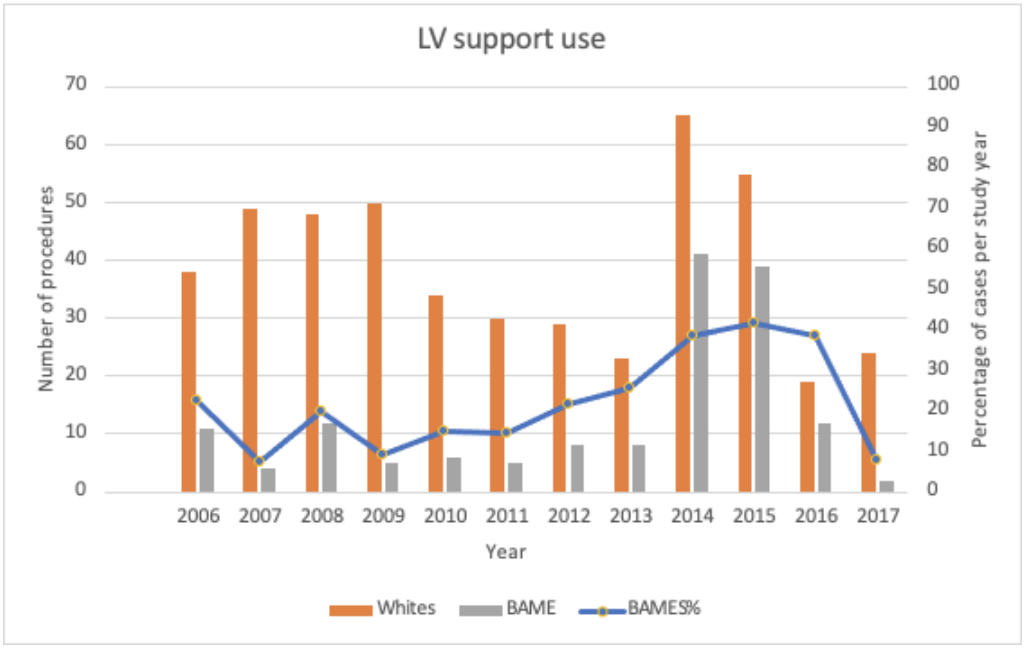

Age=>80
Number of procedures
Percentage of cases per study year
2500
2000
1500
1000
500
0
100
90
80
70
60
50
40
30
20
10
0
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
Year
White
BAME
%BAME


Previous CABG
Number of procedures
Percentage of cases per study year
3500
3000
2500
2000
1500
1000
500
0
100
90
80
70
60
50
40
30
20
10
0
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
Year
Whites
BAME
BAME%


LMS PCI
1400
1200
1000
800
600
400
200
0
Number of procedures
100
90
80
70
60
50
40
30
20
10
0
Percentage of cases per study year
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
Year
Whites
BAME
BAME%


CTO PCI
3000
2500
2000
1500
1000
500
0
Number of procedures
100
90
80
70
60
50
40
30
20
10
0
Percentage of cases per study year
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
Year
Whites
BAME
BAME%





Abbreviations: CHiP, complex high-risk percutaneous coronary interventions; CABG, coronary artery bypass graft; CTO, chronic total occlusion, LV left ventricle; LMS , left main stem; PCI, percutaneous coronary intervention.

5.4.2 CHiP baseline clinical and procedural characteristics and temporal trends

Table 5.1 presents an overview of the baseline clinical and procedural characteristics categorised by ethnicity. Of the total CHiP procedures, 84% (89,038 cases) were performed in Whites, while 16% (16,911 cases) were performed in BAME patients. The median age of Whites (70.6 years) was 1.5 years higher than that of BAME patients (68.1 years).

When considering cardiovascular risk factors, BAME patients had a higher prevalence of diabetes mellitus, hypertension, previous history of MI, and previous history of PCI. Conversely, White patients had a higher prevalence of stroke, PVD, and current and former smokers.

Table 5-1: Baseline and procedural characteristics of patients with stable angina undergone CHiP procedure, stratified by ethnicity.

VARIABLES	TOTAL, N	WHITE	BAME	P-VALUE
NUMBER OF PARTICIPANTS	105,949	89,038 (84%)	16,911 (16%)	
AGE MEDIAN (YEARS), (IQR)	70.2 (61.5-79)	70.6 (62-79.4)	68.1 (58.9-76.5)	< 0.001
MALES	81,961 (77.3%)	68,505 (77%)	13,456 (80%)	< 0.001
BMI, KG (IQR)	28.1 (25.3-31.4)	28.3 (25.4-31.6)	27.5 (24.7-30.8)	< 0.001
CHIP FACTORS (TYPES)				
• AGE >80 YEARS	23,948 (22.6%)	21,014 (23.6%)	2,934 (17.4%)	< 0.001
• PRIOR CORONARY ARTERY BYPASS	35,610 (34.2%)	29,266 (33.4%)	6,344 (38.3%)	< 0.001
• CHRONIC RENAL FAILURE	11,545 (11.3%)	9,072 (10.6%)	2,473 (15.2%)	< 0.001
• POOR LV FUNCTION	5,431 (8.7%)	4,459 (8.6%)	972 (9.5%)	= 0.002

• LEFT MAIN INTERVENTION	11,913 (11.4%)	9,908 (11.3%)	2,005 (12%)	= 0.010
• CHRONIC TOTAL OCCLUSION PCI	32,055 (32%)	26,890 (31.9%)	5,165 (32%)	= 0.769
• SEVERE CORONARY CALCIFICATIONS	20,047 (22.9%)	17,564 (23%)	2,483 (18.8%)	< 0.001
• USE OF LV SUPPORT	617 (0.61%)	464 (0.5%)	153 (1.0%)	< 0.001
CARDIOVASCULAR RISK FACTORS				
• HYPERTENSION	66,943 (66.7%)	55,985 (66.5%)	10,958 (68%)	< 0.001
• HYPERCHOLESTEROLAEMIA	65,944 (65.7%)	55,294 (65.6%)	10,650 (66%)	= 0.368
• DIABETES MELLITUS	26,689 (26.4%)	20,051 (23.6%)	6,638 (41.1%)	< 0.001
• SMOKING HISTORY				< 0.001
NEVER	38,827 (42%)	30,753 (40%)	8,074 (54.5%)	
FORMER	45,106 (49%)	39,710 (51%)	5,396 (36.4%)	
CURRENT SMOKERS	8,709 (9.4%)	7,354 (9.5%)	1,355 (9.1%)	
• FAMILY HISTORY OF CORONARY ARTERY DISEASE	42,811 (46%)	36,151 (46%)	6,660 (46%)	= 0.946
• HISTORY OF MI	43,056 (43%)	35,831 (42.5%)	7,225 (44.9%)	< 0.001
• PREVIOUS PCI	40,031 (38.6%)	32,838 (37.6%)	7,193 (43.7%)	< 0.001
• PREVIOUS STROKE	4,863 (4.8%)	4,286 (5.1%)	577 (3.6%)	< 0.001
• HISTORY OF PERIPHERAL VASCULAR DISEASE	7,279 (7.3%)	6,423 (7.6%)	856 (5.3%)	< 0.001
• LEFT VENTRICLE EJECTION FRACTION				= 0.001
>50%	43,989 (70.7%)	36,923 (71%)	7,066 (69.33%)	
30%-50%	12,783 (20.6%)	10,629 (20.3%)	2,154 (21.13%)	
<30%	5,431 (8.7%)	4,459 (8.6%)	972 (9.54%)	
PHARMACOLOGY (IN-LAB)				
• WARFARIN	1,957 (2%)	1,735 (2.1%)	222 (1.5%)	< 0.001
• GPIIBIIIA INHIBITORS	7,116 (7.2%)	6,068 (7.3%)	1,048 (6.8%)	= 0.022
• CLOPIDOGREL	77,787 (81.9%)	65,954 (81.9%)	11,833 (81.8%)	= 0.486
• PRASUGREL	891 (0.94%)	707 (0.88%)	184 (1.27%)	< 0.001
• TICAGRELOR	3,495 (3.6%)	2,871 (3.5%)	624 (4.3%)	< 0.001
VASCULAR ACCESS				< 0.001
• RADIAL	46,846 (45.2%)	40,761 (46.8%)	6,085 (37.5%)	
• FEMORAL	48,204 (46.6%)	39,175 (45%)	9,029 (54%)	
• MULTIPLE ACCESSES	8,383 (8.1%)	7,073 (8.1%)	1,310 (8%)	
CIRCULATORY SUPPORT				
• NO SUPPORT	101,000 (99.3%)	84,965 (99.5%)	16,035 (99%)	< 0.001
• IABP	579 (0.57%)	434 (0.51%)	145 (0.9%)	< 0.001
• IMPELLA	41 (0.04%)	31 (0.04%)	10 (0.06%)	= 0.139

NUMBER OF TREATED CORONARY NARROWING				<0.001
• 1	68,342 (65%)	57,952 (65.8)	10,390 (62.2)	
• 2	26,093 (24.9%)	21,663 (24.6)	4,430 (26.5)	
• 3+	10,318 (9.9%)	8,438 (9.5)	1,880 (11.2)	
PROCEDURAL DEVICES				
• NONE	69,484 (77%)	58,771 (76%)	10,713 (81%)	<0.001
• CUTTING BALLOON	12,540 (14%)	10,917 (14.5%)	1,623 (12.5%)	<0.001
• ROTATIONAL ATHERECTOMY	7,662 (8.4%)	6,808 (8.9%)	854 (6.6%)	<0.001
• LASER ATHERECTOMY	518 (0.6%)	452 (0.6%)	66 (0.5%)	= 0.198
NUMBER OF STENTS USED				< 0.001
• 0	15,058 (14.3%)	12,849 (14.6%)	2,209 (13.1%)	
• 1	43,688 (41.6%)	36,563 (41.4%)	7,125 (42.4%)	
• 2	26,501 (25.3%)	22,265 (25.3%)	4,236 (25.2%)	
• 3+	19,759 (18.8%)	16,517 (18.7%)	3,242 (19.3%)	
TARGET VESSEL PCI				
• LEFT MAIN	11,913 (11.4%)	9,908 (11.3%)	2,005 (12%)	= 0.010
• LEFT ANTERIOR DESCENDING	41,699 (40.1%)	35,091 (40.1%)	6,608 (39.7%)	= 0.225
• LEFT CIRCUMFLEX	26,365 (25.4%)	21,744 (24.9%)	4,621 (27.7%)	< 0.001
• RIGHT CORONARY	36,774 (35.3%)	31,102 (35.6%)	5,672 (34%)	< 0.001
• GRAFT VESSEL	10,381 (9.9%)	8,790 (10%)	1,591 (9.5%)	= 0.044
NUMBER OF TREATED CORONARY ARTERIES				< 0.001
• 0	2,406 (2.3%)	2,212 (2.5%)	194 (1.2%)	
• 1	78,099 (74.4%)	65,868 (74.7%)	12,231 (72.7%)	
• 2	19,849 (18.9%)	16,326 (18.5%)	3,523 (21%)	
• 3+	4,685 (4.5%)	3,818 (4.3%)	867 (5.2%)	

Abbreviations: CHiP, complex high risk percutaneous coronary intervention; GPIIbIIIa, glycoprotein IIaIIIb; PCI, percutaneous coronary intervention; BMI, body mass index; KG, kilogram.

Temporal changes in baseline clinical and procedural characteristics are presented in Table 5.2, which demonstrated similar differences to observed in the overall cohort (Table 5.1). Notably, there was a gradual increase in the age of both White and BAME patients over time. In Group 1 (2006-2009), the median age for Whites was 68.8 years compared to 66.4 years for BAME patients, while in Group 3 (2014-2017), the median age increased to 71.9 years for Whites and 69 years for BAME patients. This trend was also observed for most cardiovascular risk factors and CHiP factors.

Table 5-2 Temporal changes of baseline and procedural characteristics of patients with stable angina undergone CHiP procedure, stratified by ethnicity.

	Group 1 (2006-2009)		**P-value Group 1**	**Group2 (2010-2013)**		**P-value Group 2**	**Group 3 (2014-2017)**		**P-value Group 3**
Variables	Whites	BAME		Whites	BAME		Whites	BAME	
Number of participants	24,694	4,644		30,797	5,317		33,547	6,950	
Age (Median) years	68.8	66.4		70.6	68.6		71.9	69	< 0.001
Males, n	18,805 (76.2%)	3,722 (80.2 %)		23,841 (77.4%)	4,187 (78.8%)		25,859 (77.1%)	5,547 (79.8%)	< 0.001
CHiP factors (types)									
• Age >80 years	4,655 (18.8%)	537 11.6%)	< 0.001	7,294 (23.7%)	962 (18.1%)	< 0.001	9,065 (27.0%)	1,435 (20.6%)	< 0.001
• Prior CABG	10,124 (42.2%)	1,870 (42.1 %)	< 0.001	9,449 (31.2%)	1,918 (36.8%)	< 0.001	9,693 (29.1%)	2,556 (37.1%)	< 0.001
• Chronic Renal Failure	1,199 (5.2%)	307 (7.0%)	< 0.001	3,035 (10.2%)	845 (16.7%)	< 0.001	4,838 (14.8%)	1,321 (19.4%)	< 0.001
• Poor LV function	1,280 (9.7	297 (11.2 %)	0.006	1,482 (7.8%)	283 (8.7%)	0.092	1,697 (8.5%)	392 (8.9%)	0.309
• Left main PCI	2,006 (8.3%)	338 (7.4%)	0.022	3,221 (10.6%)	552 (10.6%)	0.995	4,681 (14.2%)	1,115 (16.3%)	< 0.001
• CTO PCI	7,852 (33.9%)	1,467 (32,3 %)	0.042	9,566 (32.8%)	1,720 (34.7%)	0.010	9,472 (29.8%)	1,978 (30.0%)	0.770
• Severe vascular calcifications	3,145 (14.5%)	873 (21.9 %)	< 0.001	6,862 (26.4%)	655 (16.3%)	< 0.001	7,557 (26.4%)	955 (18.4%)	< 0.001
• Left ventricle support	185 (0.8%)	32 (0.8%)	0.653	116 (0.4%)	27 (0.5%)	0.156	165 (0.5%)	94 (1.4%)	< 0.001
Cardiovascular risk factors									
Hypertension	13,920 (60.4%)	2,375	< 0.001	19,739 (68.4%)	3,602 (70.9%)	< 0.001	22,326 (69.1%)	4,981 (75.2%)	< 0.001

		(53.6 %)							
Hypercholesterolaemia	15,152 (65.8%)	2,406 (54.3 %)	< 0.001	19,447 (67.4%)	3,512 (69.1%)	0.014	20,695 (64.0%)	4,732 (71.5%)	< 0.001
Diabetes mellitus	4,833 (20.5%)	1,711 (38.2 %)	< 0.001	7,102 (24.7%)	2,090 (41.8%)	< 0.001	8,116 (24.9%)	2,837 (42.5%)	< 0.001
Smoker			< 0.001			< 0.001			< 0.001
Never	8,407 (39.9%)	2,044 (51.2 %)		10,326 (38.3%)	2,568 (55.8%)		12,020 (40.3%)	3,462 (55.5%)	
Former	10,424 (49.5%)	1,535 (38.5 %)		14,005 (51.9%)	1,641 (35.7%)		15,281 (51.2%)	2,220 (35.6%)	
Current smoker	2,211 (10.1%)	411 (10.3 %)		2,618 (9.7%)	391 (8.5%)		2,525 (8.5%)	553 (8.9%)	
Family history of CAD	10,148 (49.2%)	1,831 (50.3 %)	0.223	12,560 (46.2%)	2,095 (45.7%)	0.576	13,443 (43.8%)	2,734 (43.7%)	0.911
History of MI	9,323 (41.8%)	1,881 (44.5 %)	0.001	12,686 (43.6%)	2,262 (44.9%)	0.095	13,822 (42.0%)	3,082 (45.2%)	< 0.001
Previous PCI	7,025 (29.5%)	1,625 (36.7 %)	< 0.001	11,537 (38.0%)	2,294 (44.3%)	< 0.001	14,276 (43.1%)	3,274 (47.8%)	< 0.001
Previous stroke	1,049 (4.5%)	155 (3.5%)	0.002	1,627 (5.6%)	167 (3.3%)	< 0.001	1,610 (4.9%)	255 (3.9%)	< 0.001
History of PVD	1,553 (6.7%)	212 (4.7%)	< 0.001	2,551 (8.8%)	297 (5.9%)	< 0.001	2,319 (7.2%)	347 (5.2%)	< 0.001
LV ejection fraction <30%	1,280 (9.7%)	297 (11.2 %)	0.006	1,482 (7.8%)	283 (8.7%)	0.092	1,697 (8.5%)	392 (8.9%)	0.309
Pharmacology (in-lab)									
Warfarin	371 (1.8%)	46 (1.1%)	0.005	605 (2.1%)	59 (1.3%)	0.001	759 (2.5%)	117 (1.9%)	0.015
GPIIbIIIa inhibitors	3,437 (15.1%)	603 (14.3 %)	0.194	1,803 (6.3%)	300 (6.2%)	0.773	828 (2.7%)	145 (2.3%)	0.109
Clopidogrel	17,034 (81.1%)	3,432 (85.3 %)	0.001	24,762 (85.4%)	3,857 (85.8%)	0.421	24,158 (79.4%)	4,544 (76.3%)	0.001
Prasugrel	3 (0.01%)	1 (0.02 %)	0.627	316 (1.1%)	92 (2.1%)	0.001	388 (1.3%)	91 (1.5%)	0.118
Ticagrelor	0	0		228 (0.8%)	45 (1.0%)	0.135	2,643 (8.7%)	579 (9.7%)	0.010
Vascular access			< 0.001			< 0.001			< 0.001
Radial	6,045 (25.5%)	832 (18.9 %)		13,841 (45.7%)	1,645 (32.0%)		20,875 (63.3%)	3,608 (52.4%)	
Femoral	17,058 (71.9%)	3,465 (78.7 %)		14,243 (47.0%)	3,084 (59.9%)		7,874 (23.9%)	2,480 (36.1%)	
Multiple accesses	634 (2.8%)	106 (2.4%)		2,192 (7.2%)	412 (8.0%)		4,247 (12.9%)	792 (11.5%)	
Circulatory support									
• **No support**	22,491 (99.2%)	4,241 (99.3 %)	0.653	29,804 (99.6%)	5,124 (99.5%)	0.156	32,670 (99.5%)	6,670 (98.6%)	0.001
• **IABP**	185 (0.8%)	32 (0.8%)	0.653	116 (0.4%)	27 (0.5%)	0.156	133 (0.4%)	86 (1.27%)	0.001
• **Impella**	0	0		0	0		31 (0.1%)	10 (0.2%)	0.231
Number of treated coronary narrowing			0.193			<0.001			<0.001
• **1**	15,847 (65.0%)	2,937 (63.9 %)		20,660 (67.4%)	3,297 (62.5%)		21,445 (64.9%)	4,156 (60.8%)	
• **2**	6,110 (25.0%)	1,210		7,254 (23.7%)	1,353 (25.7%)		8,299 (25.1%)	1,867 (27.3%)	

			(26.3 %)						
•	**3**	2,409 (9.9%)	446 (9.7%)		2,753 (8.9%)	623 (11.8%)		3,276 (9.9%)	811 (11.9%)	
Procedural devices										
•	**Cutting Balloon**	2,022 (9.3%)	751 (18.9 %)		4,366 (16.8%)	389 (9.7%)		4,529 (15.8%)	483 (9.3%)	< 0.001
•	**Rotational atherectomy**	1,080 (4.9%)	118 (2.9%)		2,554 (9.8%)	264 (6.6%)		3,174 (11.1%)	472 (9.1%)	< 0.001
•	**Laser atherectomy**	82 (0.4%)	19 (0.5%)	0.361	220 (0.8%)	19 (0.5%)	0.013	150 (0.5%)	28 (0.5%)	0.888
Number of stents used				0.035			0.011			0.001
•	**0**	3,515 (14.5%)	592 (12.9 %)		4,350 (14.2%)	697 (13.2%)		4,984 (14.9%)	920 (13.3%)	
•	**1**	10,118 (41.8%)	1,956 (42.5 %)		13,010 (42.5%)	2,245 (42.4%)		13,435 (40.3%)	2,924 (42.3%)	
•	**2**	6,003 (24.8%)	1,171 (25.5 %)		7,681 (25.1%)	1,296 (24.5%)		8,581 (25.7%)	1,769 (25.6%)	
•	**3+**	4,581 (18.9%)	878 (19.1 %)		5,596 (18.3%)	1,057 (19.9%)		6,340 (19.0%)	1,307 (18.9%)	
Target Vessel PCI										
•	**Left main stem**	2,006 (8.3%)	338 (7.4%)	0.022	3,221 (10.6%)	552 (10.6%)	0.995	4,681 (14.2%)	1,115 (16.3%)	<0.001
•	**LAD**	8,612 (35.9%)	1,699 (35.9 %)	0.175	12,259 (40.4%)	2,134 (41.0%)	0.396	14,220 (43.1%)	2,775 (40.1%)	0.001
•	**Left circumflex**	6,077 (25.3%)	1,217 (26.5 %)	0.106	7,564 (24.9%)	1,490 (28.7%)	0.001	8,103 (24.6%)	1,914 (27.9%)	< 0.001
•	**Right coronary artery**	8,347 (34.8%)	1,635 (35.5 %)	0.321	10,995 (36.3%)	1,801 (34.6%)	0.025	11,760 (35.6%)	2,236 (32.6%)	< 0.001
•	**Graft**	4,074 (16.9%)	625 (13.6 %)	0.001	2,546 (8.4%)	462 (8.9%)	0.240	2,170 (6.6%)	504 (7.4%)	0.019
Number of target vessel PCI				< 0.001			< 0.001			< 0.001
•	**0**	1,926 (7.9%)	139 (3.0%)		159 (0.5%)	23 (0.4%)		127 (0.4%)	32 (0.5%)	
•	**1**	17,251 (70.8%)	3,407 (73.8 %)		23,755 (77.5%)	3,873 (73.1%)		24,862 (74.8%)	4,951 (71.7%)	
•	**2**	4,322 (17.7%)	911 (19.7 %)		5,459 (17.8%)	1,104 (20.8%)		6,545 (19.7%)	1,508 (21.8%)	
•	**3+**	863 (3.5%)	158 (3.4%)		1,265 (4.1%)	295 (5.5%)		1,689 (5.1%)	414 (6.0%)	

Abbreviations: CHiP, complex high risk percutaneous coronary intervention; CABG, coronary artery bypass graft; CTO, chronic total occlusion; CAD, coronary artery disease; GPIIbIIIa, glycoprotein IIaIIIb; LV, left ventricle; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

Further stratification into White, Asian, Black, and other ethnic minorities demonstrated that among the BAME population, Asian patients accounted for the majority (7.7%) of the cases, while Blacks represented 0.8% of the cases (Table 5.3).

Table 5-3 Baseline and procedural characteristics of patients with stable angina who undergone CHiP procedure, stratified into four groups according to ethnicity (Whites/blacks/Asians/and other Minority Ethnic group).

Variables	Whites	Black	Asians	Oriental and others	P-value
Number of participants	89,038 (84%)	805 (0.8%)	7,904 (7.7%)	7,904 (7.5%)	
Age Median in years (IQR)	70.6 (62-79.4)	69.7 (58-77.7)	66 (57.7-77.4)	70 (60.8-79)	< 0.001
Males, n (%)	68,505 (76.9%)	558 (69.3%)	6,763 (82.4%)	6,135 (77.6%)	< 0.001
CHiP factors (types)					
Age >80, years	21,014 (23.6%)	160 (19.8%)	977 (11.9%)	1,797 (22.7%)	< 0.001
Prior CABG	29,266 (33.4%)	247 (31%)	3,857 (47.5%)	2,240 (29.3%)	< 0.001
Chronic Renal Failure	9,072 (10.6%)	184 (23.6%)	1,255 (15.9%)	1,034 (13.6%)	< 0.001
Poor LV function	4,459 (8.6%)	61 (13,1%)	446 (9.7%)	465 (9.1%)	< 0.001
Left main PCI	9,908 (11.3%)	83 (10.6%)	1,227 (15.3%)	695 (8.9%)	< 0.001
CTO PCI	26,890 (32%)	249 (33.4%)	2,437 (31.5%)	2,479 (32.6%)	= 0.383
Severe vascular calcifications	17,564 (23%)	68 (9.5%)	908 (12.1%)	1,507 (30.4%)	< 0.001
Use of LV support	464 (0.6%)	14 (1.8%)	81 (1%)	58 (0.8%)	< 0.001
Cardiovascular risk factors					
Hypertension	55,985 (66.5%)	624 (79.1%)	5,945 (74.7%)	4,389 (59.4%)	< 0.001
Hypercholesterolaemia	55,294 (65.6%)	554 (70.2%)	5,861 (73.7%)	4,235 (57.3%)	< 0.001
Diabetes mellitus	20,051 (23.6%)	352 (45%)	4,072 (51.7%)	2,214 (29.5%)	< 0.001
Smoker					< 0.001
Never	30,753 (39.5%)	398 (57.6%)	4,289 (60.9%)	3,387 (47.8%)	
Formers	39,710 (51%)	219 (31.8%)	2,223 (31.5%)	2,954 (41.7%)	
Current smoker	7,354 (9.5%)	73 (10.6%)	539 (7.6%)	743 (10.5%)	
Family history of CAD	36,151 (46.4%)	218 (30.9%)	3,178 (44.1%)	3,264 (49.7%)	< 0.001
History of MI	35,831 (42.5%)	313 (40%)	3,796 (48.1%)	3,116 (42%)	< 0.001

Previous PCI	35,831 (42.5%)	313 (40%)	3,796 (48.1%)	3,116 (42%)	< 0.001
Previous stroke	4,286 (5.1%)	30 (3.8%)	240 (3%)	307 (4.2%)	< 0.001
History of PVD	6,423 (6.7%)	65 (8.3%)	65 (4.4%)	440 (5.9%)	< 0.001
LV ejection fraction					< 0.001
• ***>50%***	36,923 (70%)	316 (67.9%)	3,283 (71.4%)	3,467 (67.7%)	
• ***30-50%***	10,629 (22.4%)	88 (18.9%)	873 (18.9%)	1,193 (23.2%)	
• ***<30%***	4,459 (8.6%)	61 (13.2%)	446 (9.7%)	465 (9.1%)	
Pharmacology (In-lab)					
Warfarin	1,735 (2.2%)	7 (1.1%)	67 (1%)	148 (2.1%)	< 0.001
GPIIbIIIa inhibitors	6,068 (7.3%)	47 (2.2%)	551 (7.4%)	450 (6.2%)	= 0.003
Clopidogrel	65,954 (82%)	542 (85.2%)	5,660 (82.7%)	5,631 (80.4%)	< 0.001
Prasugrel	707 (0.8%)	4 (0.6%)	114 (1.7%)	66 (1%)	< 0.001
Ticagrelor	2,871 (3.5%)	29 (4.6%)	338 (4.9%)	257 (3.7%)	< 0.001
Vascular access					< 0.001
Radial	40,761 (46.4%)	337 (42.4%)	2,979 (36.8%)	2,769 (36.5%)	
Femoral	39,175 (45.4%)	403 (50.7%)	4,452 (55%)	4,174 (55.6%)	
Multiple accesses	7,073 (8.2%)	55 (6.9%)	663 (8.2%)	592 (7.9%)	
Circulatory support					
No support	84,965 (99.45%)	755 (98.05%)	7,878 (98.98%)	7,402 (99.21%)	< 0.001
IABP	434 (0.51%)	14 (1.82%)	77 (0.97%)	54 (0.72%)	< 0.001
Impella	31 (0.04%)	1 (0.13%)	4 (0.05%)	5 (0.07%)	= 0.335
Number of treated coronary narrowing					< 0.001
• 1	57,952 (65.8%)	505 (63.9%)	5,051 (61.9%)	4,834 (62.5%)	
• 2	21,663 (24.6%)	203 (24.9%)	2,176 (26.7%)	2,051 (26.4%)	
• **3+**	8,438 (9.6%)	89 (11.2%)	934 (11.4%)	857 (11.1%)	
Procedural devices					
None	58,771 (76%)	651 (90.5%)	6,612 (87.1%)	3,450 (69.3%)	< 0.001
Cutting Balloon	10,917 (14.5%)	35 (4.8%)	516 (7.7%)	1,072 (21.3%)	< 0.001
Rotational atherectomy	6,808 (8.9%)	31 (4.4%)	378 (4.7%)	445 (8.9%)	< 0.001
Laser atherectomy	452 (0.6%)	2 (0.3%)	37 (0.5%)	27 (0.5%)	= 0.484
Number of stents used					< 0.001
• **0**	12,849 (14.6%)	121 (15.1%)	1,060 (12.9%)	1,028 (13.1%)	
• 1	36,563 (41.4%)	316 (39.6%)	3,513 (43.1%)	3,296 (42%)	
• 2	22,265 (25.3%)	193 (24.2%)	2,022 (24.8%)	2,021 (25.7%)	
• **3+**	16,517	168	1,563	1,511	

	(18.7%)	(21.1%)	(19.7%)	(19.2%)	
Target Vessel PCI					
Left main	9,908 (11.3%)	83 (10.6%)	1,227 (15.3%)	695 (8.9%)	< 0.001
Left anterior descending	35,091 (40.2%)	330 (42.1%)	2,904 (36.1%)	3,374 (43.1%)	< 0.001
Left circumflex	21,744 (24.9%)	232 (29.6%)	2,369 (29.5%)	2,020 (25.8%)	< 0.001
Right coronary artery	31,102 (35.6%)	277 (35.3%)	2,617 (32.5%)	2,778 (35.5%)	< 0.001
Graft	8,790 (10.1%)	57 (7.3%)	920 (11.4%)	614 (7.8%)	< 0.001
Number of target vessel PCI					< 0.001
• **0**	2,212 (2.5%)	9 (1.1%)	155 (1.9%)	30 (0.4%)	
• 1	65,868 (74.7%)	591 (74.2%)	5,883 (72.4%)	5,757 (73%)	
• 2	16,326 (18.5%)	159 (19.9%)	1,670 (20.5%)	1,694 (21.5%)	
• **3+**	3,817 (4.3%)	38 (4.8%)	425 (5.2%)	404 (5.1%)	

Abbreviations: CHiP, complex high risk percutaneous coronary intervention; CABG, coronary artery bypass graft; CTO, chronic total occlusion; CAD, coronary artery disease; GPIIbIIIa, glycoprotein IIaIIIb; LV, left ventricle; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

There were variations in procedural characteristics between White and BAME patients. White patients had higher rates of graft PCI (10.5% vs 9.5%, p=0.04), while BAME patients had higher rates of LMS PCI (12% vs 11.3%, p=0.01) (Table 5.1). Among the BAME population, Asians had the highest rates of LMS PCI (15.3%) and graft vessel PCI (11.4%) (Table 5.3). BAME patients appeared to have more extensive disease in the coronary arteries compared to White patients, as they more frequently received treatment for multiple lesions or vessels. However, White patients had higher rates of extensive vascular calcification, indicated by the increased use of cutting balloons (14.2% vs 12.5%, p<0.001) and rotational atherectomy (8.9% vs 6.6%, p<0.001). Radial access was less frequently used for CHiP procedures in the BAME population compared to Whites (37.5% vs 46.8%, p<0.001), and BAME patients had fewer procedures performed using multiple access sites (8.0% vs 8.1%, p<0.001) (Table 5.1).

When examining temporal trends in procedural characteristics (Table 5.2), there was a gradual increase in CHiP procedures performed via radial access in both BAME patients (18.9% in Group 1 to 52.4% in Group 3) and White patients (25.5% in Group 1 to 63.3% in Group 3). However, throughout the study quarters, CHiP procedures performed via radial access in BAME patients consistently remained lower than those in White patients. In contrast, trends for using calcium modification devices showed a different pattern. In the first two quarters (Group 1 and Group 2 in Table 5.2), BAME patients had higher rates for cutting balloon and rotational atherectomy use compared to White patients. However, in the last quarter (Group 3), White patients had significantly higher rates for both cutting balloon and rotational atherectomy use compared to BAME patients.

Pharmacotherapy prescriptions showed variations between the two ethnic groups. Warfarin and Glycoprotein IIb/IIIa inhibitors were prescribed at a higher frequency in White patients. In contrast, prasugrel and ticagrelor were more frequently prescribed in BAME patients, particularly in the Asian population (Asian vs Whites: Prasugrel 1.7% vs 0.8%; Ticagrelor 4.9% vs 3.5%).

Further stratification into four ethnic groups (Table 5.3) revealed that Warfarin was more commonly prescribed in other ethnic minorities (2.1%) compared to Asians (1%) and Blacks (1.1%), with a p-value greater than 0.001. Similarly, Glycoprotein IIb/IIIa inhibitors were more commonly prescribed in Asians (7.4%) than Whites (7.3%), with a p-value less than 0.001.

5.4.3 Clinical outcomes and outcome trends

The crude outcomes, stratified by ethnicity, are presented in Table 5.4. Overall, there were no significant differences in crude in-hospital mortality and MACCE between White

and BAME patients. However, BAME patients had lower rates of major bleeding events compared to White patients (0.5% vs 0.9%, respectively; p<0.001).

After adjusting for variations in baseline clinical and procedural characteristics, BAME patients had similar odds for mortality (aOR, 1.07 , 95% CI 0.8-1.5**;** p=0.659) and MACCE (aOR, 0.9; 95% CI 0.8-1.1; p=0.564) compared to White patients. BAME patients had 30% lower odds of experiencing major bleeding events compared to White patients (Table 5.4). Similar findings were observed when further stratifying into four ethnic groups (Table 5.5).

Table 5-4 CHiP crude and adjusted outcomes of patients with stable angina, stratified by ethnicity.

Variables	Overall	White	BAME	Adjusted Odds Ratio (95% CI)
Mortality	308 (0.3%)	258 (0.3%)	50 (0.3%)	aOR 1.1 (0.8-1.5), p=0.659
Major bleeding events	850 (0.9%)	758 (0.9%)	92 (0.5%)	aOR 0.7 (0.6-0.9), p=0.002
MACCE	1,538 (1.5%)	1,312 (1.5%)	226 (1.3%)	aOR 1.0 (0.8-1.1), p=0.564

Abbreviation: CHiP, complex high risk percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

Table 5-5 Crude CHiP outcomes of patients with stable CAD, stratified by ethnicity into Whites, Blacks, Asians, and other Ethnic Minorities.

Variables	Whites	Blacks	Asians	Other ethnic minorities	P value
Mortality	258 (0.3%)	2 (0.3%)	23 (0.3%)	25 (0.3%)	0.967
Major bleeding events	758 (0.9%)	8 (1.0%)	45 (0.6%)	39 (0.5%)	<0.001
MACCE	1,312 (1.5%)	14 (1.7%)	119 (1.5%)	93 (1.2%)	0.176

Abbreviation: CAD, coronary artery disease; CHiP, complex high risk percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events

Table 5.6 showed that the lowest odds for major bleeding events seen in BAME patients (aOR, 0.5, 95% CI, 0.4-0.8; p=0.002) were mainly recorded in the "Other" ethnic minorities.

Table 5-6 Adjusted outcomes of CHiP in patients with stable angina according to ethnicity (comparable, Whites)

Variables	Mortality	95% CI	P value	Bleeding	95% CI	P value	MACCE	95% CI	P value
Black	0.6	0.1-2.7	0.572	1.1	0.5-2.2	0.743	1.09	0.6-1.8	0.754
Asian	1.1	0.7-1.7	0.827	0.7	0.5-1.0	0.095	1.07	0.8-1.3	0.503
Ethnic minorities	1.1	0.7-1.7	0.613	0.5	0.4-0.8	0.002	0.8	0.6-1.02	0.088

Abbreviation: CHiP, complex high risk percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events, CI, confidence interval.

Propensity score matching analysis confirmed no differences in clinical outcomes between the groups (Table 5.7).

Table 5-7 Propensity scores matching analysis on 10 imputed datasets, reporting ATE

Variable	ate (95% CI)	aOR (95% CI)	P value
Death	-.0002824 (-.0018619 .0012972)	0.9 (0.6-1.8)	0.723
Major bleeding events	-.0029836 (-.0053202 -.000647)	0.7 (0.6-0.9)	0.013
MACCE	-.002438 (-.0057853 .0009094)	0.8 (0.6-1.1)	0.153

Abbreviations: ATE, estimated treatment effect; MACCE, major adverse cardio and cerebrovascular events ; aOR, adjusted odd ratio.

Temporal trends of crude outcomes among the ethnic groups indicated stable mortality rates with no significant differences observed. MACCE rates showed a gradual decrease over time. Major bleeding events rate remained unchanged in White patients, while a gradual decline was observed among the BAME patients (Table 5.8).

Table 5-8 Temporal changes of adverse outcomes of CHiP in patients with stable angina, stratified by ethnicity.

Variables	Group 1 (2006-2009)		P value Group 1	Group 2 (2010-2013)		P value Group 2	Group3 (2014-2017)		P value Group 3
	Whites	BAME		Whites	BAME		Whites	BAME	
Mortality	74 (0.3%)	9 (0.2%)	0.213	73 (0.3%)	26 (0.5%)	0.001	111 (0.3%)	15 (0.2%)	0.117
Major bleeding events	208 (0.8%)	30 (0.7%)	0.171	278 (0.9%)	40 (0.8%)	0.278	272 (0.8%)	22 (0.3%)	<0.001
MACCE	439 (1.8%)	71 (1.4%)	0.234	460 (1.5%)	93 (1.8%)	0.161	413 (1.2%)	62 (0.9%)	0.017

Abbreviation: CHiP, complex high risk percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events

5.5 Discussion

This analysis of a large national cohort comprising 105,949 CHiP procedures records conducted on patients with stable CAD represents the first study to investigate ethnic variations in baseline demographics, cardiovascular risk factors, procedural characteristics, and clinical outcomes. The key findings of the study can be summarised as follows: 1) BAME patients were, on average, younger than their White counterparts and exhibited a poorer cardiometabolic risk profile. They also presented with more extensive coronary artery disease, as evidenced by a higher likelihood of undergoing

multivessel PCI. 2) Prevailing CHiP types among BAME patients included previous CABG, CTO vessel PCI, and interventions targeting severe vascular calcification. 3) In-hospital mortality and MACCE rates did not exhibit significant differences across the ethnic groups, even after adjusting for covariate discrepancies. However, the odds of experiencing major bleeding events were significantly lower among BAME patients. These findings shed light on the ethnic disparities in baseline characteristics, procedural preferences, and clinical outcomes among patients undergoing CHiP procedures for stable CAD.

Previous studies have highlighted disparities in baseline characteristics and cardiovascular risk factors among ethnic groups requiring PCI for stable CAD[133, 134]. However, it is important to note that the ethnic case-mix in this analysis differs from that observed in contemporary studies conducted in the USA focusing on PCI by ethnicity. This discrepancy reflects known societal differences, where the majority of non-white patients in the UK are represented by Asians, as opposed to a majority of Black patients in the USA. Nevertheless, the cardiovascular risk profile of BAME patients in this analysis was comparable to that observed in studies conducted in the USA [124]. On average, BAME patients were younger and exhibited a worse cardiometabolic profile compared to Whites, with higher prevalence rates of hypertension, diabetes mellitus, chronic renal failure, and impaired LV function. Among BAME patients, Asians had the highest burden of cardiometabolic disease. These findings highlight the significance of considering the unique ethnic case-mix and associated cardiovascular risk profiles when analysing and interpreting the results of studies examining PCI outcomes in different populations.

Additionally, previous studies focusing on specific categories of CHiP procedures have reported similar findings to those observed in this analysis, indicating no significant

differences in clinical outcomes among ethnic groups. For example, observational studies conducted using the Pan-London Percutaneous Coronary Intervention Registry, which examined PCI outcomes specifically among patients with a history of CABG (which was the most common CHiP factor in this analysis), reported comparable mortality risks between Asians and White patients (Multivariable, aOR 1.07, 95% CI; 0.97-1.17)[135].

Furthermore, the second most common CHiP factor observed in this study was PCI to a CTO vessel, in both White and BAME patients. Interestingly, a retrospective analysis conducted in the USA identified that black ethnicity was a predictor for lower success rates in CTO PCI (HR 0.6, 95% CI (0.50- 0.92); p=0.013[136]. In this analysis, extensive vascular calcification was more common in the White patients than BAME, this could be related to the fact that White patients were more likely to have heavier vascular calcification because they were older compared to BAME patients; in line with our findings, a multicentre retrospective analysis from the USA on 12,445 patients demonstrated that severe vascular calcification was more common in White patients compared to BAME patients (aOR for severe vascular calcifications, 1.57 , 95% CI (1.42,1.73); p<0.001)[70]. This analysis also indicated that severe vascular calcification was associated with older age (aOR, 1.04 , 95% CI (1.03, 1.04), p<0.001) and previous history of PVD (aOR, 1.32, 95% CI (1.13, 1.54), p=0.0004) both of which were more prevalent among White patients in our study. Moreover, ethnicity's impact on the angiographic characteristics and on the clinical outcomes following PCI were studied in 1863 females with CAD who were pooled from the PLATINUM Diversity and PROMUS ELEMENT PLUS post-approval studies [133]. The same study found that African American women had larger reference vessels diameter and fewer lesion calcifications compared to White women; whereas Hispanic women had longer, less tortuous coronary lesion and more

calcific disease than White patients. Despite differences, risks of death and MACCE were similar between the White, African Americans, and Hispanic groups[133]

This analysis has shown that PCI into a LMS was more common among BAME patients than White patients. Previous work from a single centre retrospective analysis from the USA around outcomes of LMS PCI reported that African American ethnicity/race was an independent risk factor for worse outcomes (HR 2.71, 95% CI 1.44-5.10; p=0.002)[125]. Of note, a greater proportion of BAME patients in this study had chronic renal failure, which is similar to observations reported in a retrospective study from 4 centres in the USA on 474 chronic dialysis patients, where race or ethnicity per se was not found to be associated with worse outcomes (p=0.069)[128].

This analysis indicates that after accounting for significant variations in baseline clinical and procedural characteristics, in-hospital mortality and MACCE odds were similar among the different ethnic groups. These findings suggest that ethnicity per se does not serve as an indicator of poorer short-term clinical outcomes. This aligns with the conclusions drawn from numerous studies investigating PCI outcomes (non-CHiP) in a broader context[122, 123, 137]. However, this study revealed that the odds of major bleeding events were significantly lower in the BAME population compared to White patients. Several potential explanations can account for this finding. Firstly, BAME patients were generally younger than White patients, which may lead to a lower likelihood of severe vascular calcifications. Consequently, the use of calcium modification devices during PCI procedures, which can potentially increase the risk of coronary perforation and subsequent bleeding complications, was less frequent among BAME patients. However, it is important to note that BAME patients had higher rates of CHiP procedures performed via the femoral access site, a method associated with higher bleeding risk. Additionally, BAME patients more frequently required elective intra-aortic balloon pump (IABP)

support and were prescribed more potent antiplatelet medications such as Ticagrelor or Prasugrel compared to White patients. In contrast, a higher proportion of White patients in this study met some of the higher-risk bleeding criteria according to the Academic Research Consortium definition [99, 132] such as age => 80, the use of glycoprotein IIb IIIa inhibitors and anticoagulation (warfarin), as well as history of stroke . In support of this, an analysis from a single centre in the USA looked at major bleeding event rates following complex-PCI on 9244 patients according to ethnicity. The study found significantly higher rates of White patients meeting the higher bleeding risk criteria and experiencing higher rates of major bleeding events following PCI than BAME patients[138].

This observation where younger BAME patients with heavier cardiometabolic burdens experience similar clinical outcomes to older White patients has been documented in previous studies around non-complex PCI outcomes in the short term. However, the same was not found true in studies looking at long-term outcomes post non-complex PCI. For example, a retrospective analysis from a multicentre complex in the USA compared the clinical outcomes of non-complex PCI among White patients and African Americans and showed no significant differences in short-term outcomes; however, worst outcomes were only observed at five years follow-ups among the African American patients (adjusted HR 1.44, 95% CI (1.03-2.00); p 0.03). [139] This raises the question of whether worse clinical outcomes following CHiP could be observed in BAME patients in the long term. However, the findings of this current study are reassuring in that a universal healthcare system with universal health coverage for patients regardless of their ethnic background shows similar complex, high-risk PCI outcomes. This suggests that differences observed in other healthcare systems may be attributed to disparities in healthcare provision.

5.6 Study limitations

There are several limitations to consider, as with all observational studies. Firstly, unmeasured confounders could exist in the clinical and procedural variables, such as frailty, socioeconomic status, control and duration of important cardiovascular risks factors like diabetes mellitus and hypertension, and the severity of lesion complexity. These unaccounted factors may impact clinical outcomes.

Secondly, there is a potential for coding and reporting errors, which could introduce bias. For instance, there may be underreporting of certain co-morbidities, and complications might rely on self-reporting without external validation.

Thirdly, the ethnic groups captured in the BCIS dataset are categorised as Asians, Black, White (Caucasians), and Other. The "Other" category likely represents a racially diverse population, which introduces heterogeneity.

Lastly, the BCIS dataset only captures in-hospital clinical outcomes, so we cannot rule out the possibility of significant differences in the longer term. Further research is needed to assess the long-term outcomes in different ethnic groups.

5.7 Conclusion

In summary, this nationwide analysis of CHiP procedures performed electively in patients with stable angina in England and Wales has revealed notable differences in the types of procedures and the ethnic composition, as well as the baseline clinical and procedural characteristics among different ethnic groups. BAME patients tended to be younger and had a higher burden of cardiometabolic conditions, along with more extensive coronary disease. However, despite these disparities, no significant differences

were observed in in-hospital mortality or MACCE following CHiP, even after adjusting for baseline characteristics. Additionally, the BAME patients had a lower risk of major bleeding events compared to White patients.

These findings suggest that ethnic background should not be a determining factor in the decision-making process for CHiP procedures. Further research efforts should focus on examining long-term outcomes according to ethnicity in CHiP procedures.

Chapter 6

CHiP Types, Trends, Characteristics, and Clinical Outcomes by Age Groups

6.1 Introduction

In accordance with the first and second objectives of the thesis, this chapter focused on examining the impact of different age groups on CHiP outcomes in patients undergoing treatment for stable angina. The aim was also to investigate the types of CHiP procedures, trends, and baseline clinical and procedural characteristics among three age groups: <65, 65-79, and 80 years and above. The findings from this chapter were presented at the American College of Cardiology (ACC) conference in April 2022, and the abstract was published in the Journal of the American College of Cardiology. Furthermore, the manuscript based on this chapter has been published in the Catheterisation and Cardiovascular Intervention Journal (CCI).

The elderly population has steadily increased over the past few decades, and this trend is expected to continue.[140] This demographic shift has significant implications for healthcare systems and providers. Developed countries, in particular, are projected to witness a substantial change in their age structure, with a nearly twofold increase in the population aged 65 years and above by 2050. It is estimated that octogenarians will constitute 4.3% of the population by then. [140]. As the population ages, the prevalence of age-related diseases, such as CAD, also increases. CAD is indeed a significant health concern among the elderly population. It ranks as the second leading cause of disability among older individuals and contributes to a considerable proportion of cardiovascular-related deaths. The impact of CAD on the elderly population is particularly noteworthy due to the increased vulnerability and unique challenges faced by older individuals[140].

Age is one of the accepted components of how CHiP is defined, and age is known to be an important predictor of worse outcomes following PCI[141]. Although no studies have directly examined CHiP outcomes according to age in the real-world setting, findings from studies focusing on specific CHiP types indicate poorer outcomes among older

individuals. For instance, worst outcomes post-PCI were observed in those elderly patients with chronic renal failure[142], those who underwent a CTO PCI[143, 144], those who received calcium modification therapy[145], and those who underwent left main PCI[146]. However, there need to be more studies specifically investigating age-stratified outcomes in patients with severely impaired LV function; although some studies from registries and trials compared revascularization (PCI and CABG) outcomes in those with impaired LV function have included older age groups[41, 147], further research is needed to assess the impact of age on outcomes in this specific population. Similarly, although studies have investigated the outcomes of PCI in patients with a prior history of CABG, there needs to be more research specifically examining age-stratified outcomes in this population[135]. Furthermore, age-stratified studies focusing on individual CHiP types have been limited by generalisation[143], being highly selective (strict exclusion criteria)[147], including acute MI cases[148], or sub-analysis of a trial that may not be representative of real-world practice.[146] Therefore, further research is needed to comprehensively understand the impact of age on outcomes in these specific patient populations.

We know from studies, examining age-stratified outcomes of PCI in general, that older patients tend to have worse outcomes[149]. Additionally, studies comparing outcomes of CHiP versus non-CHiP procedures have suggested poorer odds with CHiP[98]. However, the question of whether elderly patients undergoing a CHiP procedure experience unfavourable outcomes and how these outcomes have changed over time remains unanswered. Therefore, the objectives of this chapter were as follows:

6.2 Objectives

I. To examine the variations in CHiP types among different age groups.

II. To analyse the changes in CHiP trends over time-based on age.

III. To assess the disparities in baseline clinical and procedural characteristics among different age groups.

IV. To determine whether age is a contributing factor to poorer clinical outcomes, and if so, to identify the age category associated with the highest risk.

6.3 Methods

In Chapter 3, a comprehensive description of the methods employed in this study has been provided. Nonetheless, a concise summary of these methods will be presented in this chapter.

6.3.1 Study design and dataset

The study cohort was prospectively collected in the BCIS dataset, while the analysis was conducted retrospectively. The data for this study was obtained from the BCIS registry, which is managed by NICOR. The BCIS dataset contains various variables that provide information on patients' demographics, co-morbidities, cardiovascular risk factors, pharmacology, procedural characteristics, and in-patient clinical outcomes such as mortality, major bleeding events, stroke, and coronary perforation procedural characteristics, and in-patient clinical outcomes such as mortality, major bleeding events, stroke, and coronary perforation. More than 95% of PCI centres in England and Wales participate in data collection, amounting to 112 out of 117 centres. Ethical approval is not required for this study as the registry data has Section 251 approval under the NHS ACT

2006, which permits the usage of the dataset for research and audit purposes without the need for individual patient consent[84]. Data entry into the BCIS registry is performed by interventional operators who carry out the procedures, resulting in the addition of almost 100,000 procedure records to the registry each year[14]. The accuracy and quality of the BCIS data have been previously verified and established.[83]

6.3.2 Study population

This study included all patients admitted electively for stable angina between 1st January 2006 and 31st December 2017 who met the specified inclusion criteria, which encompassed a total of 8 patients' and procedural CHiP factors (see Chapter 2 for a detailed discussion about the inclusion and exclusion criteria for the CHiP cohort). Any observations with missing data in the age and outcome variables were excluded from the analysis. For the remaining variables, missing observations were imputed to ensure a comprehensive dataset. In the end, a final cohort of 138,831 procedure records was established. To further examine the data, all CHiP procedures were categorised into three age groups: G1 (<65 years old), G2 (65-79 years old), and G3 (80 years old and above).

6.3.3 Study endpoints

The primary focus of this study was on in-hospital all-cause mortality as the main outcome of interest. Additionally, secondary clinical outcomes were examined, including:

a) MACCE (Major Adverse Cardiovascular and Cerebrovascular Events) b) In-hospital major bleeding events.

For consistency and comparability with previous studies, the definitions of MACCE, in-hospital mortality, and major bleeding events used in this research were identical to those outlined in the endpoints/clinical outcomes sections of Chapters 4 and 5.

6.3.4 Study covariates

The covariates considered in this study encompassed several cardiovascular risk factors, co-morbidities, and baseline clinical characteristics. These included variables such as ethnicity, body mass index (BMI), sex, age, previous PCI or CABG, hypertension, hypercholesterolaemia, smoking status, LV systolic function, PVD, and diabetes. Furthermore, in-hospital outcomes such as survival status (death/alive) were recorded, along with variables associated with major bleeding events (e.g., blood transfusion, coronary perforation, tamponade, retroperitoneal bleed) and MACCE (re-infarction, stroke, emergency coronary artery bypass grafting). To calculate the BMI variable, the weight and height variables were utilised.

6.3.5 Data analyses

Following data collection, the baseline clinical and procedural characteristics were presented as the median and interquartile range for continuous variables, while frequencies and percentages were used for categorical variables. To assess the differences between the three age groups, statistical comparisons were conducted using Pearson's Chi-squared test for categorical variables and either the Wilcoxon-Mann-Whitney test or the Kruskal-Wallis test for continuous data, depending on the number of groups being compared. Details regarding missing data can be found in Supplemental Table 6.1.

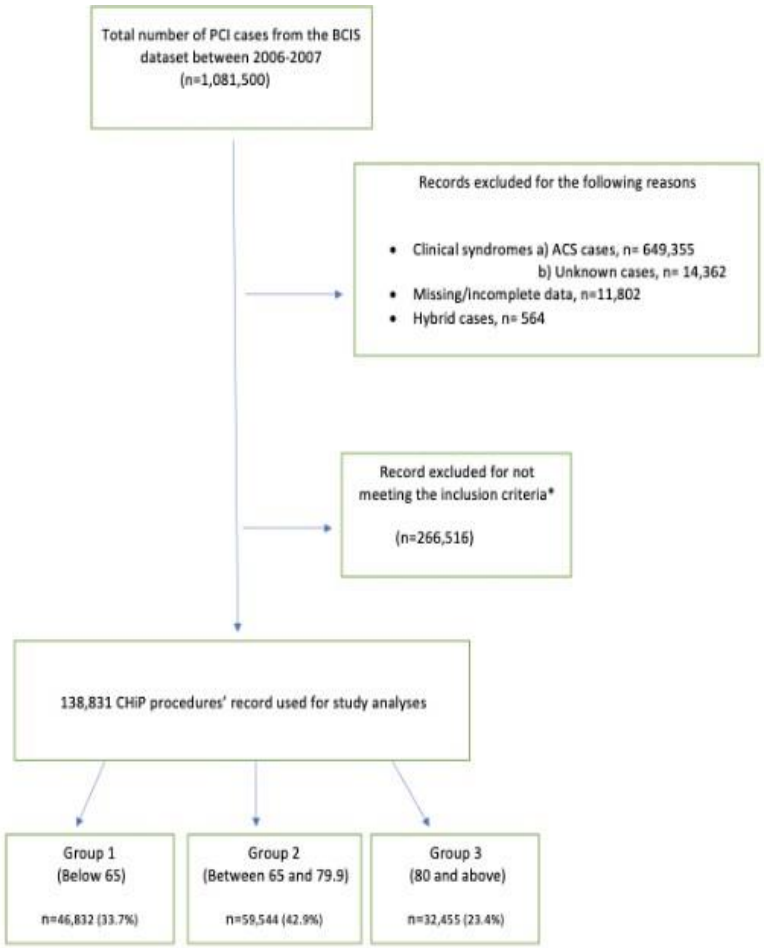
Missing data were handled using multiple imputations with chain equation methodology (MICE), creating ten datasets under the assumption that the data were missing at random (MAR).[150] Logistic regression was used to impute binary variables, linear regression for continuous variables, multinomial for nominal variables, and ordinal logistic regression. The variables included in the imputation models are age, sex, and clinical outcomes (registered in the model as regular variables); the following variables registered as imputed: ethnicity, smoking history, history of hypercholesterolaemia, hypertension, previous CABG, previous MI, previous stroke, previous PCI, diabetes mellitus, CRF, LV function, PVD, family history of CAD, pharmacology, vascular access, circulatory support, number of treated lesions, LMS PCI, severe vascular calcification, number of stents used and BMI. All analyses that followed were performed on the imputed dataset, and the results of the same were pooled using Rubin's rules.[151] In terms of variables with low event rates, the interpretation of the multivariate analysis findings was performed after considering the assumptions of the model, taking into account both the data itself and the information gathered from the literature review.[151] The multiple imputation models included variables with extensive missing observations (>20% missing), such as LV function. This decision was supported by previous studies that demonstrated the robustness of multiple imputation methods even when dealing with a high level of missing data; albeit some protection can be offered when data are missing not at random[88, 89, 152]. Multivariable logistic regression analyses were employed to determine the adjusted odds ratios (aOR), 95% confidence intervals (CI), and P-values of clinical outcomes across the three age-stratified CHIP groups. The models included the same variables as those utilised in the multiple imputation framework[151]. Stata version 14.1 was used to conduct the analyses (Stata Corp, College Station, Texas). Statistical significance was evaluated at a rate of 0.05.

6.4 Results

6.4.1 Study cohorts

Among the PCI procedure records conducted in England and Wales between 1st January 2006 and 31st December 2017, a total of 138,831 (32.7%) elective procedures were included in this analysis. The inclusion and exclusion criteria for patient selection are outlined in Figure 6.1.

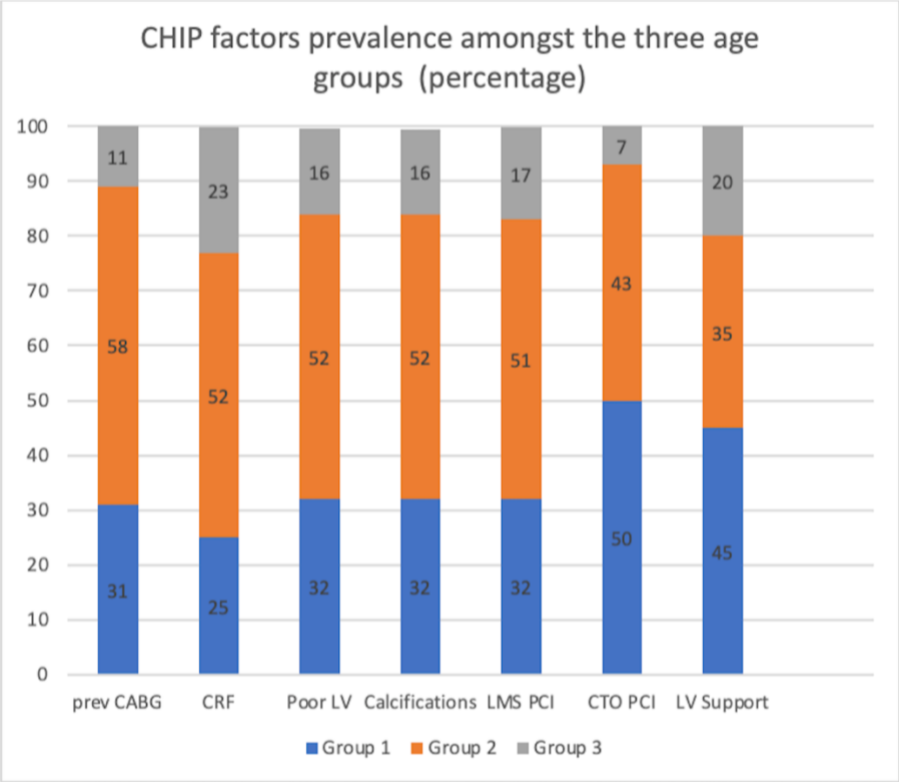
Figure 6-1 Flow diagram illustrating the process of patients inclusion and exclusion for the CHiP analyses.



Abbreviations: ACS, acute coronary syndromes; CHiP, complex, high-risk, but indicated percutaneous coronary intervention; BCIS, British Cardiovascular Intervention Society; PCI, percutaneous coronary interventions.
***Inclusion criteria: left main PCI, PCT to chronic thrombus occlusion vessel, chronic renal failure, poor left ventricle function, severe vascular calcifications, previous coronary artery bypass graft, age => 80 years.**

Details about the prevalence of each CHiP factor in the CHiP cohort, stratified by three age groups, suggested that the highest prevalence of all CHiP factors was seen in those aged 65 and above. The most common CHiP factor in the youngest age group was CTO PCI, whereas prior CABG was commonest in 65 years and above (Figure 6.2).

Figure 6-2 Prevalence of CHiP factors in patients with stable angina , stratified by three age groups (G1, <65; G2 65-79; G3 =>80).



Abbreviations: CHiP , complex high-risk percutaneous coronary interventions; CABG, coronary artery bypass graft; CTO, chronic total occlusion; LV, left ventricle; LMS, left main stem; PCI, percutaneous coronary intervention.

6.4.2 Clinical characteristics

Table 6.1 provides detailed information on the prevalence rates of CHiP factors among the different age groups. Additionally, it presents data on cardiovascular risk factors, procedural characteristics, and pharmacology stratified by age groups (Group 1: <65 years, Group 2: 65-79 years, Group 3: >=80 years).

The majority of CHiP cases (42.9%) were observed in Group 2, while Group 3, comprising octogenarians, accounted for 23.4% of the CHiP cohort. In terms of gender distribution, the majority of males (84.6%) were in Group 1, followed by Group 2 (78.5%) and Group 3 (64.9%). Regarding ethnicity, the majority of patients were of White ethnicity, with 80.5% in Group 1 and 87.7% in Group 3.

Table 6-1: Baseline clinical and procedural characteristics of patients underwent a CHiP procedure for stable angina stratified according to three age groups (Group 1, <65 years; Group 2, 65-79 years; Group 3, 80 and above years)

	Age <65 (%)	Age 65-79 (%)	Age=>80(%)	P-value
Number of participants	46,832 (33.7)	59,544 (42.9)	32,455 (23.4)	
Age Median, n (IQR)	58.1 (52.8-61.8)	72.1 (68.6-75.7)	82.9 (81.3-85.2)	P<0.001
BMI n (IQR)	29.3 (26.2-32.8)	28.1 (25.3-31.3)	26.5 (24-29.4)	P<0.001
Males, n (%)	39,610 (84.6)	46,743 (78.5)	21,074 (64.9)	P<0.001
Whites, n (%)	28,355 (80.5)	37,459 (84.4)	21,012 (87.7)	P<0.001
CHiP factors (types)				
c) Patients' factors				
• Prior CABG	13,902 (30.4)	25,094 (42.9)	4,975 (15.8)	P<0.001
• Chronic Renal Failure	3,729 (8.3)	7,677 (13.5)	3,404 (11.1)	P<0.001
• Poor LV function	2,520 (9.1)	4,053 (11.3)	1,222 (6.3)	P<0.001
d) Procedural factors				
• LMS PCI	5,214 (11.3)	8,226 (14)	2,716 (8.6)	P<0.001
• CTO PCI	22,103 (49.2)	18,611 (32.9)	3,118 (10.5)	P<0.001
• Severe coronary calcifications	8,405 (21.8)	13,273 (27)	3,992 (15.5)	P<0.001
• Use of LV support	255 (0.6)	346 (0.6)	156 (0.5)	P= 0.154
Cardiovascular risk factors				

• Hypertension	26,346 (60)	38,341 (68.5)	21,421 (70)	P<0.001
• Hypercholesterolaemia	29,059 (66.2)	37,081 (66.3)	18,703 (61.2)	P<0.001
• Diabetes	11,762 (26.4)	16,645 (29.3)	6,134 (19)	P<0.001
• Smoking				P<0.001
Never	14,575 (35.6)	21,037 (40.7)	14,141 (50.8)	
Ex-smokers	19,002 (46.4)	27,432 (53.1)	12,954 (46.5)	
Current smokers	7,354 (17.9)	3,216 (6.2)	752 (2.7)	
• Family history of CAD	22,458 (55.4)	24,081 (47.3)	9,303 (33.8)	P<0.001
• History of MI	19,114 (43.8)	25,332 (45.6)	10,978 (36.2)	P<0.001
• Previous PCI	18,329 (40)	23,501 (40.5)	10,610 (33.8)	p<0.001
• Previous stroke	1,366 (3.1)	2,950 (5.3)	1,914 (6.2)	p<0.001
• History of PVD	2,260 (5.1)	4,502 (8.1)	2,324 (7.6)	p<0.001
• LV systolic function				p<0.001
Normal (EF>50)	20,414 (73.7)	24,070 (67)	13,760 (70.8)	
Impaired (EF 30-50)	4,749 (17.2)	7,783 (21.7)	4,444 (22.9)	
Severely impaired (EF<30)	2,520 (9.1)	4,053 (11.3)	1,222 (6.3)	
Pharmacology				
• Warfarin	411 (0.9)	1,338 (2.5)	959 (3.3)	p<0.001
• GPIIbIIIa inhibitors	3,924 (9.1)	3,924 (7.8)	1,466 (4.9)	p<0.001
• Clopidogrel	34,242 (81.6)	44,533 (82.9)	24,174 (83.0)	p<0.001
• Prasugrel	545 (1.3)	493 (0.9)	102 (0.4)	p<0.001
• Ticagrelor	1,688 (4.0)	1,805 (3.3)	977 (3.3)	p<0.001
Vascular access				p<0.001
• Radial	18,954 (41.6)	25,500 (43.9)	16,349 (51.5)	
• Femoral	21,221 (46.7)	27,361 (47.2)	13,851 (43.7)	
• Multiple accesses	5,315 (11.7)	5,168 (8.9)	1,510 (4.8)	
Circulatory support				
• No support	44,258 (98.9)	56,560 (99.36)	30,744 (99.46)	P=0.154
• IABP	255 (0.6)	346 (0.6)	156 (0.5)	P=0.154
• Impella	22 (0.5)	23 (0.04)	12 (0.04)	P=0.727

Number of successful treated lesions				p<0.001
• None	5,294 (14.8)	5,616 (12)	1,682 (6.5)	
• One	16,193 (45.5)	21,972 (47.1)	13,297 (51.7)	
• Two	9,921 (27.8)	13,325 (28.6)	7,757 (30.2)	
• Three	4,224 (11.9)	5,733 (12.3)	2,989 (11.6)	
Procedural devices				
• None	30,142 (78.0)	35,969 (73.0)	21,766 (84.0)	p<0.001
• Cutting Balloon	6,277 (16.0)	7,315 (14.1)	1,650 (6.2)	p<0.001
• Rotational atherectomy	2,037 (5.3)	6,035 (12.0)	2,427 (9.3)	p<0.001
• Laser atherectomy	258 (0.7)	479 (0.9)	128 (0.5)	p<0.001
Number of stents used				p<0.001
• None	7,437 (16)	8,466 (14.5)	3,260 (10.1)	
• One stent	17,306 (37.3)	23,473 (39.7)	15,107 (46.9)	
• Two stents	11,481 (24.8)	15,116 (25.5)	8,533 (26.5)	
• Three or more stents	10,165 (21.9)	11,960 (20.3)	5,297 (16.5)	
Target Vessel PCI				
• Left main stem (LMS)	5,214 (11.3)	8,226 (14)	2,716 (8.6)	P<0.001
• LAD	18,199 (39.4)	22,373 (38.2)	16,152 (50.9)	P<0.001
• LCX	12,022 (26.0)	15,525 (26.5)	7,935 (25)	P<0.001
• RCA	18,045 (39.1)	20,706 (35.3)	10,626 (33.5)	P<0.001
• Graft	3,406 (7.4)	6,446 (11)	1,429 (4.5)	P<0.001
Number of target vessel PCI				P<0.001
• One	35,040 (75)	43,869 (74.1)	23,674 (74.1)	
• Two	8,983 (19)	11,890 (20)	6,709 (20.9)	
• Three	2,361 (5.1)	3,240 (5.9)	1,604 (5.0)	

Abbreviations: BMI, body mass index; CHiP, complex high risk percutaneous coronary intervention; CABG, coronary artery bypass graft; CTO, chronic total occlusion; CAD, coronary artery disease; GPIIbIIIa, glycoprotein IIaIIIb; LV, left ventricle; LMS, left main stem; LCX, left circumflex; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery.

6.4.3 CHiP factors

The prevalence of CHiP factors varied among the three age groups. Among patients under 65 years of age, the most common CHiP factor was CTO PCI, accounting for 49.2% of cases, followed by prior CABG (30.4%) and severe vascular calcifications (21.8%). In the age group of 65-79 years (Group 2), prior CABG was the most prevalent factor (42.9%), followed by CTO PCI (32.9%) and severe vascular calcifications (21.8%). Among octogenarians (Group 3), the most common CHiP factor was prior CABG (15.8%), followed by severe vascular calcifications (15.5%) and chronic renal failure (11.1%). Except for PCI to a CTO vessel, all CHiP factors were more prevalent in Group 2. More detailed information can be found in Table 6.1.

6.4.4 Cardiovascular risk factors

Hypertension was the most prevalent cardiovascular risk factor across all three age groups, with the highest prevalence observed among the elderly patients (Group 3). Octogenarians had the lowest prevalence of prior MI or prior PCI, as well as diabetes mellitus, with a prevalence of 19%. Among patients under 65 years of age, the highest prevalence was observed for current smoking (17.9%) and a family history of CAD (55.4%). More detailed information can be found in Table 6.1.

6.4.5 Procedural characteristics

No significant differences were observed in certain procedural characteristics among the study groups. The use of LV support devices, such as Impella (P=0.727) and IABP (P=0.154), did not vary significantly between the age groups. Additionally, PCI into a single lesion was the most common procedure across all three age groups, with percentages of 45.5% in Group 1, 47.1% in Group 2, and 51.7% in Group 3. However, there were differences in the use of calcium modification devices among the groups. Cutting balloons were predominantly used in Group 2 (12%). Moreover, the

octogenarians in Group 3 had the lowest rates of calcium modification device usage, with 84% of them not having received any such devices, compared to 73% in Group 2 and 78% in Group 1.

The most frequently targeted vessel for revascularisation via PCI was the LAD vessel in all three age groups, with percentages of 39.4% in Group 1, 38.2% in Group 2, and 50.9% in Group 3 (P<0.001). Among patients aged 65-79 years (Group 2), PCI to a graft or a LMS vessel was more common compared to the other age groups (Graft , 11%; LMS, 14%).

Radial artery access was the preferred approach for CHiP procedures in the octogenarian age group, accounting for 51.5% of cases. In Group 2, 43.9% of patients underwent CHiP via radial access, while in Group 1, the percentage was 41.6%. The prescription rate for warfarin was higher among octogenarians (3.3%). In contrast, the youngest age group (Group 1) had higher prescription rates for Prasugrel (1.3%) and Ticagrelor (4.0%).

6.4.6 Clinical Outcomes

Table 6.2 presents the age-stratified crude clinical outcomes. Among the three age groups, the highest in-hospital mortality rate of 0.5% was observed in patients aged 80 years and above, compared to 0.3% in Group 2 and 0.2% in Group 1 (p<0.001). Octogenarians also had the highest rates of major bleeding events (1.0%) and MACCE (1.7%). In contrast, Group 1 exhibited the lowest rates of major bleeding events (0.7%) and MACCE (1.3%).

Table 6-2: Crude outcomes of CHiP procedures undertaken among patients with stable angina stratified into three age groups (Group 1, <65 years; Group 2, 65-79 years; Group 3, 80 and above years).

Variables	>65, n (%)	65-79, n (%)	>=80, n (%)	P-value
Mortality	76 (0.2)	194 (0.3)	147 (0.5)	P<0.001
Major bleeding	312 (0.7)	519 (0.9)	297 (1.0)	P<0.001
MACCE	602 (1.3)	921 (1.6)	556 (1.7)	P<0.001

Abbreviation: CHiP, complex high risk percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

Adjustment for baseline clinical and procedurals covariates confirmed increased odds for mortality with increasing age (Group 2: aOR 1.7, 95% CI (1.3-2.2); Group 3: aOR 2.7, 95% CI (1.9-3.6) compared to Group 1). Similarly, the odds of both major bleeding events (Group 2: aOR 1.3, 95% CI (1.2-1.6), Group 3: aOR 1.5, 95% CI (1.2-1.7)) and MACCE (Group 2: aOR 1.2, 95% CI (1.0-1.3), Group 3: aOR 1.3, 95% CI (1.2-1.5)) increased across the age groups compared to group 1 (Table 6. 3).

After adjusting for baseline clinical and procedural covariates, the analysis revealed increased odds of mortality with advancing age; Group 2 had an aOR of 1.7 (95% CI 1.3-2.2), while Group 3 had an aOR of 2.6 (95% CI 1.9-3.6) compared to Group 1. Similarly, the odds of experiencing major bleeding events increased with age, with Group 2 having an aOR of 1.3 (95% CI 1.2-1.6) and Group 3 having an aOR of 1.5 (95% CI 1.2-1.7) compared to Group 1. Additionally, the odds of experiencing MACCE also increased across the age groups, with Group 2 having an aOR of 1.2 (95% CI 1.0-1.3) and Group 3 having an aOR of 1.3 (95% CI 1.2-1.5) compared to Group 1 (Table 6.3).

Table 6-3: Adjusted odds of adverse outcomes post CHiP in patients with stable angina according to three age groups (Group 1, <65 years; Group 2, 65-79 years; Group 3, 80 and above years). (Comparable, Group 1)

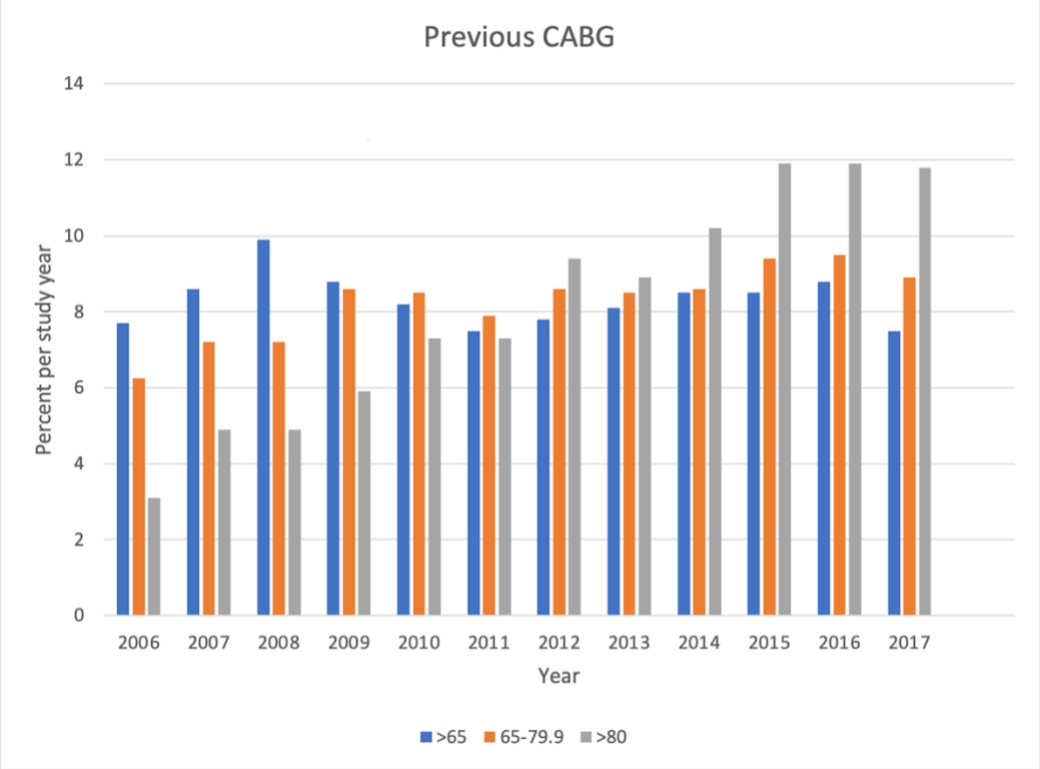
Variables	Group 2 OR	95% CI	P-value	Group 3 OR	95% CI	P-value
Mortality	1.7	1.3-2.3	<0.001	2.6	1.9-3.6	<0.001
Major bleeding	1.3	1.1-1.5	<0.001	1.4	1.1-1.7	<0.002
MACCE	1.2	1.0-.1.3	0.006	1.3	1.1-1.5	<0.001

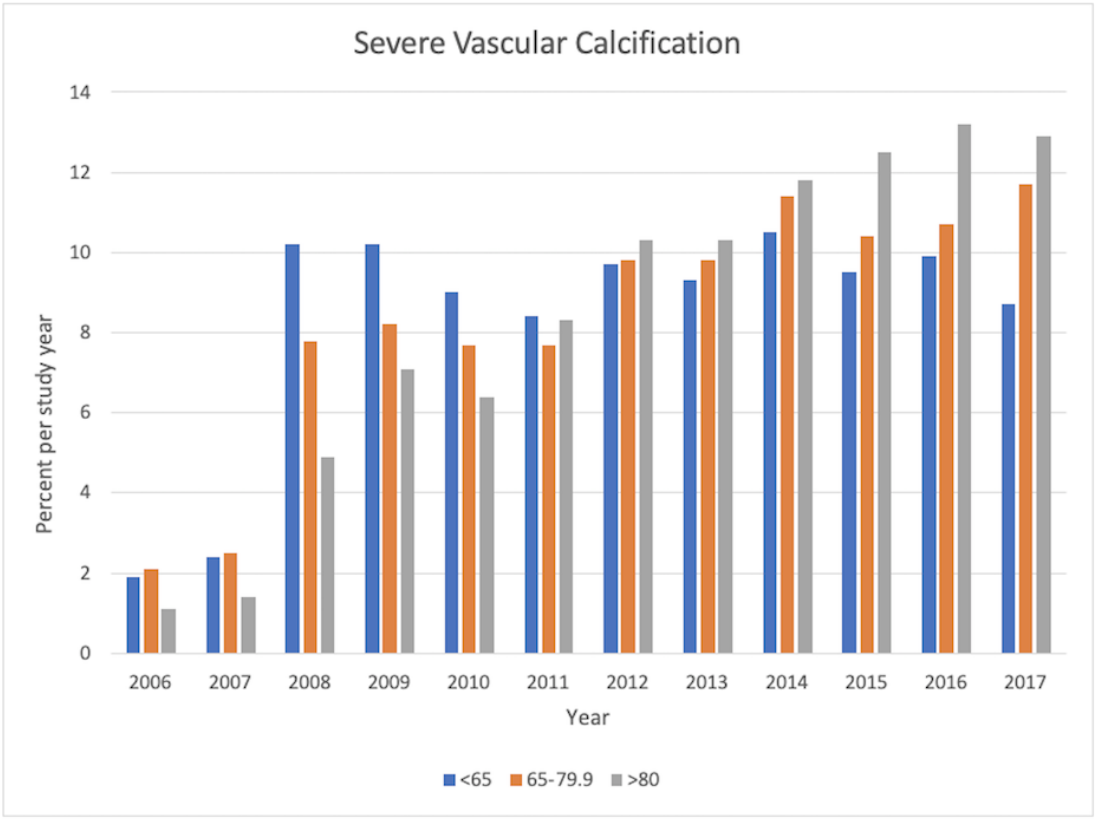
Abbreviation: CHiP, complex high-risk but indicated percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

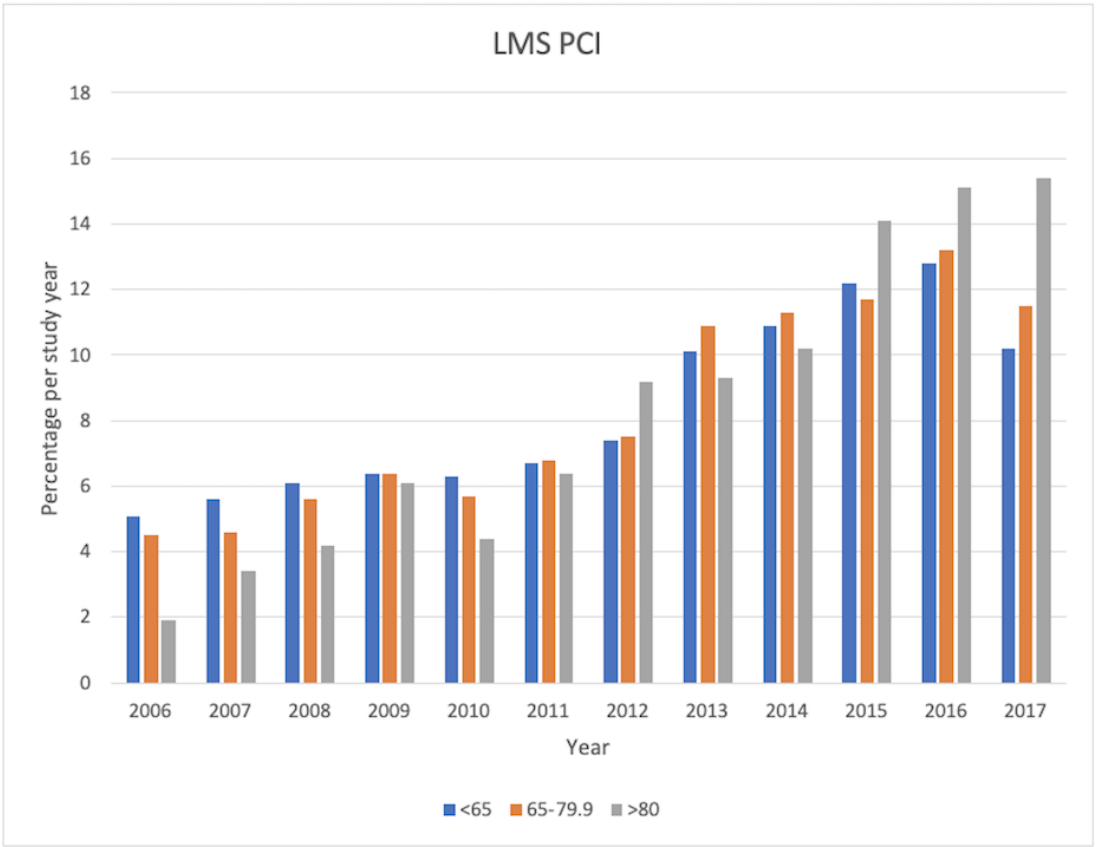
6.4.7 Temporal Trends

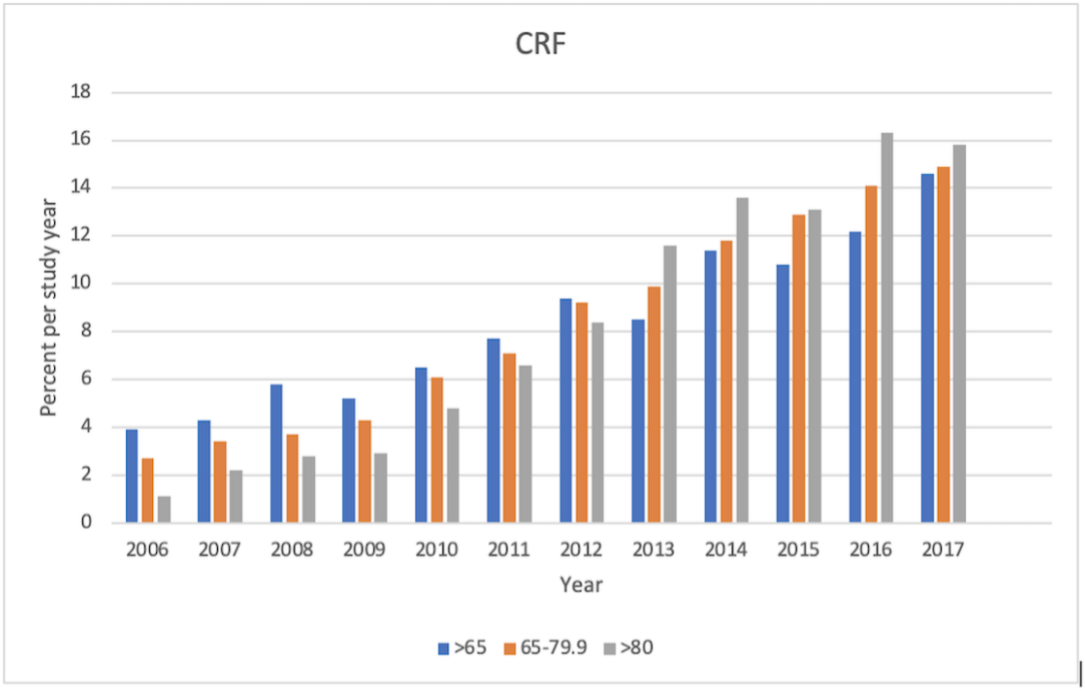
The temporal changes in the prevalence of each CHiP factor according to age are shown in Figure 6.3. Over time and across all age groups, there was an increase in the prevalence across the different types of CHiP cases. The elderly patients (Group 3) had the greatest expansion in the prevalence of prior CABG, PCI for LMS and CTO vessels, and those who received treatment for calcific vascular disease.

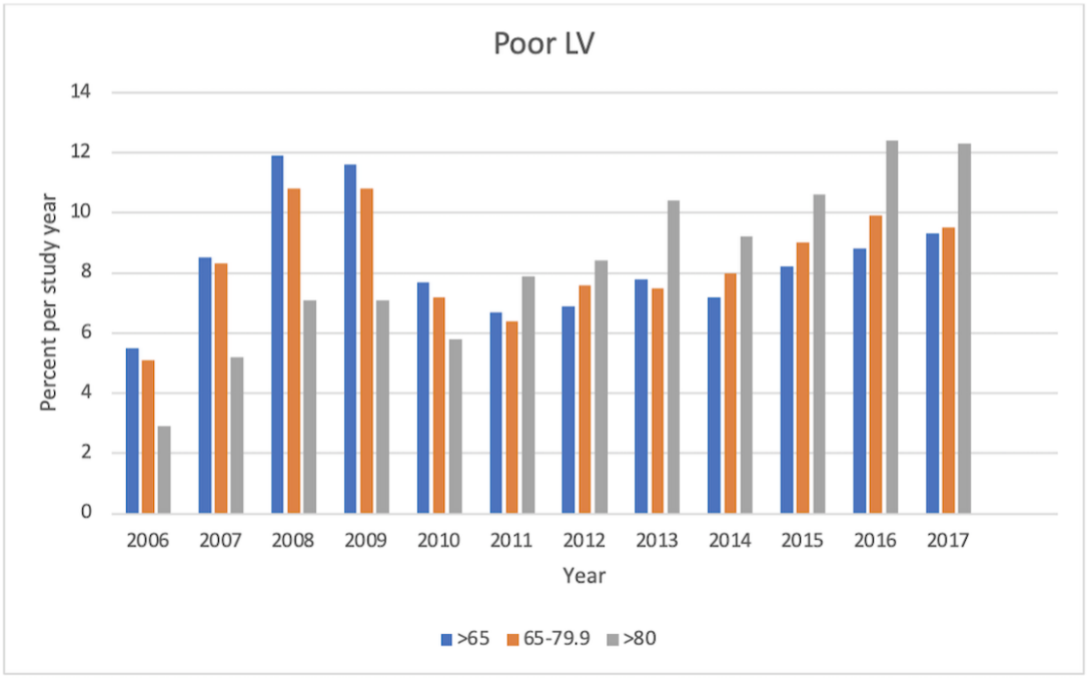
Figure 6-3 Temporal changes in prevalence of each CHiP factor among patients with stable angina who underwent a CHiP procedure, stratified according to age into three groups Group 1, <65 years; Group 2, 65-79 years; Group 3, 80 and above years).

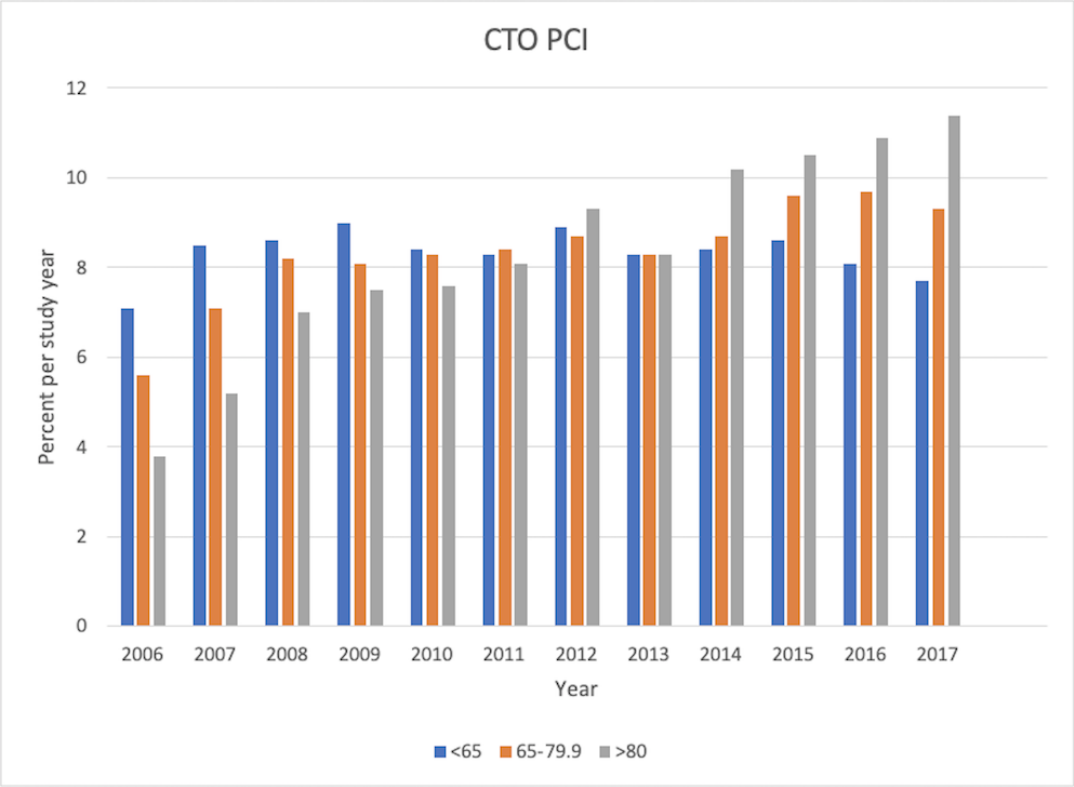


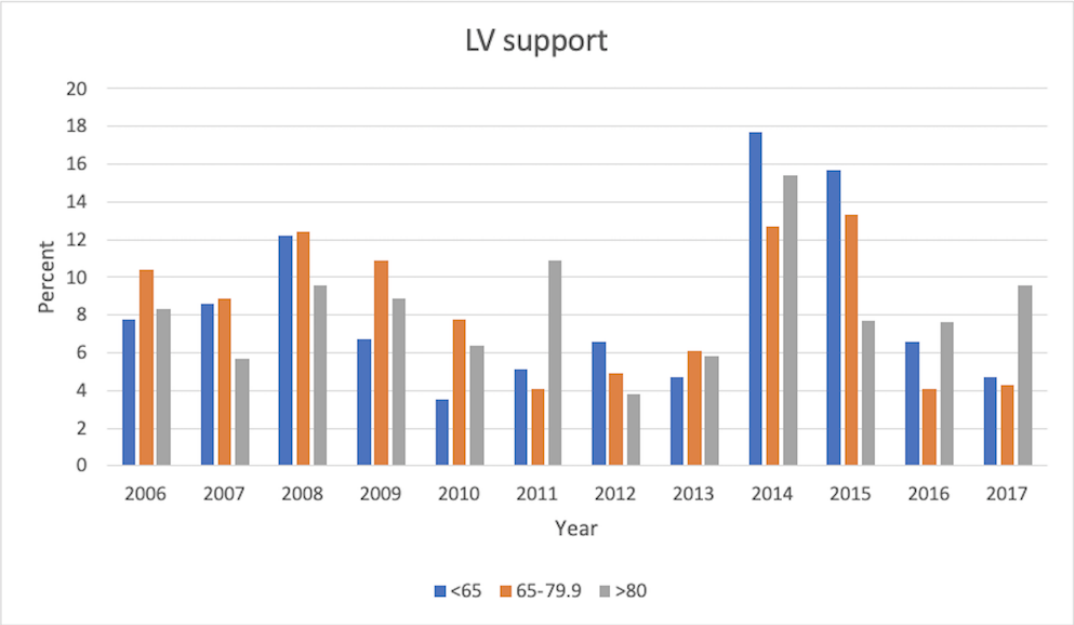

Severe Vascular Calcification
Percent per study year
0
2
4
6
8
10
12
14
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year
<65
65-79.9
>80


LMS PCI
Percentage per study year
0
2
4
6
8
10
12
14
16
18
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year
<65
65-79.9
>80


CRF
Percent per study year
18
16
14
12
10
8
6
4
2
0
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year
>65
65-79.9
>80


Poor LV
Percent per study year
14
12
10
8
6
4
2
0
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Year
>65
65-79.9
>80





Abbreviation: CHiP, complex high-risk but indicated percutaneous coronary interventions; CABG, coronary artery bypass graft; CTO, chronic total occlusion; LV, left ventricle; LMS, left main stem; PCI, percutaneous coronary intervention.

Table 6.4 presents the temporal changes in baseline clinical and procedural characteristics and clinical outcomes among the three age groups. Overall, the prevalence of cardiovascular risk factors increased in all three groups, except for current smokers in those aged 65 years and above. Specifically, Group 2 showed a prevalence of 6.5% (≤2011) compared to 6% (>2011), while Group 3 had a prevalence of 3% (≤2011) compared to 2.5% (>2011), with a p-value of <0.001. Some cardiovascular risk factors, such as prior myocardial infarction, hypercholesterolaemia, and previous stroke, did not exhibit significant changes over time in the three groups.

In contrast, there was an increase in the utilisation of radial access for procedures across all age groups, with the greatest increase observed among octogenarians (≤2011: 31% vs >2011: 64%), with a p-value of <0.001. Interestingly, the trends in in-patient mortality did not show significant changes across all age groups (Group 1, p<0.051; Group 2, p<0.450; Group 3, p<0.0.185). Furthermore, there were significant declines in major bleeding events and MACCE rates across all age groups. The most significant decline was observed among the older patients in Group 3. For MACCE, the rates were 2.1% (≤2011) compared to 1.5% (>2011), and for major bleeding events, the rates were 1.2% (≤2011) compared to 0.6% (>2011), with p-values of <0.001 for all comparisons.

Table 6-4 Temporal trend of baseline and procedural characteristics and clinical outcomes of CHiP undertaken in patients with stable angina stratified according to three age groups (< 65, 65-79, and 80 and above years)

Age group	< 65 years		p-value	65-79 years		p-value	=>80 years		p-value
Year of study	=<2011	>2011		=<2011	>2011		=<2011	>2011	
Total number	22,499	24,333		25,844	33,700		22,499	24,333	
Hypertension	11,816 (56%)	14,530 (63%)	< 0.001	15,521 (64%)	22820 (72%)	< 0.001	7,690 (67%)	13,731 (72%)	< 0.001
Hypercholesterolaemia	13,824 (66%)	15,235 (66%)	0.246	16,089 (67%)	20,992 (66%)	0.224	7,021 (61%)	11,682 (61%)	0.519
DM	5,099 (23%)	6,663 (29%)	< 0.001	13,824 (66%)	15,235 (66.4%)	< 0.001	1,999 (17%)	4,135 (21%)	< 0.001
Current smokers	3,348 (18%)	4,006 (18.4%)	< 0.001	1,414 (6.5%)	1,802 (6%)	0.019	311 (3%)	441 (2.5%)	< 0.001
Previous MI	8,910 (44.5%)	10,204 (43%)	0.008	10,682 (47%)	14,650 (45%)	< 0.001	4,008 (36%)	6,970 (36%)	0.553
Previous PCI	7,499 (35%)	10,830 (45%)	< 0.001	8,753 (35%)	14,748 (45%)	< 0.001	3,275 (28%)	7,335 (37%)	< 0.001
Previous stroke	640 (3%)	726 (3%)	0.490	1,230 (5%)	1,720 (5.5%)	0.088	720 (6%)	1,194 (6%)	0.952
PVD	1,047 (5%)	1,213 (5%)	0.159	1,956 (6%)	1,194 (6%)	0.734	942 (8%)	1,382 (7%)	0.003
Radial access	6,092 (28%)	12,862 (54%)	< 0.001	6,946 (28%)	18,554 (56%)	< 0.001	3,744 (31%)	12,605 (64%)	< 0.001
Mixed access	1,154 (5%)	4,161 (17%)	< 0.001	967 (4%)	4,201 (13%)	< 0.001	304 (2.5%)	1,206 (6%)	< 0.001
Clinical outcomes									
• Death	45 (0.2%)	31 (0.1%)	0.051	79 (0.3%)	115 (0.3%)	0.450	64 (0.5%)	83 (0.4%)	0.185
• Major Bleeding	178 (0.8%)	134 (0.6%)	0.001	233 (0.9%)	286 (0.9%)	0.491	146 (1.2%)	151 (0.6%)	< 0.001
• MACCE	347 (1.5%)	255 (1.1%)	< 0.001	462 (1.8%)	459 (1.4%)	< 0.001	260 (2.1%)	296 (1.5%)	< 0.001

Abbreviations: CHiP, complex high-risk percutaneous coronary intervention; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; MACCE, major adverse cardiovascular and cerebral events.

6.5 Discussion

This study provides valuable insights into the age-specific characteristics, CHiP factors, and clinical outcomes in patients undergoing a CHiP procedure for stable CAD. This large analysis of 138,831 CHiP procedure' records undertaken in patients with stable CAD reveals a distinct pattern of lower cardiovascular risk profiles as patients age. Among the

octogenarians, there was a lower prevalence of smokers, diabetes mellitus, and hypercholesterolaemia compared to the younger age populations. Furthermore, the study demonstrates age-related variations in CHiP factors. Procedures involving the revascularisation of CTO vessels, prior CABG, and severe vascular calcifications were more frequently observed in the younger population. Conversely, prior CABG, severe vascular calcifications, and chronic renal failure were more commonly encountered in the octogenarians. The analysis reveals that clinical outcomes varied with age, even after adjusting for differences in baseline clinical and procedural covariates. In-hospital mortality, major bleeding events, and MACCE odds were considerably worse among individuals aged 65 and above, with nearly three-fold higher odds observed among octogenarians. Moreover, trends in mortality within the same age group remained relatively stable over time. However, there were noteworthy declines in the trends of major bleeding events and MACCE, with the most significant decrease observed among the octogenarian population.

Studying the higher-risk cohort of octogenarians is of paramount importance, particularly considering the well-documented increase in the prevalence of CAD with age. CAD, to date, remains the leading cause of morbidity and mortality worldwide . [153] Evidence pertaining to the invasive management of stable CAD in the elderly often originates from observational studies, which suffer from limitations such as generalisability concerns[154]or being outdated, small in scale, and inadequately powered [140]. Moreover, the randomised controlled trials, which provide the primary basis for evidence regarding PCI in older populations, consistently under-enrolled older age participants [155, 156].

Significant differences were observed in the baseline clinical characteristics among the study groups. Hypertension was found to be the most prevalent cardiovascular risk factor

across all age groups, with the octogenarians showing the highest prevalence. However, it was notable that Group 2 had the heaviest co-morbid burden. This observation suggests that individuals with significant cardiovascular co-morbidities may either experience higher mortality rates before reaching 80 years of age or that physicians tend to select patients with fewer co-morbidities as age increases. A study conducted on a USA registry, which investigated outcomes of non-complex PCIs in patients with stable angina across different age groups, reported similar findings [Hypertension: 80.4% vs 66.5% (octogenarian vs age <60); Diabetes: 20.8% vs 29.3% (octogenarian vs age <80)]. [157] The same was also found in a similar study from the Cath PCI registry [hypertension 80.88 % vs 77.89 ; (octogenarian vs age<80); diabetes 34.12% vs 26.39%][25].

In addition, there were notable differences in the procedural characteristics among the study groups. Specifically, the use of the radial artery access approach was more commonly observed in the octogenarian group compared to the other age groups, likely due to the recognition of higher bleeding risks associated with advanced age. Conversely, the younger patients exhibited higher rates of PCI for CTOs, which often necessitate the use of larger sheaths via femoral access and the application of calcium modification devices (both seen at higher rates in younger age patients).

Prior history of CABG was found to be the most common CHiP variable among the octogenarian group. This finding aligns with previous studies suggesting long-term benefits associated with CABG, which may delay the need for further interventions until the later stages of patients' lives. For instance, the AWESOME trial (The Angina With Extremely Serious Operative Mortality Evaluation) compared long-term outcomes between patients undergoing PCI and CABG and included a substantial proportion of patients aged 70 years or older. Although no significant difference in long-term survival was observed, the PCI group exhibited a higher incidence of unstable angina and repeat

revascularisation[158]. Other trials have also demonstrated the survival benefits of CABG, improvement in anginal symptoms, and reduced need for subsequent revascularisation procedures. [159]. These findings have been corroborated by large meta-analyses, further supporting the advantages of CABG in certain patient populations[160, 161].

There was a gradual increase in the number of CHiP procedures performed in the octogenarian group as well as the other two age groups over the 12-year study period. This trend was observed in higher-risk patients below 80 years of age who underwent left main stem (LMS) PCI procedures or had a history of chronic renal failure (CRF). These findings may indicate the wider adoption of new management strategies following changes in guidelines, such as the LMS guidelines[162, 163], or expert consensus in, for example, the management of a CTO vessel [62] using new crossing algorithms [35, 164 165], as well as the increased availability of advanced technologies in managing cases with severe vascular calcifications[166] and advanced heart failure[42]. Moreover, the increased availability of procedural devices, such as fractional flow reserve [16, 162, 167] and intravascular ultrasound or optical coherence tomography [168], helped better assessment of disease severity, complexity (calcium identification) and guided decision making which facilitated better outcomes [169]. For example, the 2015 LMS European Society guidelines recommendation favoured PCI or CABG in low-risk patients (class I-B for both) [163]. In contrast, the 2011 American guidelines gave a low-risk patient class II-B recommendation for PCI [162]. This could have contributed to the increase in the rates of LMS PCI cases seen across all age groups.

Despite lower co-morbidity burden and CAD complexity in the octogenarian compared to the other two groups, outcomes odds were worse even after adjusting for covariates. For example, mortality odds were almost twofold higher in Group 2 and

threefold higher in the octogenarian, and trends suggest no change of the same over time. This finding suggests that older age is an independent risk for mortality. Indeed, age has been consistently shown to be an important predictor of adverse outcomes in all contemporary PCI risk scores studied [80, 170-173]. Although CRF has been adjusted for, it is worth noting that previous studies have demonstrated an association between higher mortality odds and CRF, which happens to be the third most common factor observed in the octogenarian population undergoing CHiP procedures. Supporting this notion, a study from the National Cardiovascular Network suggested a significant increase in in- hospital mortality following PCI among the octogenarian with a history of renal failure or severe LV impairment (Mortality in the octogenarian: 0.79% (with no risk factors) vs 7.2% (with renal insufficiency or EF<35%)[174]. Other studies suggested worse mortality odds even with chronic kidney disease (estimated glomerular filtration rate (eGFR) between 30-59)[175]. Moreover, there could be unmeasured variables in the older age group that are considered effect modifiers and hence contributed to the observed high mortality rates, such as age-related physiological changes, anaemia, frailty, and poor control of other risk factors like hypertension or diabetes in the octogenarian. Another important factor that could be added to the list of possibilities for the observed higher events rate in the elderly population could be the type of PCI performed in those with a prior history of CABG (the most common factor in the octogenarian), as some studies suggested that outcomes of PCI to a native coronary artery in a patient with grafts had the highest in- patient, 30-day and 1-year mortality as compared with those patients who had PCI in grafts[176]. Furthermore, evidence from trials suggests that mortality continue to be higher in older age at 30 days follow up post PCI [177, 178].

Despite the increased mortality odds in the elderly population, several studies have suggested that novel and minimally invasive coronary revascularisation approaches should be considered for this age group due to their potential applicability and benefits.

For instance, a survey conducted on a large cohort of 1,410,069 patients who underwent PCI, as reported in the Cath PCI registry, found that individuals aged 80 or above had the highest risk of complications (mortality rate of 3.6% in the 80 and above age group compared to 1.26% in the 60-79 age group; $p<0.0001$). However, it is noteworthy that the group aged 80 and above also experienced the greatest absolute reduction in mortality (odds ratio of 0.95; 95% CI, 0.92 to 0.97)[25].

Major bleeding events odds were 30% higher in the octogenarian and 20% higher in those 65 years and above. Despite higher rates of radial access and less use of procedural devices among those 80 years and above, their odds for major bleeding events were higher even after adjustment for covariates. This could be explained in part by higher rates of warfarin prescriptions, and other unmeasured confounders such as frailty and anaemia [179].

Similarly, MACCE odds increased with increasing age. Higher MACCE odds in the elderly group could be related to less responsiveness to clopidogrel in those elderly with chronic renal failure/dysfunction, both seen at higher rates in Group 3. In support of this, a retrospective study examined outcomes of PCI in those with stable CAD and stage 3-5 CKD found low responsiveness to clopidogrel among those with moderate to severe kidney dysfunction and that this was associated with higher odds of MI, stroke, and death within 1 year [180].

Some studies around PCI outcomes in the elderly suggested that PCI outcomes appear to be comparable to CABG. For example, a subgroup analysis according to age from the Syntax trial (Synergy between PCI with Taxus and Cardiac Surgery) that compared PCI versus CABG outcomes in patients with complex CAD[18], revealed that elderly with complex CAD risk of death at 10 years or MACCE at 5 years did not differ among the

two groups. A finding that contradicted results from observational studies that reported favourable CABG outcomes [154].

6.6 Study limitations

Like any observational study, this investigation has several limitations that should be acknowledged. First, there is a risk of reporting and coding errors, which may introduce potential biases. For example, there could be underreporting of specific co-morbidities, and the complications associated with the procedures were self-reported without external validation. Additionally, there may be unmeasured confounders in the baseline clinical and procedural variables, such as socioeconomic status, frailty, anaemia[181], control of cardiovascular risk factors such as hypertension and diabetes, and lesion complexity that may impact the clinical outcomes we report.

Furthermore, it is important to note that the BCIS dataset used in this study does not provide information on the completeness of revascularisation. Although statistical significance was achieved due to the large number of patients, some variables in the results section demonstrated small differences. The clinical significance of these small differences remains unclear. Lastly, it should be highlighted that the BCIS dataset only captures in-hospital outcomes, and thus, significant differences in longer-term outcomes cannot be ruled out.

6.7 Conclusion

This analysis reveals notable disparities in the CHiP procedures performed and the clinical outcomes observed among the three age groups. The octogenarian population

exhibited higher rates of hypertension and stroke compared to those below 80 years old. Despite having a lower burden of cardiometabolic co-morbidities compared to the younger age groups, the octogenarians had significantly higher odds of experiencing mortality, major bleeding events, and MACCE. These findings suggest that older age is an independent risk factor and is associated with poorer outcomes in CHiP procedures. Interestingly, the trends for in-hospital mortality remained relatively stable within the same age group. In contrast, there was a consistent decline in the trends of MACCE and major bleeding events over the study years, with the most substantial reduction observed in the octogenarian cohort.

These findings highlight the importance of considering age as a significant factor in risk assessment and decision-making when performing CHiP procedures. Older patients, especially octogenarians, may require additional attention and tailored management strategies to optimize outcomes. Moreover, continued efforts should be made to understand better the specific challenges and complexities associated with CHiP procedures in older populations. Future studies could explore the potential impact of unmeasured confounders, such as socioeconomic status, frailty, and lesion complexity, on clinical outcomes in this age group. Finally, longer-term outcomes beyond the in-hospital period should be investigated to fully assess the overall impact and efficacy of CHiP procedures in different age groups.

Chapter 7

Complex High-risk Percutaneous Coronary Intervention Types, Trends, and Outcomes According to Vascular Access Site

7.1 Introduction

The previous chapters of this thesis focused on examining trends, baseline differences, and clinical outcomes in special populations (females, individuals from Black, Asian, and Minority Ethnic (BAME) backgrounds, and the elderly). In this chapter, the focus shifts to investigating the association between the type of vascular access approach (radial or femoral) and CHiP clinical outcomes, as well as exploring differences in baseline characteristics among patients undergoing a CHiP procedure in England and Wales according to the access site.

The findings from this chapter were presented at the European Society of Cardiology (ESC) - Barcelona 2022 conference, and the abstract has been published in the European Heart Journal. Additionally, a manuscript with detailed analysis of the data is published in Catheterization and Cardiovascular Interventions journal.

The transradial access (TRA) was introduced to overcome some of the disadvantages seen with the default access at that time, the transfemoral access (TFA). The transfemoral approach was introduced by Judkins [182] as a better option to the trans-brachial approach because it is a large calibre vessel that accommodates high profile equipment and bigger size guides needed, especially when complex procedures such as rotational atherectomy or bifurcation treatment was required. The femoral artery approach has several advantages, such as: 1) Technical ease and shorter procedure time: The femoral artery's larger size and accessibility allow for easier catheter and guidewire placement. It facilitates certain angulations by removing arms from the chest fields. 2) Reduced radiation exposure: Positioning the patient's arms away from the chest field and increasing the distance of the operator from radiation source decrease radiation exposure for both

the patient and the physician. 3) Rare occurrence of distal arterial occlusion beyond the intervention site. [183].

However, these benefits were challenged with the increased incidence of periprocedural major bleeding complications, mortality and even MACCE due to femoral access site complications requiring blood transfusions and/or surgical repair of fistulae, pseudoaneurysms, or even nerve damage. Moreover, readmission for management of access site bleeding and infection following TFA procedures is not rare. Other reasons includes post procedure care and patient comfort issues as patients needed to lay flat in bed for at least six hours post procedure which translates to longer hospital stays and more costs. [184]

The use of radial artery approach has emerged as an appealing alternative to the TFA for several reasons: 1) It offers easier access to the radial artery and better control of bleeding issues. 2) Patients experience greater comfort as they do not need to stay overnight in the hospital and can resume normal activities sooner, such as sitting up, eating, and walking to the bathroom. 3) Compared to TFA, it reduces pain and discomfort. 4) It decreases the need for extended nursing care and overnight hospital stays, resulting in cost reduction. 5) Radial artery access can cut down infection rates and can be used in patients receiving anticoagulation therapy.

The initial reports on PCIs undertaken via the TRA approach in the treatment of CAD emerged more than three decades ago[185, 186]. Since then, PCIs undertaken via TRA have been shown to significantly decrease mortality, major bleeding events, and MACCE in several randomised controlled trials (RCTs)[187-189]. TRA adoption for PCI in Europe, the United Kingdom, and worldwide has increased significantly over the past decades. This is not only due to the confirmed benefits related to major bleeding and death events

compared to TFA but also because of the previously mentioned factors such as decreased healthcare costs, patients' preferences, and comfort[190]. In line with the mounting evidence, the North American and European guidelines have endorsed a "radial first" strategy[191, 192] and its used is classed IA according to the European Society of Cardiology [7]; the radial artery is now the commonest access site used for PCIs in Europe and many other countries (e.g. South Asia)[193]. In the UK, almost 90% of the PCIs are performed via the TRA and it expected to grow more according to the latest published BCIS audit figures[194]. This has facilitate the path toward utilising the TRA for higher risk and more complex PCIs (CHiP).

Studies around CHiP clinical outcomes and differences in baseline procedural and clinical characteristics according to the access site undertaken are limited to small or non-randomised control trials [189, 195-198], selective studies that investigated one of the CHiP factors only[199-201], limited geographical regions [202, 203], or international surveys [190]. Therefore, the question of whether “radial first” can achieve similar benefits in PCI outcomes in a CHiP procedure remains unanswered.

The primary objective of this study was to examine the association between vascular access choice in CHiP and clinical outcomes, as well as to determine if there have been any changes in this association over time. This investigation utilised data from a comprehensive national registry.

7.2 Objectives

The objectives of this chapter can be summarised as follows:

I. To examine differences in baseline clinical characteristics of patients who underwent a CHiP procedure based on the chosen access site.
II. To investigate differences in baseline procedural characteristics of patients who underwent a CHiP procedure based on the chosen access site.

III. To analyse differences in the types of CHiPs performed based on the chosen access site.

IV. To assess differences in clinical outcomes among patients who underwent a CHiP procedure based on the chosen access site.

V. To examine trends in the utilisation of CHiP procedures based on the type of vascular access.

7.3 Methods

In Chapter 3, a comprehensive description of the methods employed in this study has been provided. Nonetheless, a concise summary of these methods will be presented in this chapter.

7.3.1 Study design

The study design employed in this research is consistent with previous studies mentioned in chapters 3-5, involving the analysis of prospectively collected observational data. The data utilised for this study were obtained from the BCIS registry, which has been extensively discussed in chapter 3. The BCIS registry is managed by NICOR and collects comprehensive information on demographics, cardiovascular risk factors, co-morbidities, procedural characteristics, interventions, pharmacological treatments, in-patient peri-procedural complications, and mortality related to PCI procedures in England and Wales. The registry captures data from over 95% (112 out of 117) of the PCI centres in the UK on an annual basis[14]. All the information used in this study was prospectively collected by healthcare professionals. Prior to being transferred to the central NICOR servers, the data are encrypted to ensure security. As mentioned in earlier chapters, ethical approval is not required for this study since the data collection has section 251 approval under the NHS Act 2006[83]. Furthermore, data entry into the BCIS registry is mandatory for

professional revalidation. [14]. The quality and accuracy of the BCIS dataset have been established through previous studies and statistical analyses.[84].

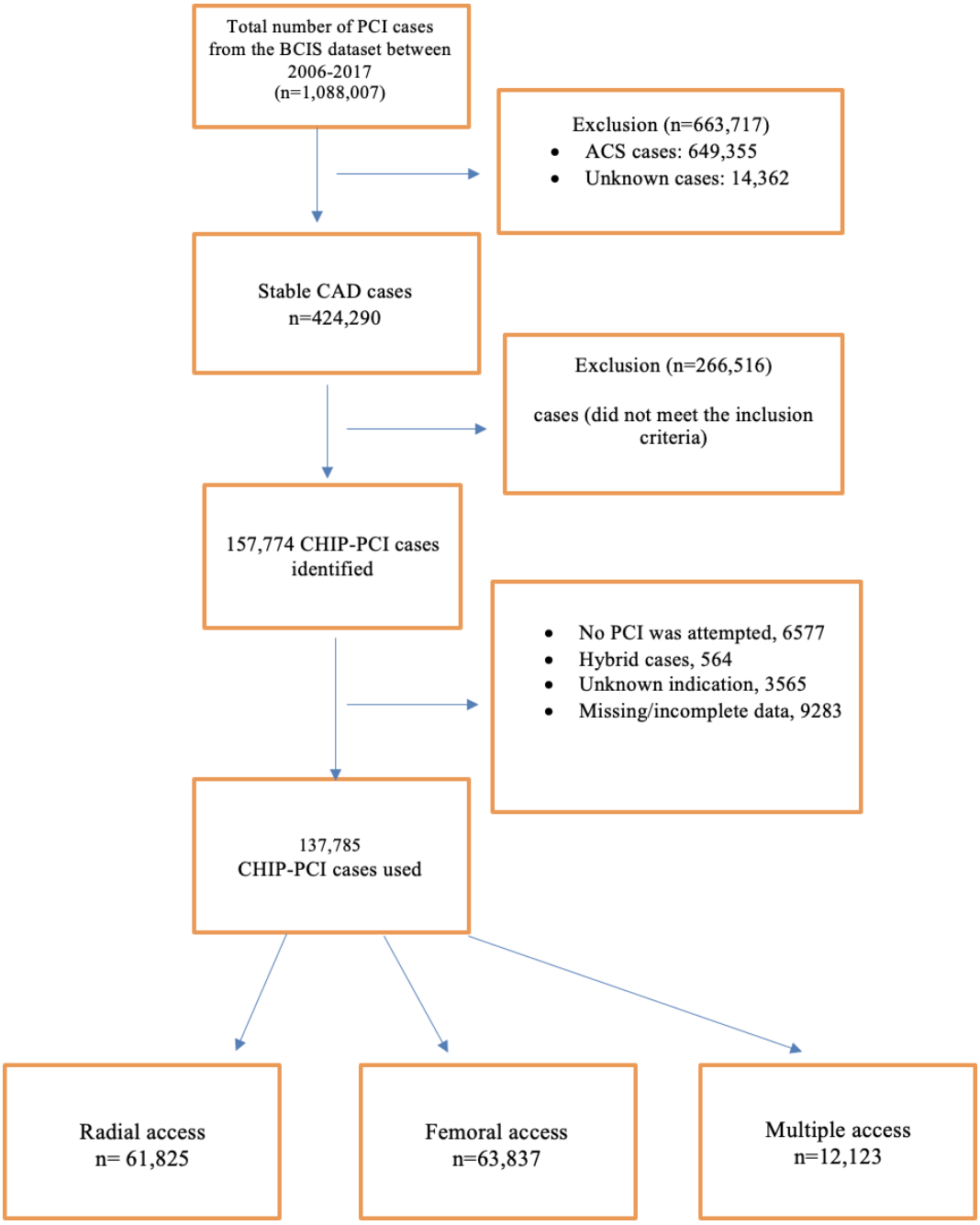
7.3.2 Study population

All patients who underwent a CHiP for stable angina in England and Wales between January 1, 2006, and December 31, 2017, were included in the study cohort. The data used for this analysis were obtained from the BCIS registry. The selection of the CHiP cohort was based on our defined CHiP criteria, as described in Chapter 2. These criteria included patients who met at least one of the following four patient characteristics: age ≥ 80 years, severely impaired left ventricular function, previous CABG, or chronic renal failure . Additionally, patients who met at least one of the four procedural characteristics were included: left main (LMS) PCI, severe vascular calcifications, chronic total occlusion PCI, or the need for left ventricular support. [98]The collected CHiP data were then categorised into three groups: Radial access, Femoral access, and Multiple access.

The definition of LV support, poor LV function, severe vascular calcifications, and CRF were the same as with previous studies (see study population section in Chapters 4-6) and discussed in detail in Chapter 2.

The process of inclusion and exclusion criteria are shown in Figure 7.1. A total 137,785 study cohort was selected for the study (Radial access: 61,825; Femoral access: 63,837; and Multiple access: 63,837)

Figure 7-1: Flow diagram illustrating the process of patients' inclusion and exclusion for the CHiP analysis



Abbreviations: CHiP, complex, high-risk percutaneous coronary interventions; PCI, percutaneous coronary interventions; CAD, coronary artery disease; ACS, acute coronary syndrome.

7.3.3 Study endpoints

The outcomes of interest were categorised into primary and secondary outcomes. The primary outcome was defined as in-hospital all-cause mortality. The secondary outcomes included in-hospital major bleeding events and in-hospital major adverse cardiovascular and cerebral events (MACCE). The definitions for major bleeding events and MACCE were consistent with those used in previous studies, as described in the clinical outcomes and study endpoints section of Chapters 4-6.

7.3.4 Study covariates

Demographic data of the patients, including age, sex, ethnicity, weight, and height, were collected. Additionally, information on clinical baseline characteristics and cardiovascular risk factors , procedural characteristics were also obtained. Body Mass Index (BMI) was calculated using the weight and height information available in the BCIS dataset.

7.3.5 Statistical analysis

The patients' variables were summarised as median (interquartile range) for continuous non-parametric data and frequencies (percentages) for categorical data. To compare the patients' baseline characteristics and procedural details, Pearson's Chi-squared test was used for categorical data, and the Kruskal-Wallis test was used for continuous data. Supplemental Table 7.1 provides information on the missing data for each variable included in the study.

The missing data was imputed using multiple imputations with chained equations to create 10 datasets, assuming that data were MAR. Age, access, sex, and outcomes variables were registered as complete variables in the imputation models. Variables imputed were the following: ethnicity, history of hypercholesterolaemia, previous MI,

previous CABG, previous PCI, previous stroke, diabetes mellitus, hypertension, CRF, PVD, pharmacology (clopidogrel), family history of CAD, coronary imaging, LMS PCI, circulatory support, number of treated lesions, stent size and length, number of stents used, and body mass index (BMI). Subsequent analyses were performed on the imputed dataset, and results were pooled using Rubin's rule[102]. Then multivariable logistic regression analyses were performed to determine the aOR, 95% CI, and the p-value of the clinical outcomes between the groups. All models included the same variables as used in the multiple imputation framework. Finally, propensity scores matching PSM (mi estimate:teffects psmatch) were used to control imbalances and differences in the baseline characteristics between the groups. To help with a better interpretation of the results, we converted the coefficients to odds ratios. We also performed a sensitivity analysis on the non-imputed dataset to better assess the consistency of the results obtained. Stata version 14.1 was used to conduct the analyses (Stata Corp, College Station, Texas). Statistical significance was evaluated at a type I error rate of 0.05.

7.4 Results

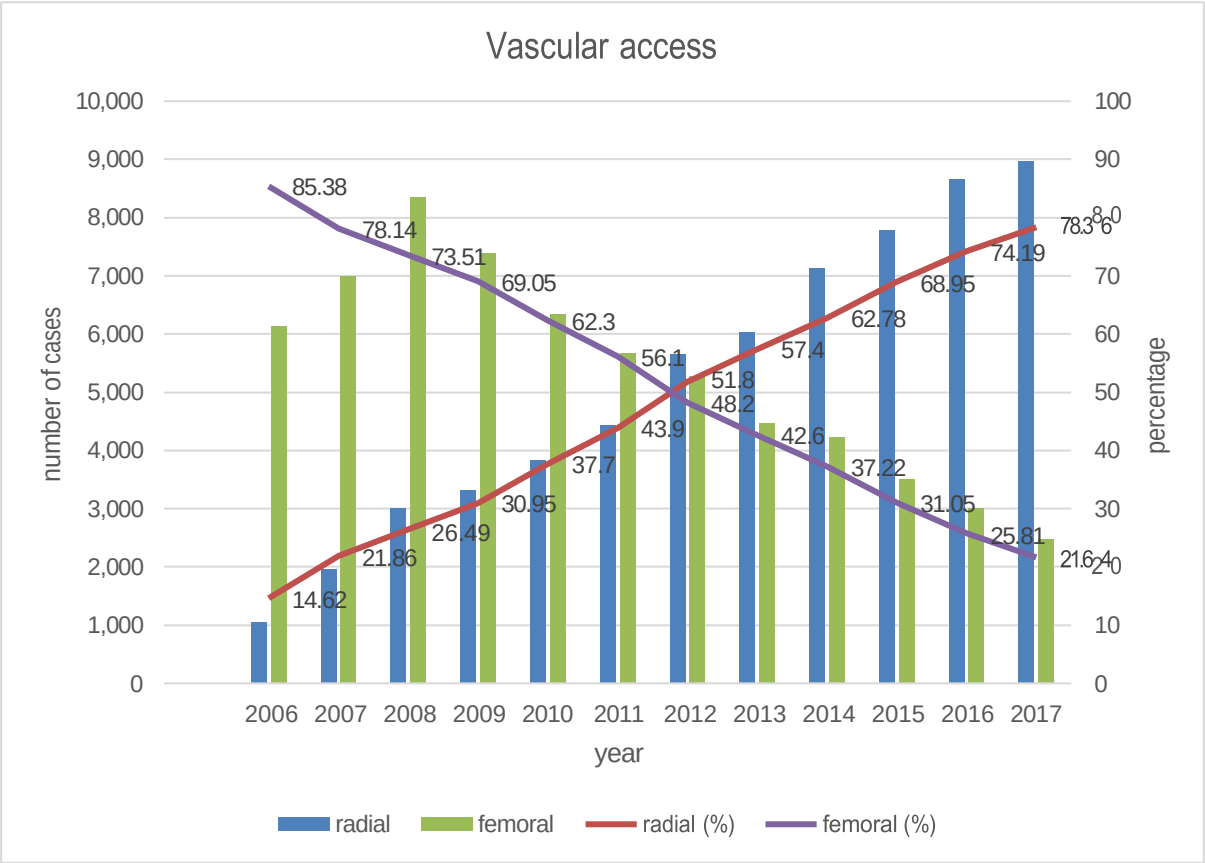
The analytical cohort of the study comprised 137,785 CHiP procedures, accounting for 29.6% of all elective PCI procedures (424,290) conducted for stable angina in England and Wales from January 1, 2006, to December 30, 2017.

7.4.1 Temporal changes in the prevalence of CHiP factors

Figure 7.2 illustrates the temporal trends in the prevalence of CHiP procedures, categorised by TRA and TFA. In 2006, the majority of CHiP procedures were performed via the TFA, accounting for 85.4% of cases, while TRA accounted for 14.6%. Over the study period, there was a gradual increase in the utilisation of TRA in CHiP procedures. By 2017, TRA had become the most commonly used access, representing 78.4% of CHiP

procedures, whereas TFA accounted for 21.6%. Furthermore, the use of Multiple accesses in CHiP procedures also exhibited an upward trend, with an increase from 2% in 2006 to 15% in 2017.

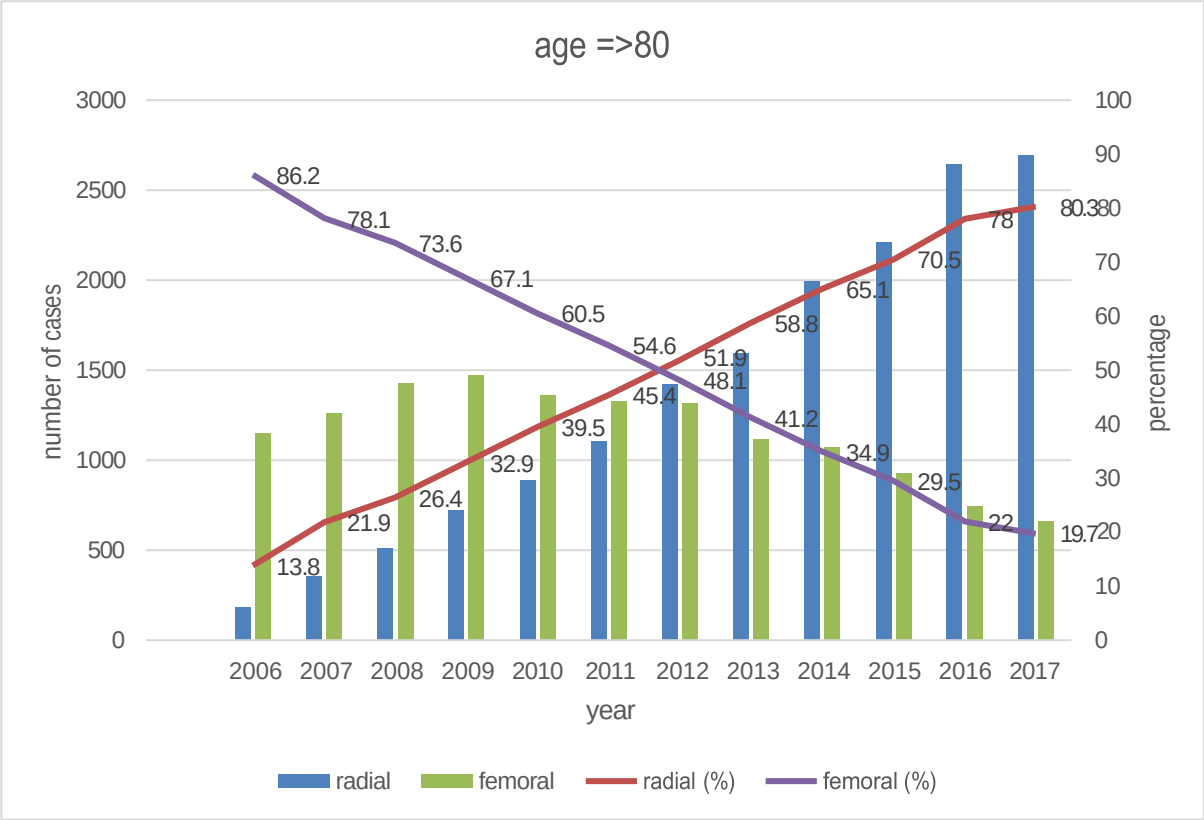
Figure 7-2 Temporal changes in CHiP procedures' prevalence and percent changes over time, stratified by access site.

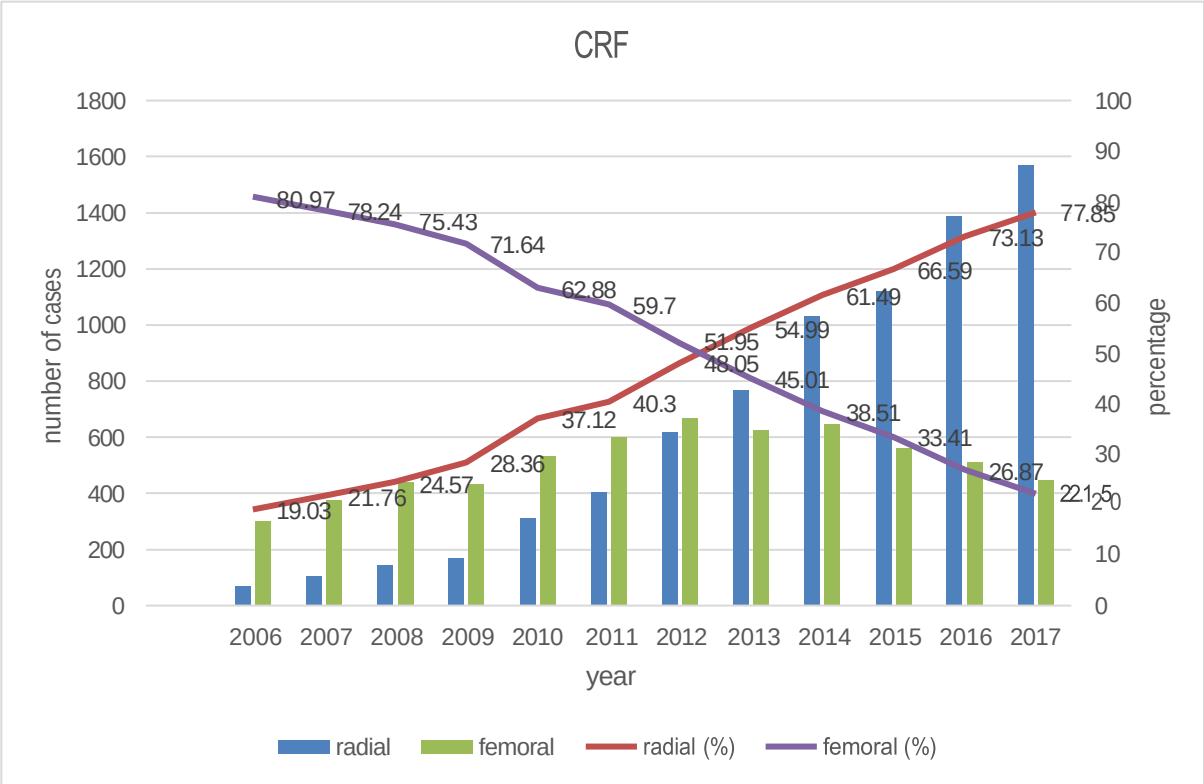


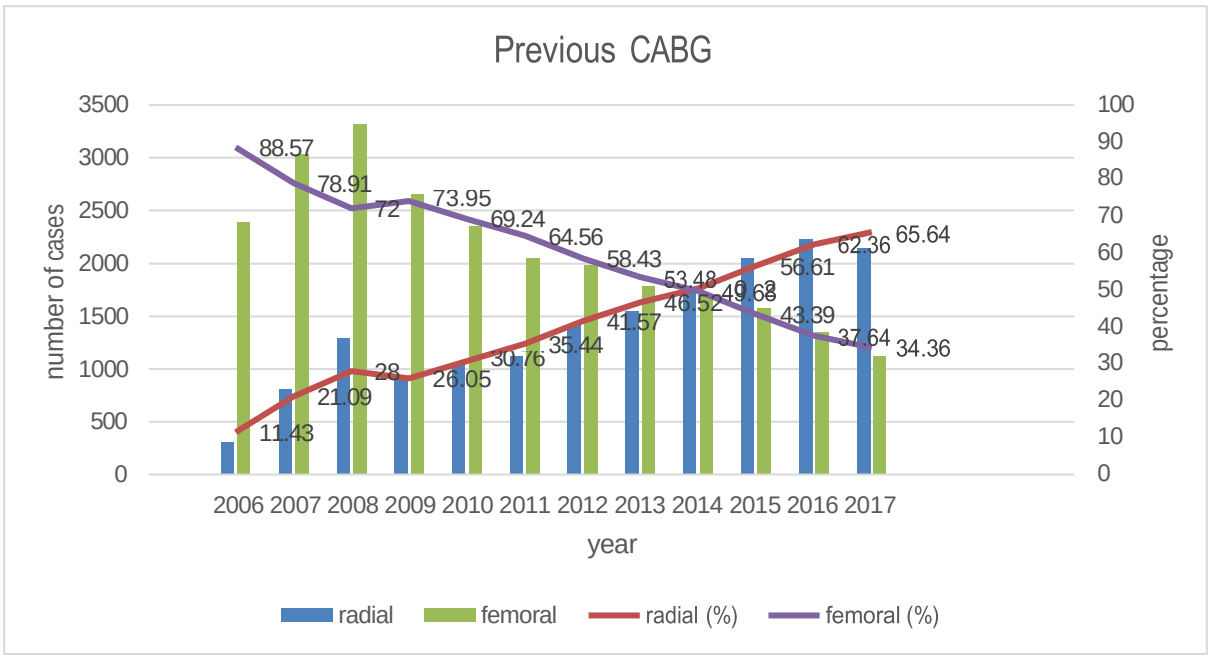
Abbreviation: CHiP, complex high-risk but indicated percutaneous coronary interventions

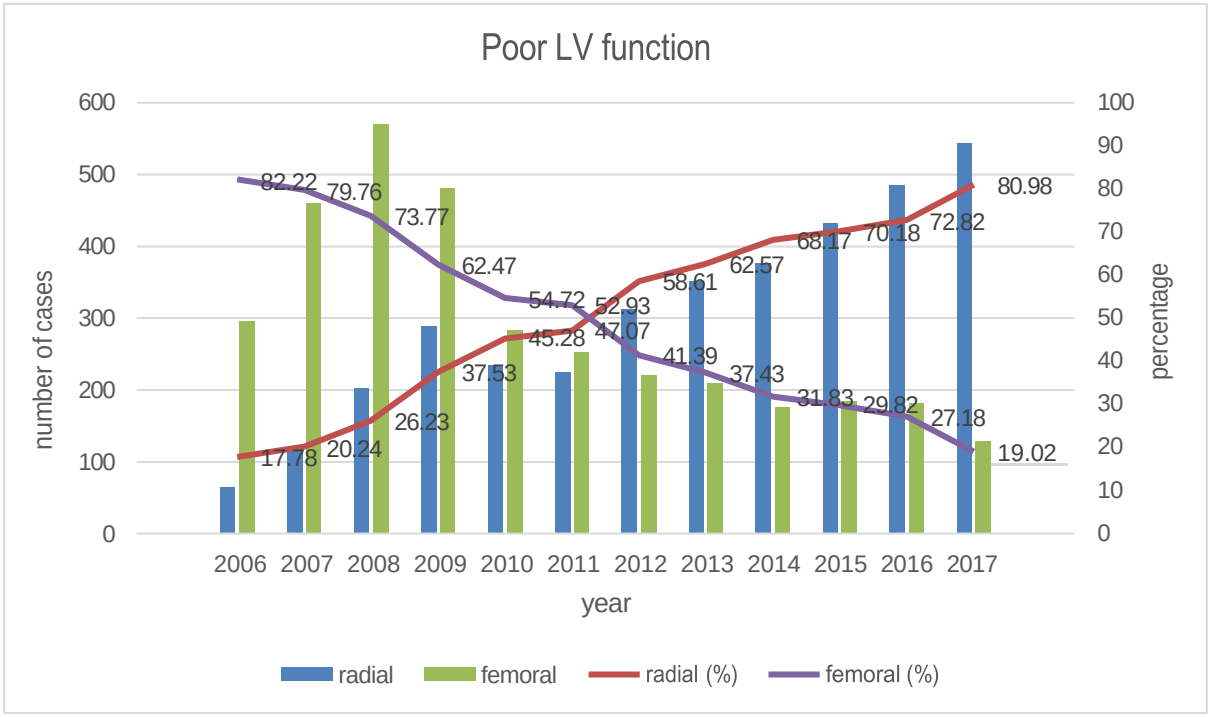
Figure 7.3 presents the temporal variations in the prevalence and percentage change of each CHiP factor based on TRA versus TFA access. Throughout all CHiP factors, TFA was the primary access utilised. However, in line with the trends observed in Figure 7.2, the adoption of TRA gradually increased over time and eventually surpassed TFA as the most commonly used access in 2017.

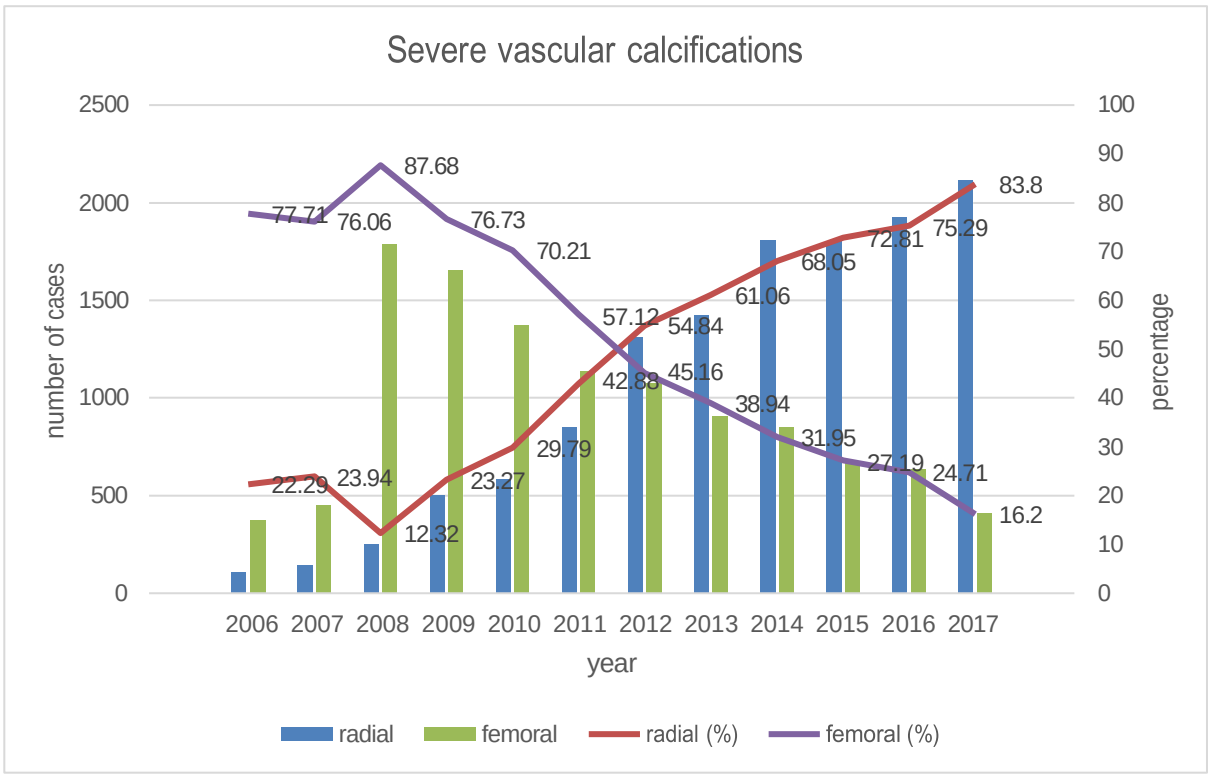
Figure 7-3: Temporal changes in prevalence of each CHiP factor among patients with stable angina and per cent change over time, stratified by access site.

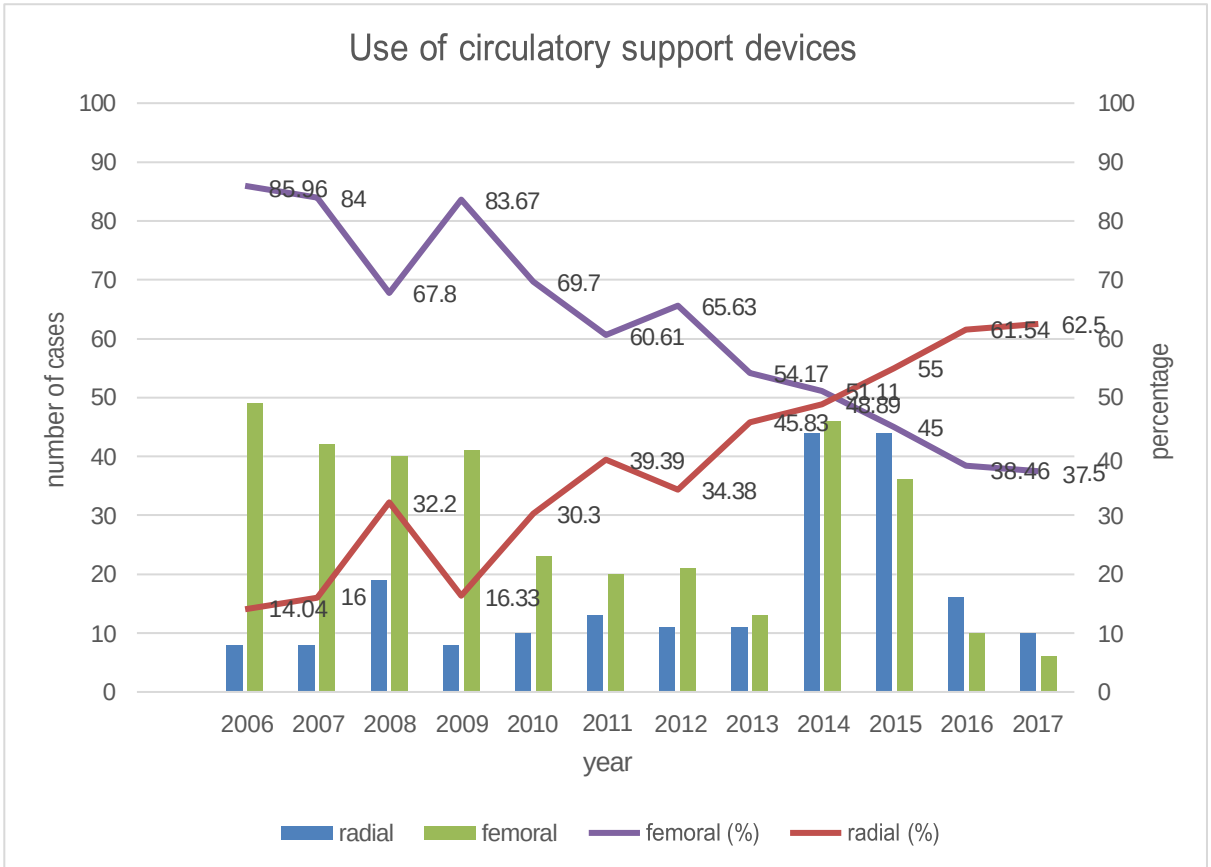


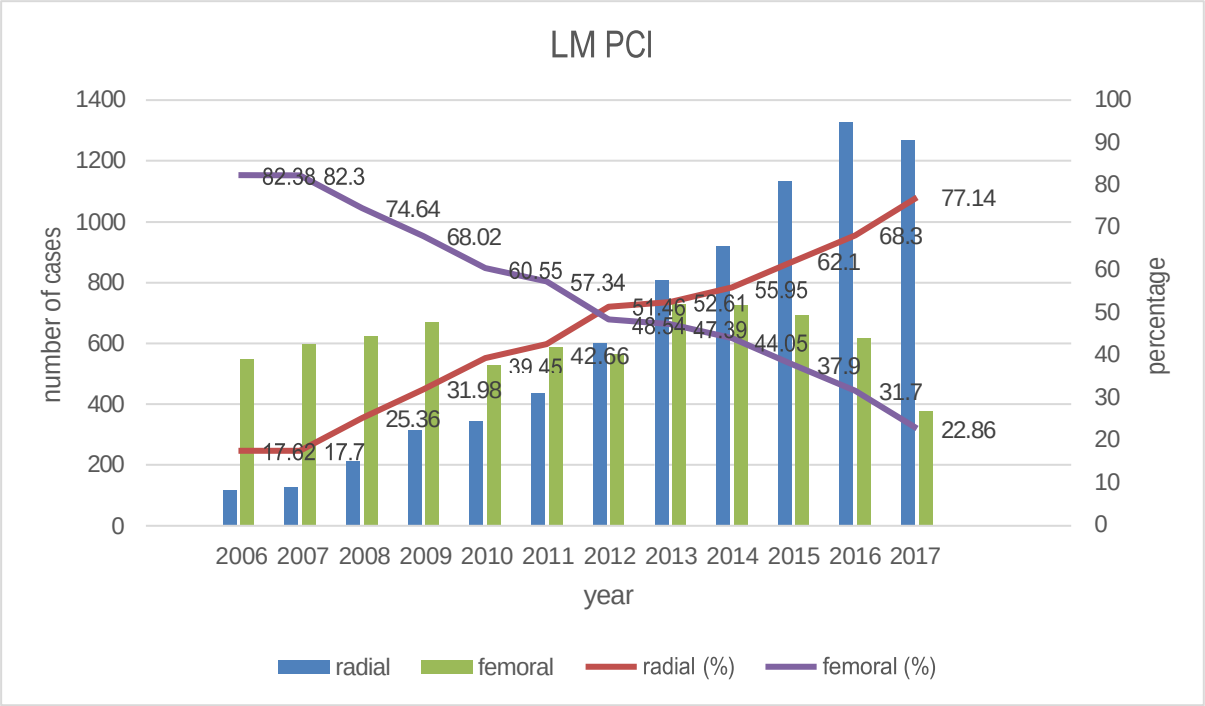


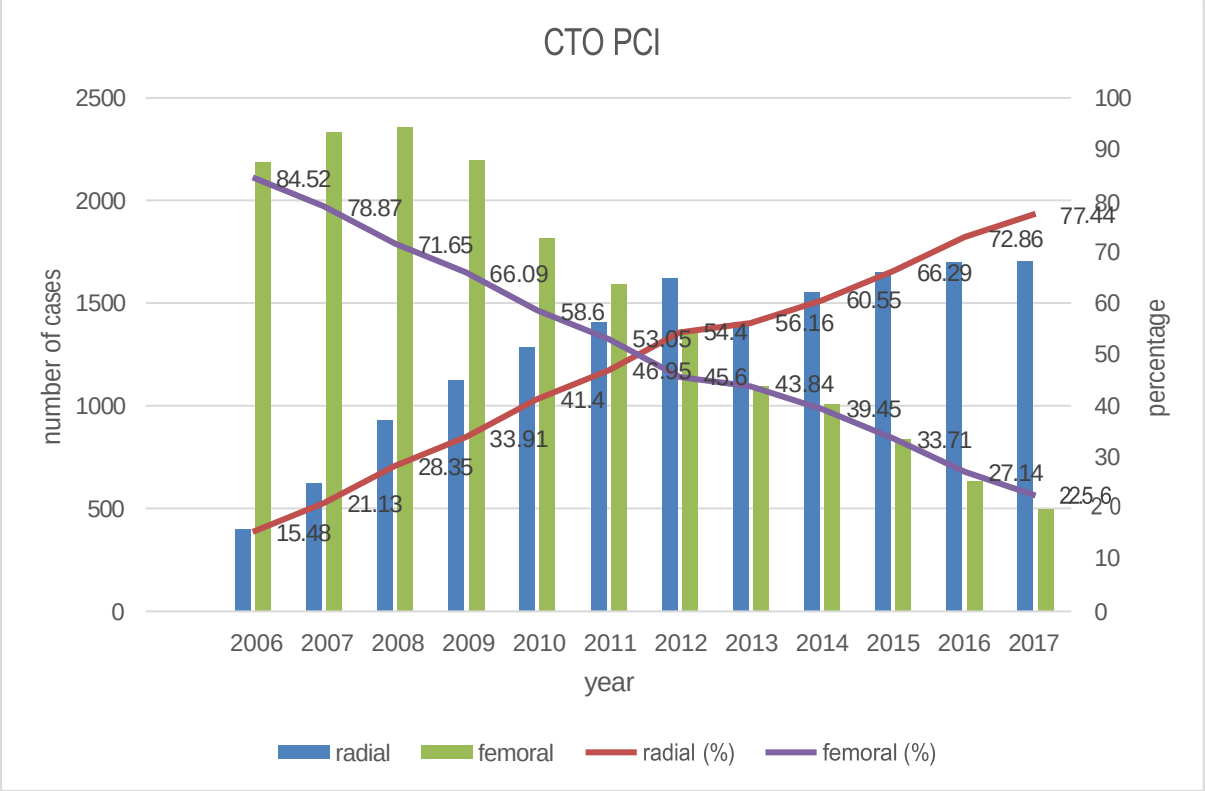

Previous CABG
number of cases
percentage
year
radial
femoral
radial (%)
femoral (%)
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
88.57
78.91
72
73.95
69.24
64.56
58.43
53.48
49.68
43.39
37.64
34.36
11.43
21.09
28
26.05
30.76
35.44
41.57
46.52
56.61
62.36
65.64


Poor LV function
number of cases
percentage
year
radial
femoral
radial (%)
femoral (%)
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
82.22
79.76
73.77
62.47
54.72
52.93
47.07
41.39
37.43
31.83
29.82
27.18
19.02
17.78
20.24
26.23
37.53
45.28
58.61
62.57
68.17
70.18
72.82
80.98


Severe vascular calcifications
number of cases
percentage
year
2500
2000
1500
1000
500
0
100
90
80
70
60
50
40
30
20
10
0
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
77.71 76.06 87.68 76.73 70.21 57.12 54.84 61.06 68.05 72.81 75.29 83.8
22.29 23.94 12.32 23.27 29.79 42.88 45.16 38.94 31.95 27.19 24.71 16.2
radial
femoral
radial (%)
femoral (%)


Use of circulatory support devices
number of cases
percentage
year
100
90
80
70
60
50
40
30
20
10
0
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
85.96 84 67.8 83.67 69.7 60.61 65.63 54.17 51.11 48.89 45 38.46 37.5
14.04 16 32.2 16.33 30.3 39.39 34.38 45.83 55 61.54 62.5
radial
femoral
femoral (%)
radial (%)





Abbreviation: CHiP, complex high risk percutaneous coronary interventions; CABG, coronary artery bypass graft; CRF, chronic renal failure; CTO, chronic total occlusion; LV, left ventricle; LMS, left main stem; PCI, percutaneous coronary intervention.

7.4.2 *Baseline clinical characteristics*

Table 7.1 provides a comprehensive overview of the baseline characteristics of the CHiP cohort, categorised by TRA, TFA, and Multiple access groups. Out of the total CHiP procedures, 61,825 (44.9%) were performed via TRA, 63,837 (46.3%) via femoral access (TFA), and 12,123 (8.8%) required multiple access sites. Notable differences in baseline clinical characteristics were observed among the groups. For instance, patients who underwent CHiP via TRA had an average age of 71.2 (95% CI, 62.4-80.3), which was one year older compared to those who underwent TFA (70.2, 61.6-78.6). TFA patients exhibited a higher prevalence of diabetes mellitus, severe LV dysfunction, and a previous history of MI or PCI. Conversely, patients who underwent CHiP via TRA demonstrated a higher prevalence of current smokers, hypertension, previous PVD, and stroke. Additionally, patients requiring multiple access sites had a higher prevalence of current smokers, as well as a previous history of PCI and MI.

Table 7-1: Baseline clinical and procedural characteristics of patients with stable angina undergoing CHiP, stratified by access site.

	Total, n	**Radial, n (%)**	**Femoral, n (%)**	**Dual, n (%)**	**P-value**
Number of participants	137,785	61,825 (44.9)	63,837 (46.3)	12,123 (8.8)	
Age Median, (IQR)	70.7 (62 -79.6)	71.2 (62.4 – 80.3)	70.2 (61.6 - 78.6)	66.8 (58.3-75)	< 0.001
BMI Median, (IQR)	28.0 (25.2-31.4)	28.1 (25.3-31.6)	27.8 (25.1-31.2)	28.9 (25.9-32.4)	< 0.001
Weight<60 kg) n, (%)	6,592 (5.3)	3,069 (4.9)	3,523 (5.5)	493 (4.1)	< 0.001
CHiP risk factors					
e) Patients' factors					
• **Age >80**	31,659 (23)	16,330 (51.6)	13,834 (43.7)	1,495 (4.7)	< 0.001
• **Prior CABG**	44,970 (33)	16,635 (37.0)	25,319 (56.3)	3,016 (6.7)	< 0.001
• **Chronic Renal Failure**	14,650 (11.1)	7,702 (52.6)	6,138 (42.0)	810 (5.5)	< 0.001

• **Poor LV function**	7,640 (9.4)	3,637 (47.6)	3,446 (45.1)	557 (7.3)	< 0.001
f) Procedural factors					
• **LMS PCI**	15,863 (11.7)	7,605 (48.0)	7,247 (45.6)	1,011 (6.4)	< 0.001
• **CTO PCI**	42,576 (32.7)	15,424 (36.2)	17,935 (42.1)	9,217 (21.7)	< 0.001
• **Severe coronary calcifications**	25,464 (22.5)	12,812 (50.3)	11,315 (44.4)	1,337 (5.3)	< 0.001
• **Use of LV support**	746 (0.6)	202 (27.1)	347 (46.5)	197 (26.4)	< 0.001
Cardiovascular risk factors					
• **Hypertension**	85,348 (65.3)	39,314 (67.4)	38,461 (64.4)	7,573 (65.6)	< 0.001
• **Hypercholesterolaemia**	84,112 (64.9)	37,260 (63.9)	38,974 (65.2)	7,878 (68.2)	< 0.001
• **Diabetes Mellitus**	34,250 (26.1)	15,335 (25.8)	15,980 (26.6)	2,935 (25.0)	< 0.001
• **Smoking**					< 0.001
Never	49,769 (41.5)	22,982 (41.8)	22,764 (42.1)	4,023 (36.7)	
Ex-smokers	58,659 (48.9)	26,652 (48.6)	26,476 (49)	5,531 (50.4)	
Current smokers	11,484 (9.6)	5,257 (9.6)	4,814 (8.9)	1,413 (12.9)	
• **Family history of CAD**	55,473 (46.8)	25,010 (45.3)	25,120 (47.8)	5,343 (49.4)	< 0.001
• **History of MI**	54,780 (42.6)	23,757 (40.2)	25,491 (44.2)	5,532 (46.7)	< 0.001
• **Previous PCI**	51,735 (38.6)	22,522 (37.1)	23,798 (38.7)	5,415 (45.3)	< 0.001
• **Previous stroke**	6,182 (4.8)	3,097 (5.3)	2,593 (4.3)	492 (4.2)	< 0.001
• **History of PVD**	8,994 (6.9)	4,174 (7.2)	3,972 (6.7)	848 (7.3)	= 0.001
• **LV systolic function**					< 0.001
Normal (EF>50)	57,077 (70.1))	27,548 (70.9)	23,518 (68.3)	6,011 (73.4)	
Impaired (EF 30-50)	16,666 (20.5)	7,646 (19.8)	7,402 (21.4)	1,618 (19.8)	
Severe (EF<30)	7,640 (9.4)	3,637 (9.4)	3,446 (10.0)	557 (6.8)	
Pharmacology					
• **Warfarin**	2,689 (2.2)	1,487 (2.7)	1,042 (1.8)	160 (1.4)	< 0.001
• **GPIIb IIIa inhibitors**	9,731 (7.6)	3,658 (6.4)	5,640 (9.6)	433 (3.7)	< 0.001
• **Clopidogrel**	102,388 (82.0)	45,734 (81.6)	47,076 (82.1)	9,578 (83.7)	< 0.001
• **Prasugrel**	1,132 (0.9)	645 (1.2)	346 (0.6)	141 (1.2)	< 0.001
• **Ticagrelor**	4,452 (3.7)	2,940 (5.2)	917 (1.6)	595 (5.2)	< 0.001
Vascular imaging					< 0.001
• **None**	92,495 (88.6)	44,051 (85.5)	48,444 (91.5)	8,614 (82.3)	
• **IVUS or OCT**	13,811 (12.0)	7,459 (14.5)	4,494 (8.5)	1,858 (17.7)	
Circulatory support					
• **No support**	130,960 (99.5)	59,379 (99.7)	60,049 (99.4)	11,532 (98.3)	< 0.001
• **IABP**	694 (0.5)	184 (0.3)	335 (0.6)	175 (1.5)	< 0.001
• **Impella**	55 (0.04)	18 (0.03)	15 (0.02)	22 (0.2)	< 0.001

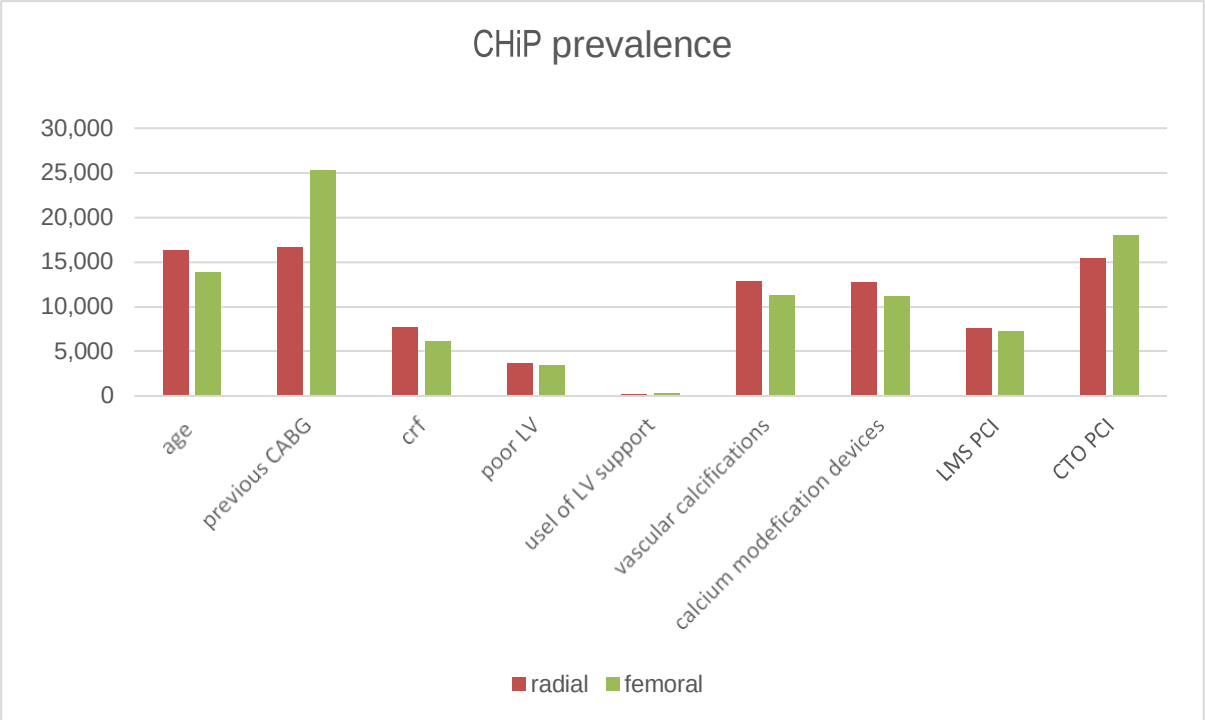
Number of treated lesions					<0.001
• **One**	87,576 (64.3)	38,452 (62.8)	40,642 (64.3)	8,482 (71.2)	
• **Two**	34,279 (25.2)	16,084 (25.3)	15,865 (25.1)	2,330 (19.6)	
• **Three**	14,421 (10.6)	6,658 (10.9)	6,663 (10.6)	1,100 (9.2)	
Stent size Median, (IQR)	3.5 (3.0-3.75)	3.5 (3.0-4.0)	3.0 (3.0-3.5)	3.5 (3.0-4.0)	< 0.001
Stent length Median, (IQR)	24 (18-38)	24 (18-38)	23 (16-30)	38 (24-60)	< 0.001
Procedural devices					
• **Cutting Balloon**	15,174 (13.4)	8,098 (15.9)	6,305 (11.9)	771 (8.3)	< 0.001
• **Rotational atherectomy**	10,358 (9.2)	4,780 (9.4)	5,049 (9.5)	529 (5.7)	<0.001
• **Laser atherectomy**	861 (0.8)	389 (0.8)	377 (0.7)	95 (1.0)	0.006
Number of stents used					< 0.001
• **One stent**	55,607 (40.6)	25,818 (41.9)	27,417 (43.2)	2,372 (19.7)	
• **Two stents**	34,929 (25.5)	16,120 (26.2)	16,103 (25.3)	2,706 (22.5)	
• **Three or more stents**	27,280 (19.9)	11,718 (19.1)	11,600 (18.3)	3,962 (32.9)	
Target Vessel PCI					
• **LMS PCI**	15,863 (11.7)	7,605 (48.0)	7,247 (45.6)	1,011 (6.4)	< 0.001
• **LAD**	55,510 (41.0)	27,763 (45.6)	23,794 (38.1)	3,953 (32.9)	< 0.001
• **LCX**	34,710 (25.6)	16,460 (27.0)	16,376 (26.2)	1,874 (15.6)	< 0.001
• **RCA**	48,135 (33.6)	20,123 (33.0)	21,250 (34.0)	6,762 (56.3)	< 0.001
• **Graft**	12,917 (9.5)	4,494 (7.3)	7,839 (12.6)	584 (4.9)	< 0.001
Failed attempts	12,575 (11.8)	4,574 (8.6)	5,587 (13.2)	2,414 (22.1)	
Number of target vessel PCI					< 0.001
• **One**	100,000 (74.7)	43,660 (72.7)	46,994 (75.9)	9,346 (78.4)	
• **Two**	26,853 (20.1)	12,804 (21.3)	12,065 (19.5)	1,984 (16.6)	
• **Three**	7,033 (5.3)	3,560 (5.9)	2,883 (4.7)	590 (4.9)	

Abbreviations: CHiP, complex high risk percutaneous coronary intervention; CABG, coronary artery bypass graft; CTO, chronic total occlusion; CAD, coronary artery disease; GPIIbIIIa, glycoprotein IIaIIIb; LV, left ventricle; LMS, left main stem; LCX, left circumflex; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery

7.4.3 CHiP factors (types)

In the overall cohort, the TRA was the more common access route for CHiP procedures compared to TFA. Specifically, the following CHiP procedures were predominantly performed via the radial artery access: Age >80 (51.6% vs. 43.7%), LMS PCI (48.0% vs. 45.6%), CRF (52.6% vs. 42.0%), severe vascular calcification (50.3% vs. 44.4%), and poor LV function (47.6% vs. 45.1%) ($p < 0.001$ for all except poor LV function, $p = 0.003$). Conversely, the TFA was more frequently utilised for CHiP procedures involving patients with a previous CABG (60.3% vs. 39.7%), PCI to a CTO vessel (53.8% vs. 46.2%), or the use of an LV support device (63.2% vs. 36.8%) ($p < 0.001$ for all) (Table 7.1, Figure 7.4).

Figure 7-4: Prevalence of CHiP factors in patients with stable angina, stratified by access site.



Abbreviations: CHiP, complex high-risk percutaneous coronary intervention; CABG, coornary artery bypass graft; LV , left ventricle; LMS, left main stem; PCI, percutaneous cornary intervenntion; CTO , chronic total occlusion.

7.4.4 Procedural characteristics

Significant differences were observed between the TRA and TFA groups, as shown in Table 7.1. Procedures performed via the TRA exhibited higher frequencies of intravascular imaging use (14.5% vs. 8.5% for TRA and TFA, respectively; $p < 0.001$) and were more likely to involve treatment for more extensive coronary disease compared to TFA. Specifically, a higher rate of treatment for two or more vessels was observed in the TRA group (36.2%) compared to the TFA group (34.1%) ($p < 0.001$). Additionally, larger stents (3.5 mm [3.0-4.0] vs. 3.0 mm [3.0-3.5]) and longer stents (24 mm [18-38] vs. 23 mm [16-30]) were deployed in the TRA group compared to the TFA group, $p<0.001$ for stent size and length. The TRA group also had a higher proportion of patients receiving two or more stents (45.3% vs. 43.6%) ($p < 0.001$). Notably, the TRA group showed higher rates of cutting balloon usage (15.4% vs. 11.4% in TFA), which suggests the presence of more extensive calcification in the TRA group. However, the multiple accesses group had the highest rates of intracoronary imaging use (17.7%), the need for longer stents (38 mm [24-60]), the use of LV support devices (1.7%), and the placement of three or more stents (32.9%) compared to the other groups.

7.4.5 Clinical Outcomes

Table 7.2 provides an overview of the crude and adjusted clinical outcomes stratified by TFA, TRA, and Multiple accesses. Crude rates for mortality were higher in the TFA group compared to the TRA group (0.3% vs. 0.2%, $p < 0.001$). Similarly, major bleeding events were more prevalent in the TFA group (0.6% vs. 0.2%, $p < 0.001$), as were MACCE (1.5% vs. 1.3%, $p = 0.002$). However, after adjusting for differences in clinical

and procedural characteristics, the TFA group exhibited higher odds for mortality (aOR 1.3, 95% CI 1.1-1.7; p = 0.008), and major bleeding events (aOR 2.9, 95% CI 2.3-3.4; p < 0.001) compared to the TRA group. MACCE odds were not significantly different in the TFA compared to TRA (aOR 1.1, 95% CI 1.1-1.3; p < 0.001).

Table 7-2: Crude and adjusted outcomes of patients with stable angina undergoing CHiP, stratified by access site.

Variables	Total, n (%)	Radial, n (%)	Femoral, n (%)	Multiple access, n (%)	aOR (CI), p-value (Femoral)	aOR (CI), p-value (Multiple accesses)
Mortality	**410 (0.3)**	**129 (0.2)**	**202 (0.3)**	**79 (0.7)**	**1.3 (1.1-1.7), 0.008**	**2.1 (1.5-2.8), <0.001**
Major bleeding events	**716 (0.5)**	**140 (0.2)**	**387 (0.6)**	**189 (1.6)**	**2.9 (2.3-3.4),>0.001**	**5.5 (4.3-6.9),>0.001**
MACCE	**2,011 (1.5)**	**796 (1.3)**	**952 (1.5)**	**263 (2.2)**	**1.1 (0.9-1.1), 0.69**	**1.4 (1.2-1.7), <0.001**

Abbreviation: CHiP, complex high risk percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

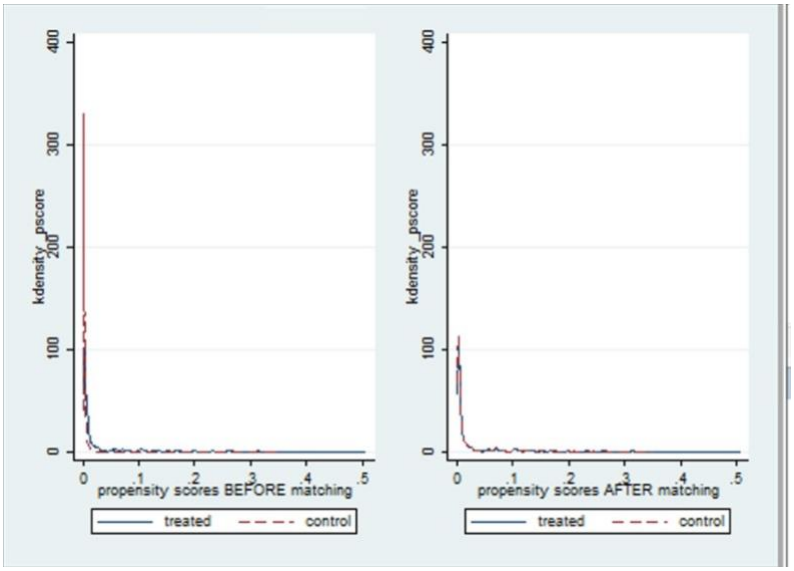
Propensity score matching was conducted to address and control for differences between the TRA and TFA groups. The findings from the propensity score matching analysis were consistent with the previous results obtained (Table 7.3 and Figure 7.5). After converting the average treatment effects into odds ratios for better result interpretation, it was observed that the odds of mortality were 50% higher in the TFA group compared to the TRA group. Similarly, the odds of MACCE and major bleeding events were 20% higher in the TFA group.

Table 7-3 Adjusted odds of adverse outcomes post CHiP undertaken via the femoral access for patients with stable angina using Propensity Score Matchings (PMS) (reference, radial access).

Variables	ATE	95% CI	aOR	95% CI	P value
Death	.0009474	.0002135 .0016812	1.5	1.1 – 1.8	0.011
MACCE	.0027964	.0010755 .0045173	1.2	1.1-1.4	0.002
Major bleeding events	.0041628	.0031793 .0051462	1.2	1.1-1.2	<0.001

Abbreviation: ATE, attributable treatment effect; CAD, coronary artery disease; CHiP, complex high-risk but indicated percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

Figure 7-5 PSM showing how well balanced the CHiP cohort



Abbreviations: PSM, propensity score matching; CHiP, complex, high-risk percutaneous coronary intervention.

7.4.6 Outcome trends

Table 7.4 provides detailed information on the temporal changes in the three groups (Q1: 2006-2009; Q2: 2010-2013; Q3: 2014-2017) stratified by TRA, TFA, and multiple access. The corresponding figures are presented in Figure 7.6.

Overall, there was a gradual increase in mortality trends in both the TFA and multiple accesses groups [(2006-2009) vs (2014-2017): TFA, 0.3% vs 0.4%; Multiple access, 0.6% vs 0.8%]. On the contrary, MACCE rates across all groups have shown a gradual decrease [(2006-2009) vs (2011-2017) : TRA, 1.6% vs 1.0 %; TFA, 1.7% vs 1.3%; Multiple access, 2.7% vs 1.9%, respectively].

Table 7-4 Temporal trends of outcomes of patients with stable CAD undergoing CHiP, stratified by access site.

a) **Crude outcomes in the first quarter, according to access site.**

Q1 (2006-2009)	Total n (%)	Radial access n (%)	Femoral access n (%)	Multiple access, n (%)	P value
Death	113 (0.3)	19 (0.2)	87 (0.3)	7 (0.6)	0.04
Major bleeding	202 (0.5)	22 (0.2)	161 (0.6)	19 (1.6)	<0.001
MACCE	667 (1.7)	156(1.6)	479 (1.7)	32 (2.7)	0.02

b) **Crude outcomes in the second quarter according to access site.**

Q2 (2010-2013)	Total n (%)	Radial access n (%)	Femoral access n (%)	Multiple access, n (%)	P value
Death	130 (0.3)	48 (0.2)	67 (0.3)	15 (0.4)	0.156
Major bleeding	243 (0.5)	47 (0.2)	143 (0.7)	53 (1.4)	<0.001
MACCE	708 (1.6)	312 (1.6)	307 (1.4)	89 (2.4)	<0.001

c) **Crude outcomes in the third quarter according to access site.**

Q3 (2014-2017)	Total n (%)	Radial access n (%)	Femoral access n (%)	Multiple access, n (%)	P value
Death	167 (0.3)	62 (0.2)	48 (0.4)	57 (0.8)	<0.001
Major bleeding	271 (0.5)	71(0.2)	83 (0.6)	117 (1.6)	<0.001
MACCE	636 (1.2)	328 (1.0)	166 (1.3)	142 (1.9)	<0.001

Abbreviation: CAD, coronary artery disease; CHiP, complex high-risk but indicated percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

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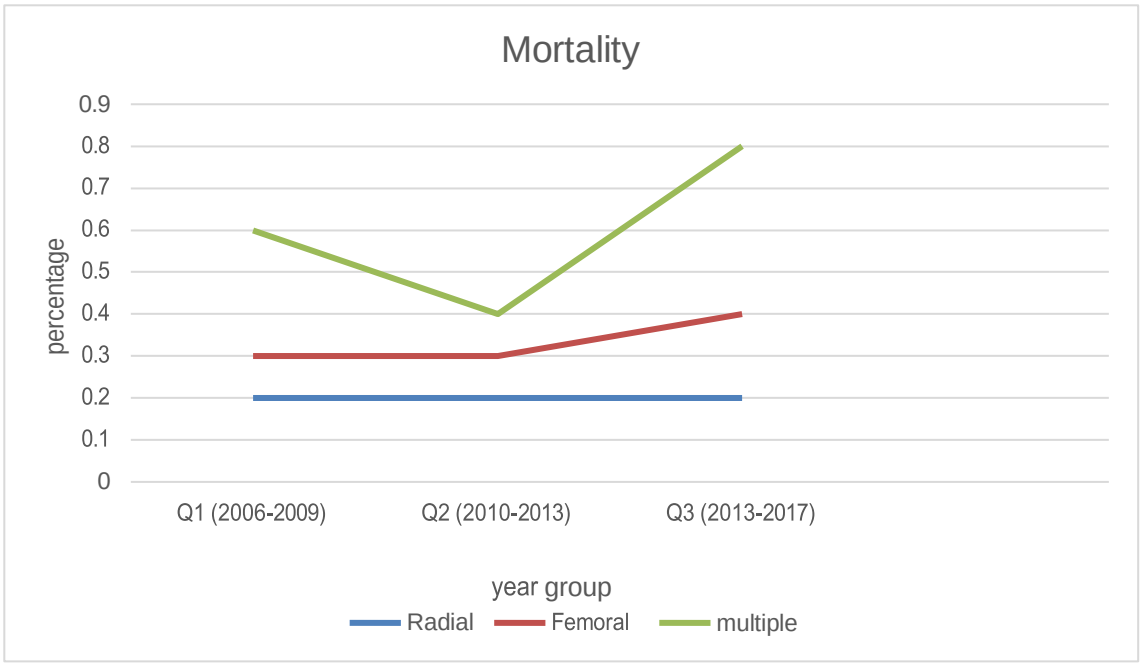
Figure 7-6: Temporal changes CHiP outcomes among patients with stable angina (per cent change over time), stratified by access site.



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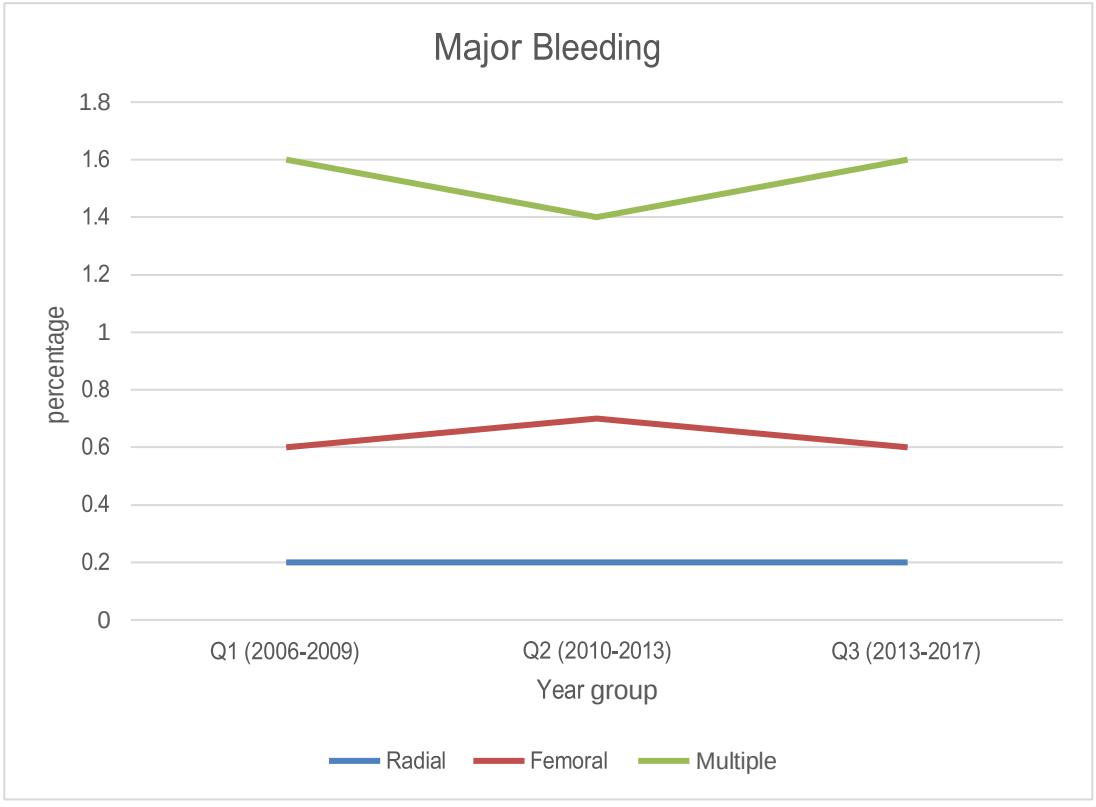

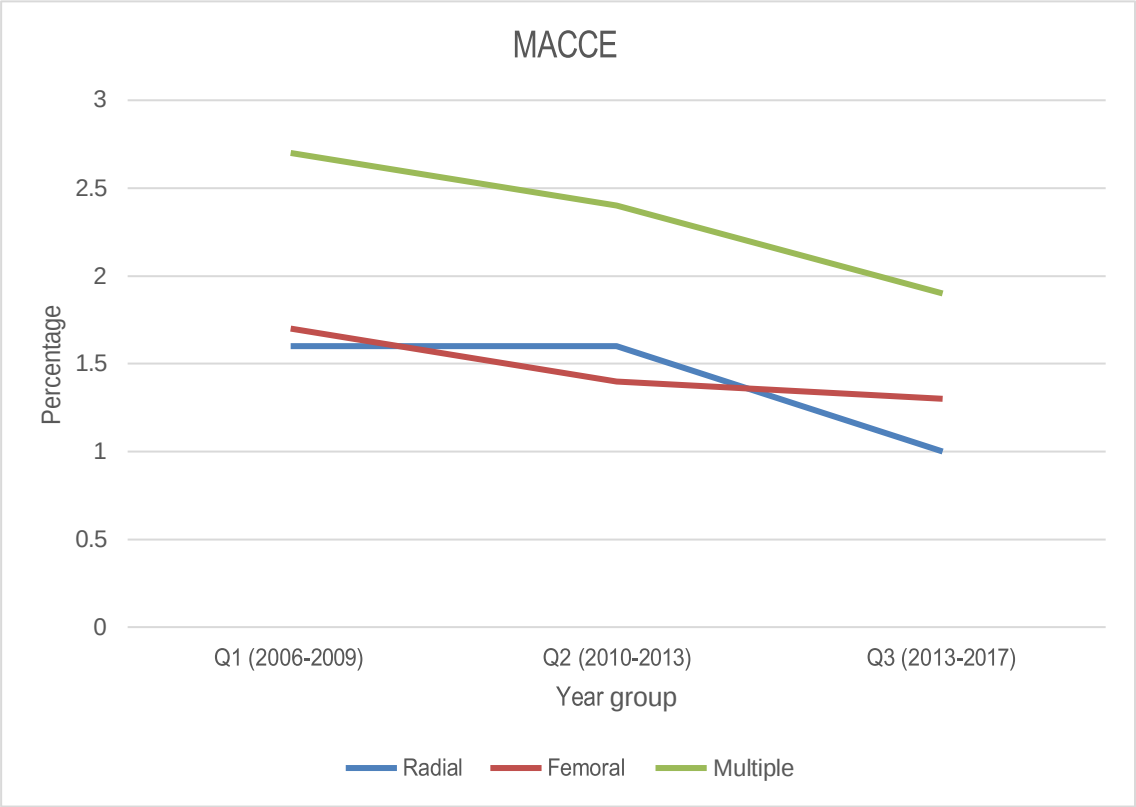

Abbreviation: CHiP, Complex, high-risk percutaneous coronary intervention; mace, major adverse cardiovascular and cerebral events.

7.5 Discussion

In this analysis of a national cohort comprising 125,662 CHiP procedures performed on patients with stable CAD between 2006 and 2017, the study focused on the type of access approach used during these procedures. The findings revealed significant differences in the choice of CHiP procedure based on the access site employed. However, over the course of the study period, TRA emerged as the most commonly used access site for CHiP procedures, increasing from 14.6% in 2006 to 78.4% in 2017. The key points summarising the analysis findings are as follows:

1) Patients in the TRA group were found to be older and had a higher prevalence of cardiovascular risk factors compared to those in the TFA group.

2) The most common types of CHiP procedures performed using the TRA access site included patients aged 80 years or above, those with chronic renal failure, severe calcification in the coronary arteries, poor LV function, and those requiring left main PCI. On the other hand, CHiP procedures more commonly performed using the TFA approach involved patients with a previous history of CABG, PCI to a CTO vessel, or cases where left ventricular support was required.
3) The study's conclusion highlighted that despite the evidence supporting the presence of more extensive coronary disease among the TRA group compared to the TFA group, the adjusted odds of in-hospital mortality, MACCE, and major bleeding events were significantly higher in the TFA group.

Evidence from several large randomised controlled trials and observational studies has consistently demonstrated the safety and benefits of using TRA compared to TFA in PCI. These studies have shown that TRA is associated with improved clinical outcomes following PCI. The findings of this current analysis further extend these established benefits to a specific subset of patients undergoing Complex High-Risk PCIs (CHiP)[115, 187, 189, 197, 204-206]. The most recent guidelines on myocardial revascularisation from the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) strongly support the use of TRA over TFA in patients with stable CAD. According to these guidelines, TRA is recommended as a Class Ia intervention, indicating a high level of evidence and a strong recommendation for all patients undergoing myocardial revascularisation (Table 7.5 and 7.6)[207, 208]. Additionally, in elderly patients with stable CAD, TRA is recommended as a Class Ib intervention, indicating a slightly lower level of evidence but still a strong recommendation, specifically to reduce access site bleeding complications (Table 7.7)[6, 209].

Table 7-5: 2018 ESC/EACTS Guidelines on myocardial revascularization. Recommendation guidelines on the use of radial access in a PCI procedure[207].

Recommendations on choice of stent and access site

Recommendations	Class[a]	Level[b]
DES are recommended over BMS for any PCI irrespective of: • clinical presentation • lesion type • planned non-cardiac surgery • anticipated duration of DAPT • concomitant anticoagulant therapy.[100,578,579,640]	I	A
Radial access is recommended as the standard approach, unless there are overriding procedural considerations.[172,638,641]	I	A
BRS are currently not recommended for clinical use outside of clinical studies.[642–650]	III	C

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BMS = bare-metal stents; BRS = bioresorbable scaffolds; DAPT = dual antiplatelet therapy; DES = drug-eluting stents; PCI = percutaneous coronary intervention.
[a]Class of recommendation.
[b]Level of evidence.

Adopted from Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. European Heart Journal. 2019;40(2):87-165.

Table 7-6: 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary[208]

Recommendations for Radial and Femoral Approaches for PCI
Referenced studies that support the recommendations are summarized in Online Data Supplement 23.

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with ACS undergoing PCI, a radial approach is indicated in preference to a femoral approach to reduce the risk of death, vascular complications, or bleeding (64-67).
1	A	2. In patients with SIHD undergoing PCI, the radial approach is recommended to reduce access site bleeding and vascular complications (67-70).

Adopted form Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(3).

Table 7-7:2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes[209]

Recommendations for elderly patients with chronic coronary syndromes

Recommendations	Class[a]	Level[b]
It is recommended that particular attention is paid to side effects of drugs, intolerance, and overdosing in elderly patients.	I	C
The use of DES is recommended in elderly patients.[508,509]	I	A
Radial access is recommended in elderly patients to reduce access-site bleeding complications.[506,507]	I	B
It is recommended that diagnostic and revascularization decisions are based on symptoms, the extent of ischaemia, frailty, life expectancy, and comorbidities.	I	C

© ESC 2019

DES = drug-eluting stents.
[a]Class of recommendation.
[b]Level of evidence.

Adopted from Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European Heart Journal. 2020;41(3):407-77.

However, it is important to acknowledge that the evidence comparing TRA and TFA outcomes in stable CAD has limitations when it comes to including and specifically describing patients with complex, high-risk CAD[210-212]. The two largest trials comparing TFA and TRA in the context of CAD, namely the RIVAL (Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndrome)[213] and MATRIX (Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX) [187] trials, provide valuable insights but have certain limitations. The RIVAL trial enrolled 7,021 patients and compared outcomes between femoral and radial access post PCI. However, it is important to note that this trial excluded patients with a prior history of CABG using the internal mammary artery. Additionally, the median age of the cohort was relatively young at 62 years. The RIVAL trial found no significant differences between the two access sites in terms of death,

stroke, and major bleeding events at 30 days (HR 0.92, 95% CI 0.72-1.17, P=0.50). On the hand, the MATRIX trial was relatively larger, with 8404 patients, and although >25% of patients were above the age of 75 and included those with previous history of a previous CABG, this study included only patients with ACS who were randomly assigned to TRA vs TFA. Nevertheless, significantly lower risk for major bleeding events as per the Bleeding Academic Research Consortium (BARC) were observed among the radial group patients RR 0.83,95% CI 0.73–0.96;P= 0.009). Also BARC 3 to 5 was significantly less in the TRA (1.6 vs. 2.3%; RR 0.67, 95% CI 0.49–0.92;P= 0.013). Moreover, all-cause mortality was decreased as well (1.6 vs. 2.2%; RR 0.72, 95% CI 0.53–0.99,P= 0.045).
While these trials provide valuable insights into the outcomes of TRA and TFA in specific patient populations, it is important to note their limitations. The RIVAL trial excluded patients with prior CABG using the internal mammary artery, which may limit the generalisability of its findings to the broader population. The MATRIX trial focused on patients with ACS, which may not directly reflect outcomes in stable CAD patients. Therefore, the evidence regarding TRA versus TFA outcomes in patients with complex CAD remains limited and warrants further investigation.

In the past, the use of TFA as the only access for complex PCI was a necessity due to the requirement for large-sized catheters and complex devices[15, 214]. However, with advancements in technology, such as the introduction of slender technology that enables the use of larger bore catheters through radial access[189], along with the development of strategies for CTO interventions[215] and various other innovations[216, 217] performing complex PCIs via the transradial access (TRA) has become safe and feasible.

This analysis revealed significant differences in the baseline characteristics among the groups undergoing CHiP. Patients with established CAD (previous MI,

previous PCI, and previous CABG) were more prevalent among the TFA group. On the contrary, those patients with cardiovascular risks for CAD (hypertension, current smokers, PVD) were more frequent in the TRA group.

The utilisation of TFA for CHiP procedures in patients with established CAD may be attributed to the anticipation of complex CAD by the interventionists. It is possible that these patients with a history of CAD may require devices of larger sizes that cannot be accommodated by the radial access. In such cases, the femoral access may be preferred to facilitate the use of larger catheters and complex devices required for the treatment of extensive and complex coronary lesions.

The utilisation of TRA approach in CHiP procedures was more common across most CHiP types, except in cases where patients required LV support, had a history of CABG, or underwent PCI for CTO. In these specific cases, TFA was more commonly employed, presumably due to complex anatomies (CABG and CTO) or the need for larger catheters and devices. Nevertheless, the worse odds for clinical outcomes observed in the overall cohort with the use of TFA should encourage interventionists to consider transradial access for PCIs in patients with prior CABG, CTO cases, or when LV support is needed. This study's findings suggest that the TRA may offer advantages in terms of clinical outcomes compared to TFA. In support of this, major bleeding events was shown to be significantly less when the TRA was used in both PCI cases undertaken for CTO indications[218]and in patients with previous history of CABG[219].

This study's findings are consistent with previous analyses that have examined clinical outcomes comparing TRA and TFA. Similar to previous studies, this analysis confirmed worse odds for in-hospital death, major bleeding events, and MACCE associated with TFA. For example, studies that included those patients on dialysis/chronic insufficiency patients demonstrated significantly lower odds for mortality and major

bleeding events in the TRA group (OR 0.19, 95% CI (0.051-0.73); p=0.015[201]. Other analyses investigating outcomes according to access site in the elderly population have also consistently shown the benefits of TRA, although these studies had some limitations[220]; Moreover, a meta-analysis of 13 studies provided further evidence of decreased odds of major bleeding events with TRA (OR 0.49, 95% CI 0.33-0.72, p=0.0002)[221]. In the context of PCI in the left main vessels, a meta-analysis of eight non-randomised controlled trials revealed no differences in MACCE odds when comparing TRA and TFA using propensity score matching data (relative risk (RR): 0.97, 95% CI 0.94-1.28, p=0.63). However, there was a significantly lower risk of major bleeding events in the TRA group (RR: 0.28, 95% CI 0.17-0.47, p<0.001) [196]. It is worth noting that no randomised controlled trials investigating outcomes for TRA versus TFA with the use of rotational atherectomy have been conducted to date. However, limited observational studies have indicated improved mortality with the use of TRA, primarily attributed to the decreased rates of major bleeding events associated with radial access (TFA: 13% vs TRA: 1%, p=0.001) [222].

In this study, the odds of in-hospital mortality were worse in the TFA group, with an aOR of 1.3 (95% CI 1.1-1.7). The mortality risk was found to be 50% higher with propensity score matching (PSM), which is higher than the risks observed in analyses focused on non-complex PCI procedures (TRA vs TFA: aOR 0.70, 95% CI 0.66-0.74) [205]. The possible explanation for this discrepancy is the higher baseline risk of major bleeding events in the TFA group. Previous studies have indicated a significant association between the radial approach (TRA) and baseline bleeding risk, with improved benefits observed in patients considered at high risk for major bleeding events[223, 224]. Supporting this are studies that have confirmed a direct association between access site complications and higher bleeding rates with significant morbidity and mortality.[225-227.]

This study provided evidence of the extension of benefits associated with the TRA to the complex percutaneous coronary intervention cohort. This extension was made possible by advancements in technology, such as the development of new-generation low-profile stents and improved delivery systems. These technological advancements have facilitated various complex PCI procedures, including bifurcations and therapies targeting calcium modification, which can now be performed using a 6-French guide.

Furthermore, the introduction of innovative technologies and techniques, such as balloon tracking, thin-walled sheaths with hydrophilic properties, and sheathless guides, has addressed the challenges associated with smaller radial arteries. These advancements have overcome previous limitations and made the TRA a viable option for a wider range of CHiP procedures.

The benefits of TRA were observed across all CHiP types, even in cases where the transfemoral approach (TFA) was commonly used. This aligns with findings from another analysis conducted across six centres in the USA, which focused on outcomes of chronic total occlusion (CTO) PCI. In that study, similar outcomes were observed between TRA and TFA, with comparable rates of major complications (TRA: 1.7% vs TFA: 1.8%; p=0.99)[228].

These findings highlight the effectiveness and versatility of the transradial approach, demonstrating its applicability and benefits across various CHiP procedures, including those traditionally associated with the transfemoral approach. The evolution of technology and techniques has played a crucial role in expanding the possibilities of the transradial approach and improving patient outcomes in complex PCI cases.

7.6 Study strength and limitations

This study represents the first national analysis that investigates the outcomes of complex percutaneous coronary intervention (CHiP) procedures in a real-world, unselected population, stratified by the access site. The study was adequately powered to detect meaningful differences among the groups. The cohort studied is representative of the UK national practice since the British Cardiovascular Intervention Society (BCIS) registry captures over 99% of PCI cases performed in England and Wales.

However, it is important to acknowledge the limitations of this study, which are consistent with those discussed in previous chapters (please refer to the study limitations section in chapters 4-6). The main limitation stems from the observational nature of the study design, which introduces potential biases. These biases may arise from errors in reporting and coding, including under-reporting of co-morbidities and reliance on self-reported procedural complications without external validation.

Furthermore, there is a possibility of unmeasured confounders that could impact the outcomes, such as the presence of anaemia, frailty, economic status, and the control of diseases like hypertension and diabetes mellitus. To address this issue, the study attempted to adjust for as many variables as possible to minimise the impact of confounding factors.

Another limitation to consider is that although the dataset clearly specifies and records the incidence of peri-procedural myocardial infarction (MI), it is not possible to determine which specific guidelines' definition (e.g., the third or fourth universal MI definition) was used for recording. This lack of standardised definition could introduce variability in the reported MI outcomes.

Lastly, it is important to note that since the dataset only captures in-hospital clinical outcomes, it is not possible to assess significant differences in longer-term outcomes or evaluate the impact of the access site on long-term prognosis.

7.7 Conclusion

In conclusion, this large analysis provides strong evidence supporting the safe and effective use of the TRA in complex percutaneous coronary intervention procedures. The study demonstrates that patients who underwent CHiP via the TRA received treatment for more complex coronary lesions, yet achieved better clinical outcomes compared to the TFA group.

The findings indicate that the TFA group had significantly worse in-hospital mortality rates, major bleeding events, and MACCE events outcomes, even after adjusting for confounding factors. In contrast, the TRA cohort showed a declining trend in mortality rates, while both the TFA and multiple access groups demonstrated a gradual increase in mortality trends.

These results suggest that wider adoption of TRA, particularly among higher-risk patients, may potentially lead to improved CHiP outcomes.

Chapter 8

Complex High-risk Percutaneous Coronary Intervention Types, Trends, and Outcomes in Non-surgical Centres

8.1 Introduction

After conducting a systematic study on the differences in complex percutaneous coronary interventions (CHiPs) among special populations such as females, individuals from Black, Asian, and Minority Ethnic (BAME) backgrounds, and the elderly, and considering certain procedural factors like vascular access approach, this chapter shifts its focus to examine how the type of cardiac catheter laboratory facilities, specifically those with onsite surgical backup (SCs) versus off-site surgical backup (NSCs), can impact CHiP clinical outcomes. The aim of this investigation is to explore potential variations in CHiP types, patients' baseline characteristics, and baseline procedural characteristics between these two types of facilities.

The findings from this chapter were presented at the American College of Cardiology (ACC) March 2023 conference, and the abstract has been published in the Journal of the American College of Cardiology (JACC) . Additionally, a manuscript with detailed analysis of the data is published in the Canadian Journal of Cardiology.

In contemporary practice, the occurrence of PCI complications necessitating emergency coronary artery bypass graft surgery is rare, accounting for less than 0.5% of cases, a significant improvement compared to the 6-10% rate observed in the 1980s[10, 229-231]. Advancements in technology have played an important role in effectively and safely managing PCI complications that previously would have required emergent CABG. These advancements include the use of covered stents, intravascular micro coils to treat perforations, and intravascular imaging for diagnosing and managing coronary dissections. Additionally, the use of more potent antithrombotic therapies and an improved understanding of optimal stent deployment have reduced the occurrence of abrupt vessel closure. As a result, over the past few decades, PCI programs without onsite

surgical cover (NSCs) have been successfully implemented in various regions worldwide, including Europe [232, 233]. In 2005 the British Cardiac Society and the BCIS guidelines published the first acknowledgments in support of PCI in NSCs and provided common standards to be followed across both types of centres (SCs and NSCs)[234]. Similarly, the Society of Cardiovascular Angiography and Intervention (SCAI) published an expert consensus, primarily based on retrospective analyses, providing recommendations and backup strategies for PCI operators who perform over 100 cases per year in NSCs. Patients' risk was categorised based on factors such as poor LV function, LMS or equivalent disease, moderate or more calcifications, CTO, and prior CABG, with high-risk patients with high-risk lesions recommended to undergo procedures only in SCs [232].

Results from observational studies [235, 236] and randomised control trials (RCT) [237, 238] around the safety of PCI in NSCs supported the continuation of the those PCI programs. However, it is important to note that these programs specifically excluded high-risk cases. For example, a retrospective analysis from the Netherlands [235] examined the outcomes of PCI and the use of fractional flow reserve (FFR) immediately following the procedure and at 6 months of follow-up. The study included patients with acute coronary syndrome (ACS) and stable ischaemic heart disease treated in NSCs between September 2011 and July 2012. The analysis demonstrated favourable results regarding the safety of PCI in NSCs, with low mortality and major adverse cardiac and cerebrovascular events. However, high-risk cases such as left main (LMS) PCI and multiple vessel PCI were referred to SCs and were excluded from the analysis. Similarly, results from the CPORT-E trial, which investigated the non-inferiority of PCI (excluding primary PCI) in NSCs compared to SCs, showed promising outcomes. The trial found that PCI in NSCs was non-inferior to PCI in SCs in terms of mortality at six weeks and major adverse cardiac events at nine months post-PCI. [237] Again, the CPORT-E trail typically excluded high

risk patients who needed LMS PCI or have poor LV function with ejection fraction <= 20% [237]. In summary, the available evidence on PCI in NSCs from observational studies and RCTs often excludes complex, high-risk interventions, representing only a small proportion of procedures. [237, 239].

The main objective of this analysis was to investigate the association between CHiP procedures in patients with stable angina and the selection of the catheter laboratory and PCI admitting facility, specifically comparing surgical centres (SCs) to non-surgical centres (NSCs). The key characteristics of this study can be summarised as follows:

8.2 Objectives

The adjectives for this study are summarised as follows:

I. To examine the differences in the baseline clinical characteristics of patients undergoing a CHiP procedure based on the type of PCI facility (SCs vs NSCs).

II. To investigate the differences in the baseline procedural characteristics of patients undergoing a CHiP procedure based on the type of PCI facility (SCs vs NSCs).

III. To determine whether CHiP procedures performed in NSCs are associated with worse outcomes compared to SCs.

IV. To analyse the temporal trends of CHiP outcomes over a period of 12 years, based on the choice of PCI facility (NSC vs SC).

8.3 Methods

8.3.1 Study design

This study design is similar to previous studies mentioned earlier in previous chapters; this is an observational, retrospective analysis of prospectively collected data on adults admitted electively for invasive management of stable ischemic heart disease in England and Wales between 2006 and 2017. As per previous studies, we collected data from the British Cardiovascular Intervention Society (BCIS) dataset. Details of this dataset is discussed in chapter 3. Briefly, the BCIS dataset is managed by the National Institute for Cardiovascular Outcomes Research (NICOR). Healthcare professionals collect data from over 95% of PCI centres annually in England and Wales. data input is required for professional revalidation[14]. The dataset includes comprehensive information on patient demographics, co-morbidities, risk factors, pharmacotherapy, procedural characteristics, and clinical outcomes such as mortality, major adverse cardiac and cerebrovascular events (MACCE), and major bleeding events. The use of BCIS dataset has been approved for research and audit purposes without the need to obtain individual patients' consent as data have section 251 approval of NHS Act 2006 [85] . The quality and accuracy of the dataset have been previously evaluated and confirmed. [84] his study adheres to the guidelines recommended by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement, ensuring comprehensive and transparent reporting of the cohort's findings.[240]

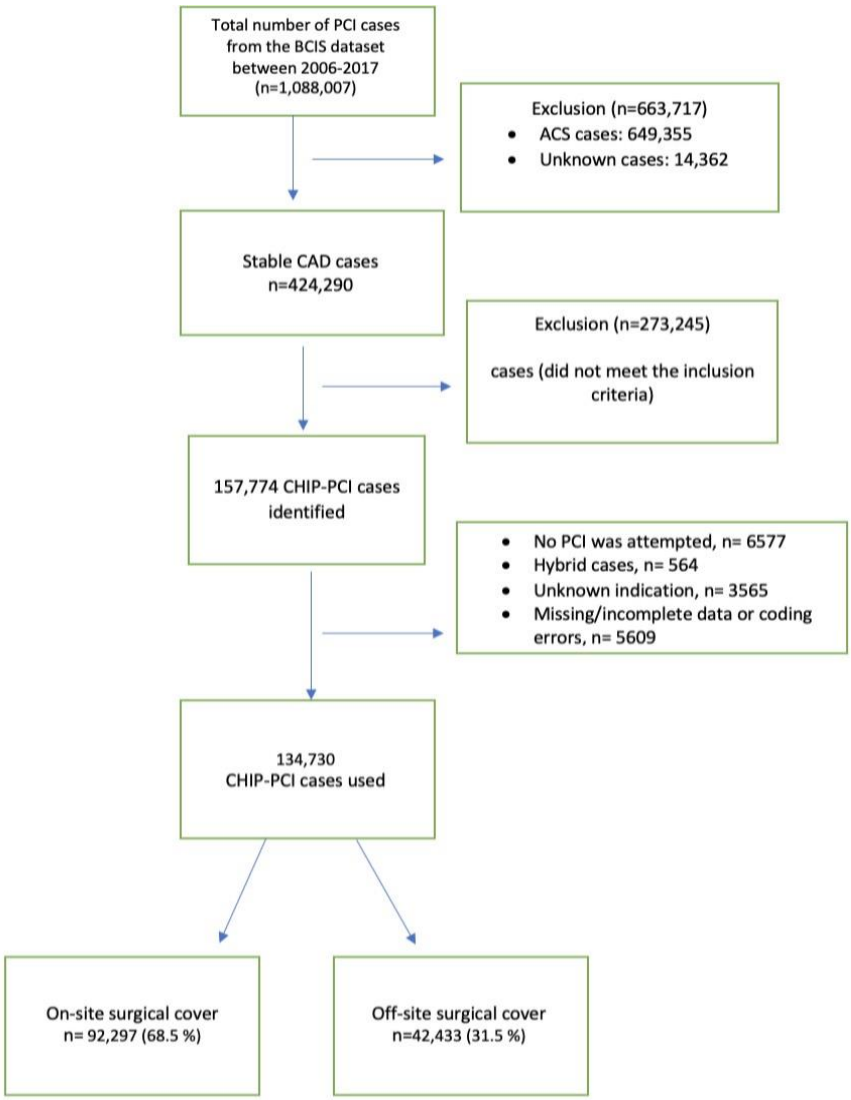
8.3.2 Study population

The study cohort comprised all adults aged 18 and above who met specific patient or procedural characteristics outlined in Chapter 2. These patients were admitted electively to hospitals in England and Wales between January 1, 2006, and December 31, 2017. The CHiP cohort included individuals with previous CABG, chronic renal failure (CRF), poor

LV function, and previous PCI involving LMS or chronic total occlusion (CTO), treatment for severe vascular calcification, or use of LV support devices. The definitions of variables such as CRF, planned LV support use, poor LV function, and extensive vascular calcification were consistent with those used in previous studies (refer to Chapter 4-7, study design and definitions sections).

The collected data were categorised based on the type of centre facility: Surgical Centre (SC) or Non-Surgical Centre (NSC). A total of 119 hospital PCI centres were identified, with 75 hospitals classified as non-surgical centres (63% of the total). Patients with missing information on clinical outcome variables or sex were excluded from the analysis, as well as centres with ambiguous coding (unclear whether they were SC or NSC) (see Figure 8.1 for further details).

Figure 8-1: Flow diagram illustrating the process of patients' inclusion and exclusion for the CHiP analysis



Abbreviations: CHiP, complex, high-risk, but indicated percutaneous coronary intervention; BCIS, British Cardiovascular Intervention Society; PCI, percutaneous coronary interventions.

**Coding errors are those variables with ambiguous terms for example: unidentified hospital code.*

**Inclusion criteria: left main PCI, PCI to chronic total occlusion vessel, chronic renal failure, poor left ventricle function, severe vessel calcifications, previous coronary artery bypass graft, and the use of LV support devices.*

8.3.3 Study endpoints

The primary outcome of interest in this study was in-hospital all-cause mortality. Secondary outcomes included major bleeding events and major cardiovascular and cerebral events (MACCE).

Major bleeding events were defined using the Bleeding Academic Research Consortium's definition for Bleeding Type 2 and above[99] . This definition encompassed access site bleeding events requiring intervention, blood transfusions, or surgery, such as arterial dissection, retroperitoneal haematoma or bleeding, or false aneurysm. It also included radiological evidence of bleeding into the brain or retroperitoneal space, as well as clinically evident bleeding into the gastrointestinal tract.

MACCE was determined by the cumulative incidence of in-hospital mortality, peri-procedural stroke, or myocardial infarction (MI). Peri-procedural MI included Q-wave or non-Q-wave MI, reinfarction, and reintervention (emergency PCI or CABG), all of which were predefined within the BCIS registry used in this study.

8.3.4 Study covariate

The analysis in this study included important patient demographics such as gender, age, weight, height, and BMI (calculated using height and weight). Additionally, key cardiovascular risk factors were considered, including hypertension, hypercholesterolaemia, diabetes mellitus, stroke, PVD, family history of CAD, and smoking status. Other co-morbidities taken into account were previous PCI, previous MI, and LV function.

Pharmacotherapy variables included the use of warfarin, glycoprotein IIb/IIIa inhibitors, clopidogrel, ticagrelor, and prasugrel.

Important procedural characteristics included the number of treated lesions and vessels, the category of the vessel treated, the size and diameter of stents used, and the number of stents deployed. Furthermore, the use of Impella or intra-aortic balloon pump (IABP), calcium modification therapy (such as rotational or laser atherectomy, cutting balloons), coronary imaging techniques (intravascular ultrasound or optical coherence tomography), and the choice of vascular access were considered in the analysis.

8.3.5 Statistical analysis

The patient baseline demographics and characteristics were presented as median values along with interquartile ranges for continuous variables, while frequencies and percentages were provided for categorical variables. Statistical tests were performed to compare the differences between groups: the Wilcoxon Rank-Sum test for continuous data and Pearson's chi-squared test for categorical data.

Supplemental Table 8.1 provided information about missing observations in the study covariates, indicating the variables for which data were not available or were missing in the analysis.

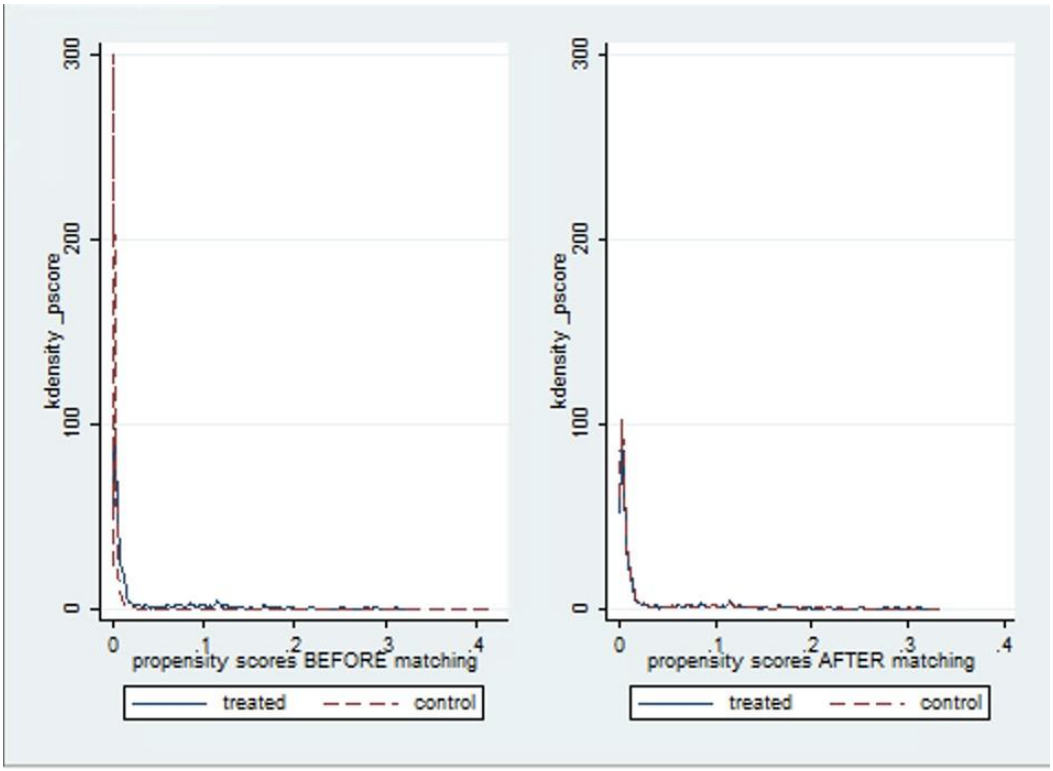
The missing data was imputed using multiple imputations with chained equations to create 10 datasets, assuming that data were MAR[150]. In the study model, the following variables were registered as complete: the type of hospital PCI facility, age, sex, and outcome variables.

On the other hand, variables with missing values were registered as imputed. These variables included ethnicity, previous MI, hypercholesterolaemia, previous CABG, previous stroke, previous PCI, hypertension, smoking, diabetes mellitus, CRF, PVD,

pharmacology, family history of CAD, LV function, vascular access, coronary imaging, LMS PCI, use of LV support, severe vascular calcifications, number of stents used, stent size and length, number of treated lesions, and body mass index (BMI).

Despite the missingness in ethnicity and LV support variables, they were included in the imputation model. This decision was based on previous studies that demonstrated the robustness of multiple imputation frameworks even in the presence of high levels of missingness. Multiple imputation techniques can provide some protection in data that are missing not at random (MNAR)[88, 89, 152]. All followed analyses were performed on the imputed dataset, and results were pooled using Rubin's rule [102]. Multivariable logistic regression analyses were conducted using Stata 14.1 software to generate adjusted odds ratios (aOR), 95% confidence intervals (CI), and p-values, examining the outcomes between the SCs and NSCs groups. Forward stepwise variable selection was employed, with an inclusion criterion of $p<0.1$, to determine the predictors included in the final multivariate model. Additionally, to assess the robustness of the results and control for baseline characteristic differences, propensity score matching (PSM) was performed. The following variables were matched: sex, age, ethnicity, previous MI, hypercholesterolaemia, previous CABG, previous PCI, hypertension, previous stroke, diabetes mellitus, smoking category, CRF, LV function category, PVD, pharmacology, family history of CAD, intracoronary imaging, vascular access, use of LV support, severe vascular calcifications, LMS PCI, number of stents used, number of treated lesions, stent size and length, and BMI. Logistic regression was then conducted to estimate the propensity score, followed by matching using the nearest neighbour algorithm (Figure 8.2).

Figure 8-2 Propensity score matching graphs showing the CHiP cohort balance before and after matching.



Abbreviations: CHiP, complex high-risk but indicated percutaneous coronary interventions.

The coefficients obtained from the logistic regression analyses were converted to odds ratios for easier interpretation of the results. Additionally, sensitivity analyses were conducted on the non-imputed dataset to further evaluate the consistency of the findings. All statistical analyses were performed using Stata version 14.1 (StataCorp, College Station, Texas). A significance level of 0.05 was used to determine statistical significance, corresponding to a type I error rate.

8.4 Results

Out of the 119 PCI centres included in the analysis, 44 (37%) were categorised as Surgical Centres (SCs), while the remaining 75 (63%) were classified as Non-Surgical Centres (NSCs). The CHiP cohort consisted of 134,730 procedure records, accounting

for approximately 31.8% of the total 424,290 records of patients admitted electively for stable CAD treatment between January 1st, 2006 and December 31st, 2017.

Table 8.1 and Figure 8.3 provide a summary of the distribution of CHiP factors among the two types of centres (SCs and NSCs). Two-thirds of procedures for each CHiP factor were performed in SCs, indicating a higher proportion in these centres compared to NSCs.

Table 8-1: Baseline clinical and procedural characteristics of patients with stable angina undergoing CHiP, stratified by type of surgical cover.

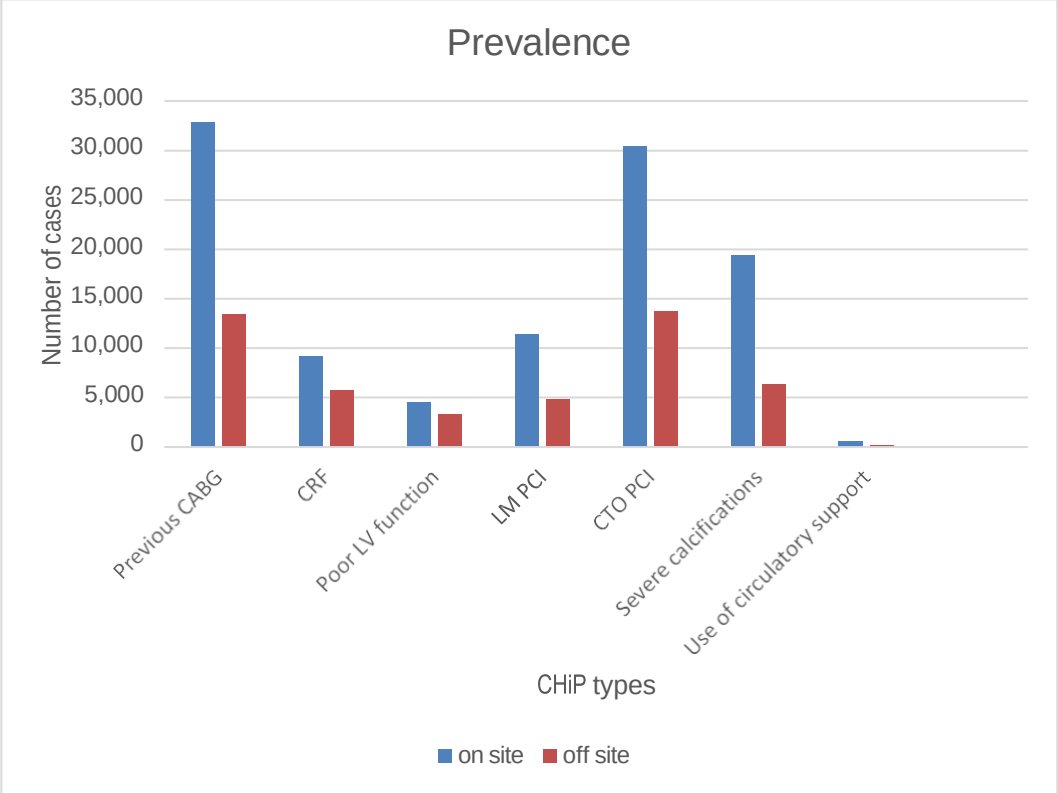
	Total, n	**On-site cover**	**Off-site cover**	**P-value**
Number of participants	134,730	92,297 (68.5%)	42,433 (31.5%)	
Female sex, n (%)	29,320 (22.7%)	29,320 (21.6 %)	9,355 (22.1%)	0.08
Age Median, (IQR)	69.5 (61.1 - 77.6)	68.8 (60.5 – 76.9)	71.2 (62.7-79.9)	< 0.001
BMI Median, (IQR)	28.1 (25.4-31.6)	28.1 (25.4-31.4)	28.2 (25.4-31.6)	< 0.001
Ethnicity				< 0.001
• **White**	84,240 (84.3%)	60,549 (85.8 %)	23,691 (87.7 %)	
• **BAME**	16,400 (16.3%)	9,991 (14.2 %)	6,409 (21.3 %)	
CHiP risk factors				
g) **Patients' factors**				
• **Prior CABG**	46,232 (33.4%)	32,818 (71.0%)	13,414 (29.1%)	< 0.001
• **Chronic Renal Failure**	14,890 (11.6 %)	9,106 (61.2%)	5,784 (38.8%)	< 0.001
• **Poor LV function**	7,835 (10.2 %)	4,574 (58.4%)	3,261 (41.6%)	< 0.001
h) **Procedural factors**				
• **LMS PCI**	16,204 (12.3 %)	11,396 (70.3%)	4,808 (29.7%)	< 0.001
• **CTO PCI**	44,129 (34.8 %)	30,399 (68.9%)	13,730 (31.1%)	< 0.001
• **Severe coronary calcifications**	25,743 (23.6 %)	19,352 (75.2%)	6,391 (24.8%)	< 0.001
• **Use of LV support**	767 (0.6%)	584 (76.1%)	183 (23.9%)	< 0.001
Cardiovascular risk factors				
• **Hypertension**	82,254 (65.0 %)	55,210 (64.2 %)	27,044 (66.9%)	< 0.001
• **Hypercholesterolaemia**	81,557 (64.5 %)	55,215 (64.2 %)	26,342 (65.1 %)	0.001

• **Diabetes Mellitus**	33,890 (26.4 %)	23,060 (26.4 %)	10,830 (26.4 %)	0.962
• **Smoking**				< 0.001
Never	47,968 (41.1 %)	33,431 (42.0 %)	14,537 (39.1 %)	
Ex-smokers	57,147 (48.9 %)	37,876 (47.6 %)	19,271 (51.8 %)	
Current smokers	11,654 (10.0 %)	8,275 (10.4 %)	3,379 (9.1 %)	
• **Family history of CAD**	54,613 (46.7%)	36,388 (45.2 %)	18,225 (49.9 %)	< 0.001
• **History of** AMI	54,211 (43.2 %)	37,338 (43.9 %)	16,873 (41.8 %)	< 0.001
• **Previous PCI**	50,695 (38.7 %)	34,192 (38.1 %)	16,503 (40.1 %)	< 0.001
• **Previous stroke**	5,882 (4.7 %)	3,564 (4.1 %)	2,318 (5.7 %)	< 0.001
• **History of PVD**	8,732 (6.9 %)	5 5,451 (6.3 %)	3,281 (8.1 %)	< 0.001
• **LV systolic function**				< 0.001
Normal (EF>50)	53,113 (69.3 %)	334,526 (70.1 %)	18,587 (67.9 %)	
Impaired (EF 30-50)	15,670 (20.5 %)	10,135 (20.6 %)	5,535 (20.2 %)	
Severe (EF<30)	7,835 (10.2 %)	4,574 (9.3 %)	3,261 (11.9 %)	
Pharmacology				
• **Warfarin**	2,562 (2.1 %)	1,747 (2.1 %)	815 (2.1%)	= 0.831
• **GPIIb IIIa inhibitors**	9,611 (7.7 %)	6,693 (7.9 %)	2,918 (7.3 %)	< 0.001
• **Clopidogrel**	98,527 (81.3 %)	64,767 (78.6 %)	33,760 (87.1 %)	< 0.001
• **Prasugrel**	1,126 (0.9%)	793 (1.0 %)	333 (0.9 %)	= 0.079
• **Ticagrelor**	4,260 (3.5%)	2,717 (3.3%)	1,543 (4.0%)	< 0.001
Vascular access				< 0.001
• **Radial artery**	58,852 (45.0 %)	37,440 (41.8 %)	21,412 (58.2 %)	
• **Femoral artery**	71,826 (55.0 %)	52,117 (58.2 %)	19,709 (47.9 %)	
Intracoronary imaging				< 0.001
• **IVUS or OCT**	13,631 (12.2 %)	8,062 (10.8 %)	5,569 (15.1 %)	
Circulatory support				
• **IABP**	713 (0.6 %)	550 (0.6%)	163 (0.4%)	< 0.001
• **Impella**	57 (0.04%)	37 (0.04%)	20 (0.05%)	0.607
Number of treated lesions				<0.001
• **One**	85,677 (64.3 %)	59,764 (65.6 %)	25,913 (61.6 %)	
• **Two**	33,293 (25.1 %)	22,020 (24.1 %)	11,273 (26.8 %)	
• **Three or more**	14,161 (10.6 %)	9,283 (10.9 %)	4,878 (11.6 %)	

Stent size Median, (IQR)	3.5 (3.0-3.75)	3.5 (3.0-3.5)	3.5 (3.0-4.0)	< 0.001
Stent length Median, (IQR)	24 (18-36)	24 (18-33)	24 (18-38)	< 0.001
Procedural devices				
• **None**	83,775 (76.6 %)	56,533 (74.7 %)	27,242 (81.3 %)	< 0.001
• **Cutting Balloon**	15,268 (14.0 %)	12,522 (16.5%)	2,746 (8.2 %)	< 0.001
• **Rotational atherectomy**	10,542 (9.6 %)	7,007 (9.3 %)	3,535 (10.5 %)	< 0.001
• **Laser atherectomy**	868 (0.8 %)	442 (0.6%)	426 (1.3 %)	< 0.001
Number of stents used				< 0.001
• **One stent**	53,483 (40.1 %)	37,221 (40.8 %)	16,262 (38.4 %)	
• **Two stents**	33,903 (25.4 %)	22,911 (25.1%)	10,992 (26.0 %)	
• **Three or more stents**	26,845 (20.1 %)	18,229 (20.0 %)	8,616 (20.4 %)	
Target Vessel PCI				
• **Left main stem (LMS)**	16,204 (12.3 %)	11,396 (12.6 %)	4,808 (11.5 %)	< 0.001
• **LAD**	52,920 (40.2 %)	35,035 (38.8 %)	17,885 (42.8 %)	< 0.001
• **LCX**	33,835 (25.6 %)	22,753 (25.2 %)	11,082 (26.5 %)	< 0.001
• **RCA**	47,210 (35.7 %)	32,118 (35.5%)	15,092 (36.1 %)	= 0.039
• **Graft**	13,397 (10.1 %)	9,958 (11.0 %)	3,439 (8.2 %)	< 0.001
Number of target vessel PCI				< 0.001
• **One**	97,392 (74.6 %)	66,836 (75.2 %)	30,556 (73.4 %)	
• **Two**	26,183 (20.1 %)	17,517 (19.7 %)	8,666 (20.8 %)	
• **Three or more**	6,994 (5.3 %)	4,587 (5.1 %)	2,407 (5.8 %)	

Abbreviations: CHiP, complex high risk percutaneous coronary intervention; CABG, coronary artery bypass graft; CTO, chronic total occlusion; CAD, coronary artery disease; GPIIbIIIa, glycoprotein IIaIIIb; LV, left ventricle; LMS, left main stem; LCX, left circumflex; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery.

Figure 8-3: Prevalence of CHiP factors (types) stratified by the type of surgical cover provided.



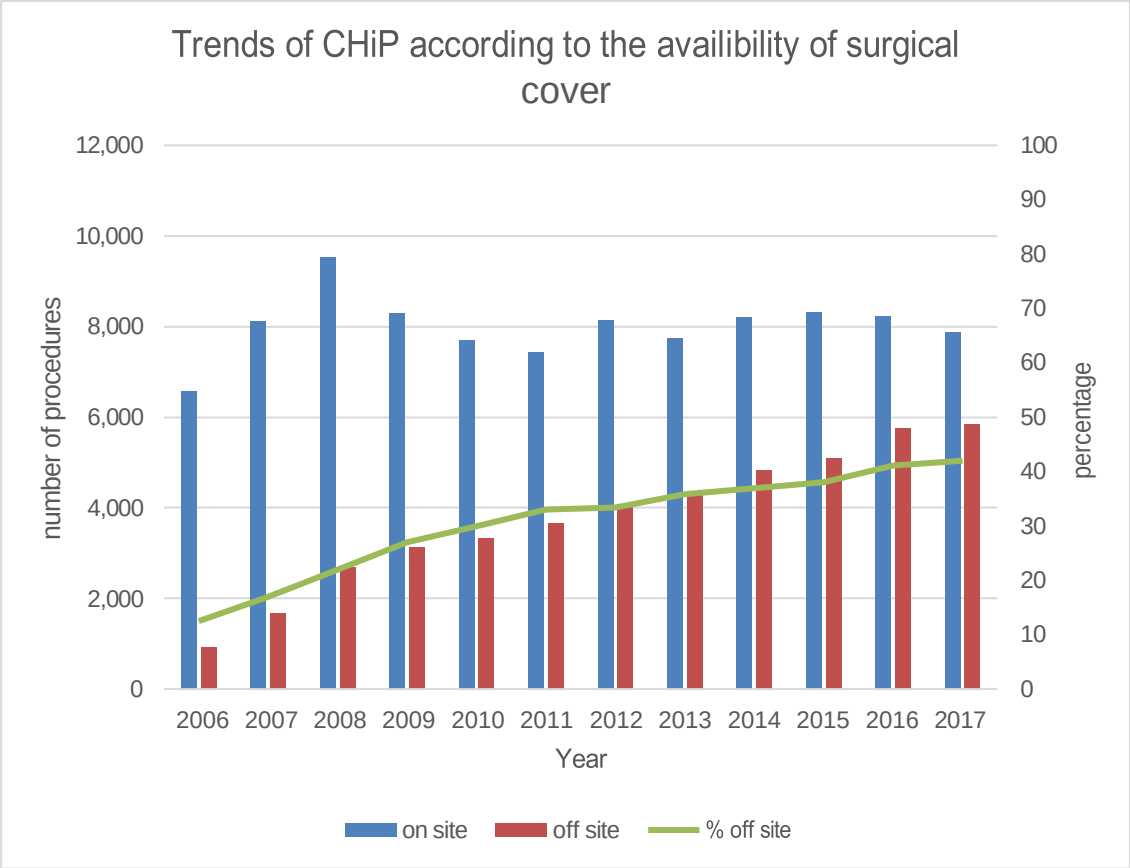
Abbreviation: CHiP, complex high risk but indicated percutaneous coronary interventions; CABG, coronary artery bypass graft; CTO, chronic total occlusion; CRF, chronic renal failure; LV, left ventricle; LMS, left main stem; PCI, percutaneous coronary intervention.

8.4.1 Temporal trends

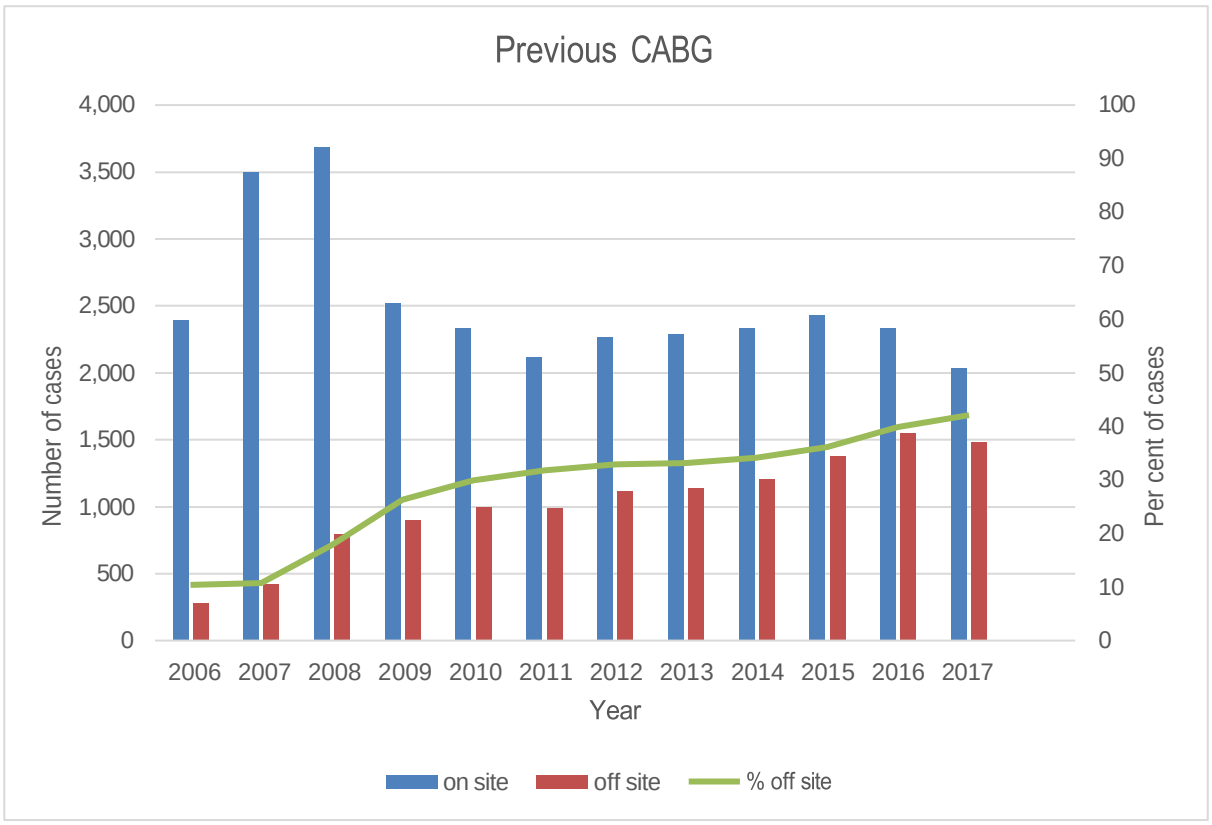
Figure 8.4 illustrates the temporal changes in the utilisation of CHiP in Non-Surgical Centres compared to Surgical Centres. The data reveals an upward trend in the number of CHiP procedures conducted in NSCs within the overall cohort. Specifically, the proportion of CHiP procedures performed in NSCs increased from 12.5% in 2006 to 42% in 2017. This trend was consistent across all CHiP factors, indicating a gradual and substantial adoption of these procedures in NSCs over the study period.

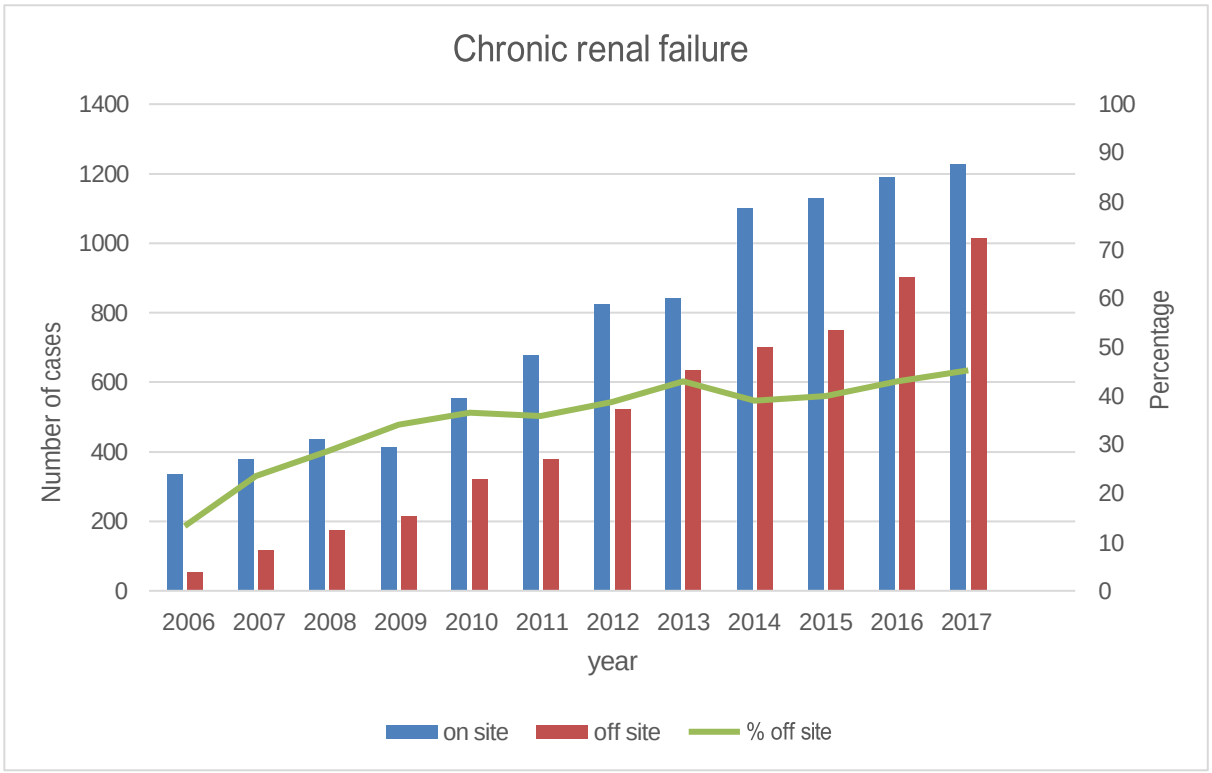
Figure 8-4: Temporal changes in CHiP procedures' prevalence and percent changes over time in the entire CHiP cohort and in each CHiP factor, stratified by the type of surgical cover.

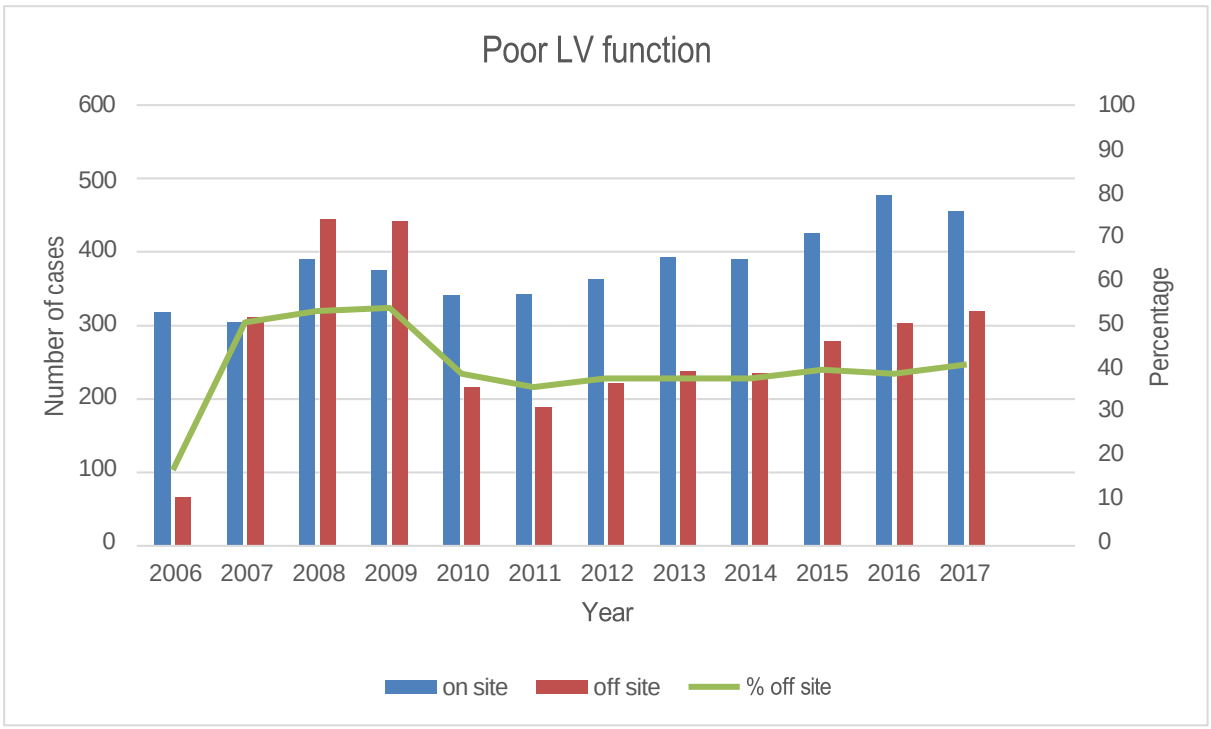
3 A) Changes in the entire cohort over time.

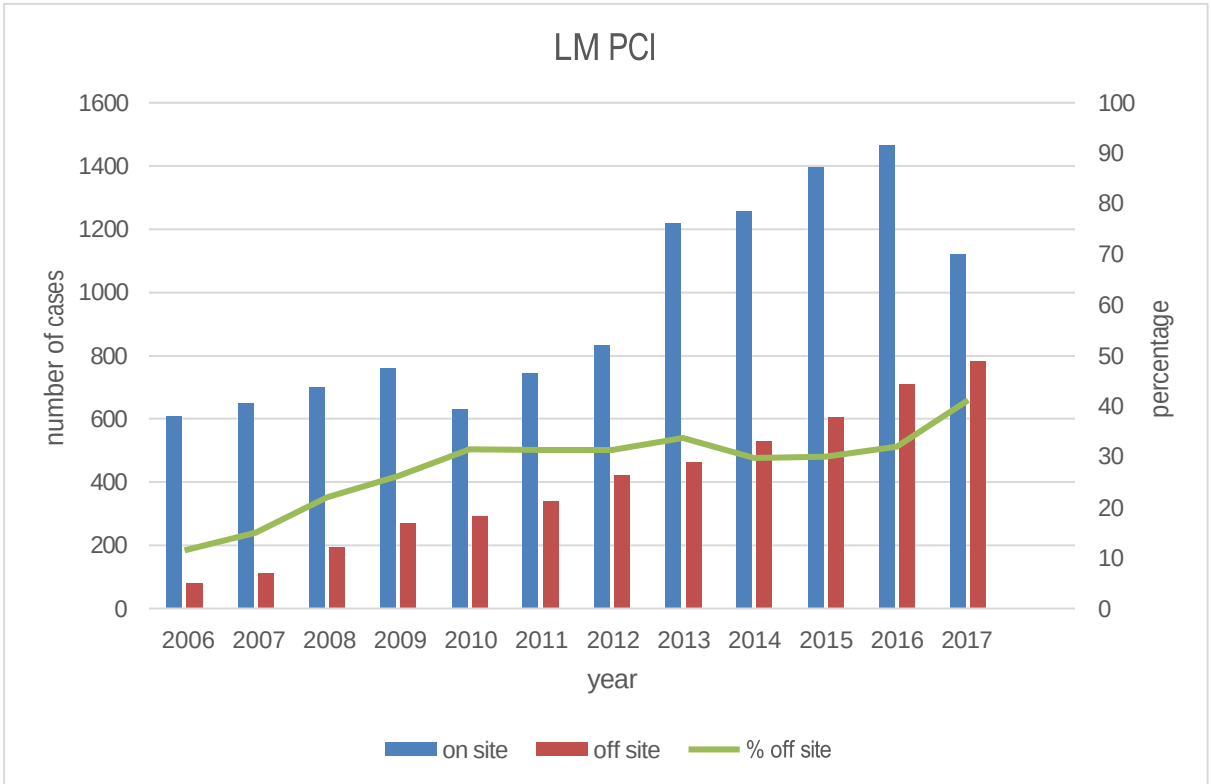


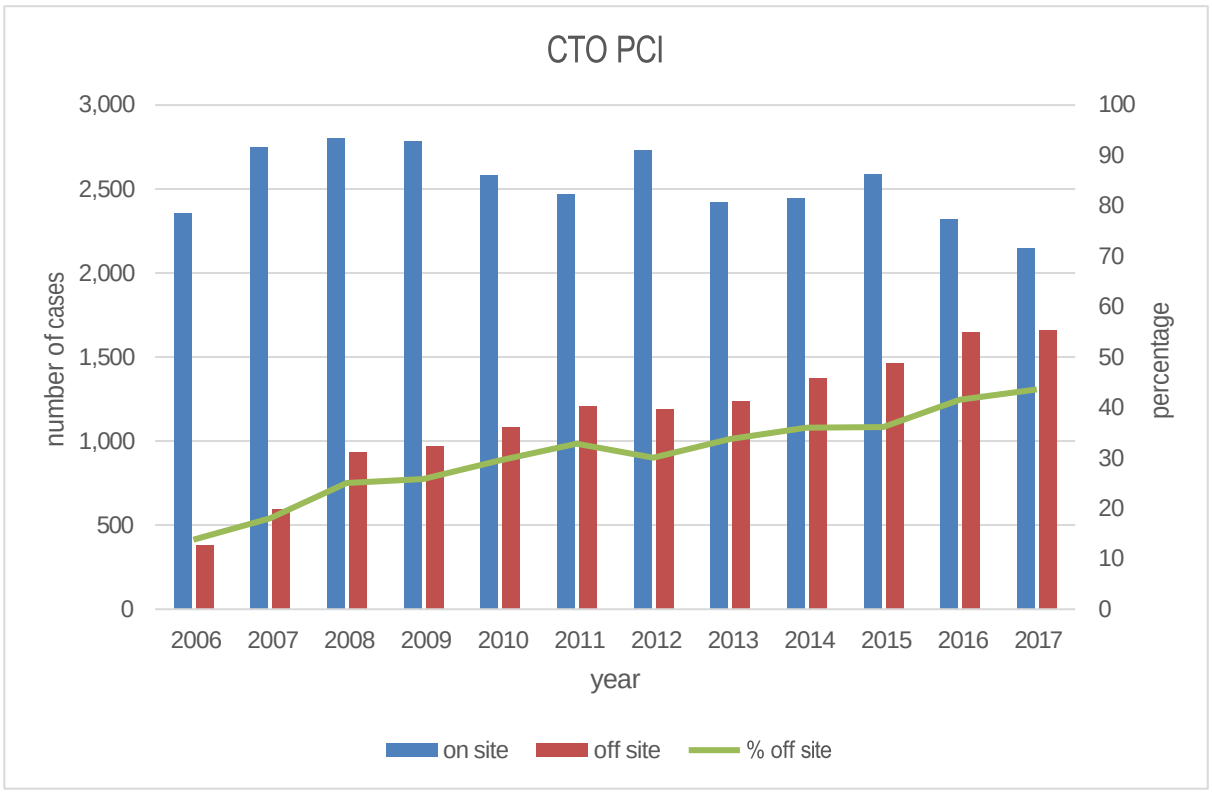
3B) Changes in individual CHiP factors

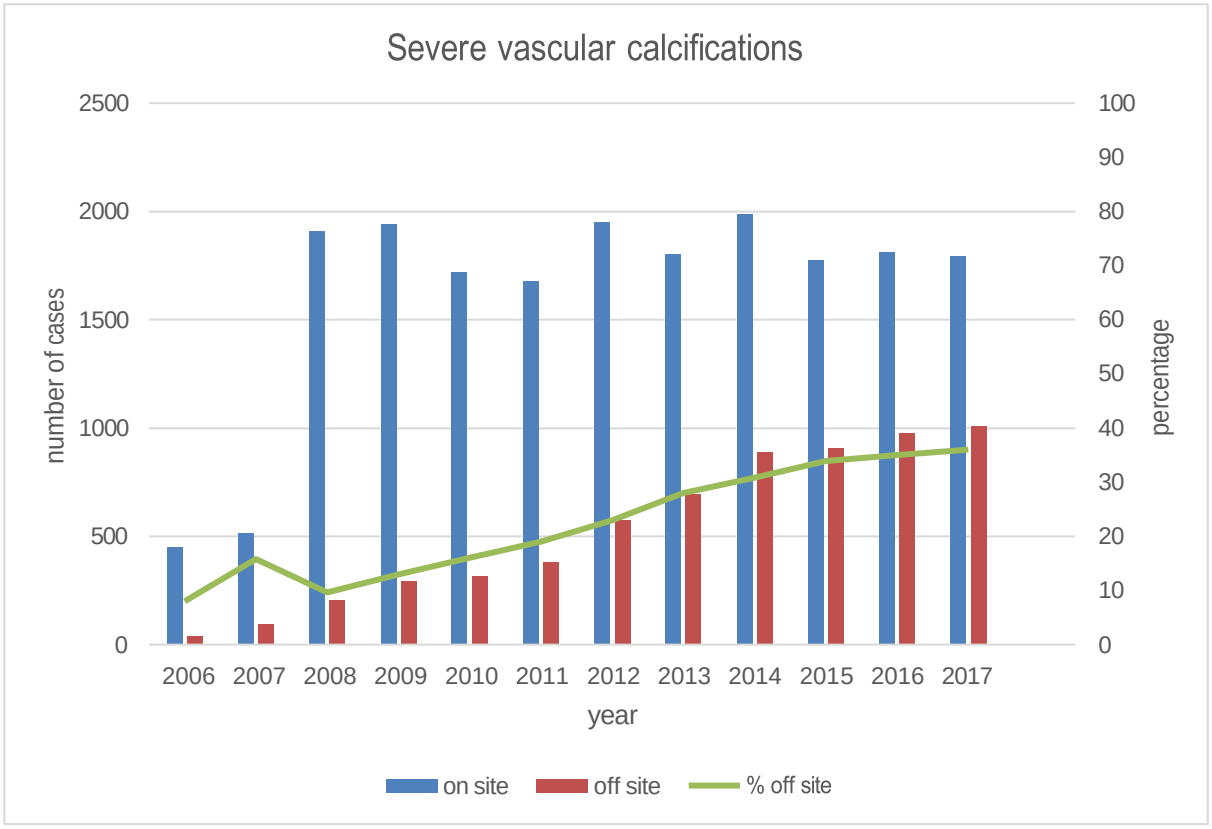

Previous CABG
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
Number of cases
100
90
80
70
60
50
40
30
20
10
0
Per cent of cases
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
Year
on site
off site
% off site


Chronic renal failure
1400
1200
1000
800
600
400
200
0
Number of cases
100
90
80
70
60
50
40
30
20
10
0
Percentage
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
year
on site
off site
% off site


Poor LV function
600
500
400
300
200
100
0
Number of cases
100
90
80
70
60
50
40
30
20
10
0
Percentage
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
Year
on site
off site
% off site


LM PCI
1600
1400
1200
1000
800
600
400
200
0
number of cases
100
90
80
70
60
50
40
30
20
10
0
percentage
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017
year
on site
off site
% off site


CTO PCI
3,000
2,500
2,000
1,500
1,000
500
0
number of cases
100
90
80
70
60
50
40
30
20
10
0
percentage
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
year
on site
off site
% off site


Severe vascular calcifications
2500
2000
1500
1000
500
0
number of cases
100
90
80
70
60
50
40
30
20
10
0
percentage
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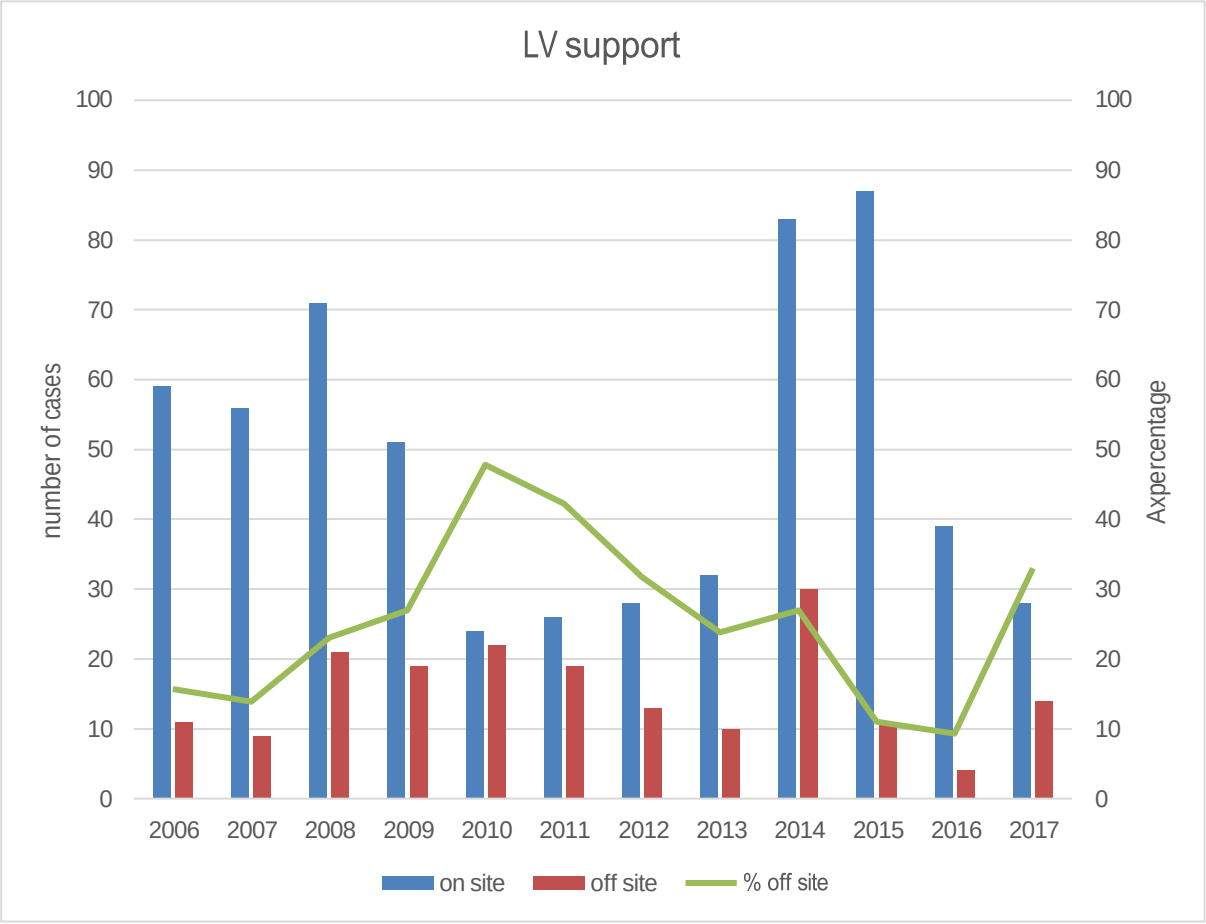
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
year
on site
off site
% off site



Abbreviation: CHiP, complex high risk percutaneous coronary interventions; CABG, coronary artery bypass graft; CRF, chronic renal failure; CTO, chronic total occlusion; LV, left ventricle; LMS, left main stem; PCI, percutaneous coronary intervention.

8.4.2 Demographic and Clinical characteristics

Table 8.1 provides an overview of the baseline clinical and procedural characteristics of the analysed cohort. Among the cases included in the study, 68.5% (n=92,297) were performed in SCs, while 31.5% (n=42,433) were performed in NSCs. On average, patients who underwent the CHiP procedure in NSCs were found to be older by 2.4 years compared to those in SCs.

Regarding the distribution of patients by sex, a similar case-mix observed between the NSC and SC groups. However, it is worth noting that patients from black, Asian, and other ethnic minority backgrounds more frequently had their CHiP procedure performed in NSCs. Furthermore, significant differences were observed in the prevalence of

cardiovascular co-morbidities between the NSC and SC groups. For example, current smokers and those with a previous history of MI were more prevalent among the SCs patients. In contrast, patients from off-site surgical cover centres had a higher prevalence of previous PCI (40.1% vs 38.1 %), severely impaired LV function (11.9% vs 9.3 %), hypertension (66.9% vs 64.2 %), hypercholesterolaemia (65.1% vs 64.2 %), family history of CAD (49.9% vs 45.2%), stroke (5.7% vs 4.1 %), and PVD (8.1% vs 6.3 %). These differences were statistically significant ($p<0.001$ for all comparisons). Overall, these findings highlight the variations in baseline characteristics between patients who underwent CHiP procedures in NSCs compared to SCs, including differences in age, ethnic background, and cardiovascular co-morbidities.

8.4.3 Procedural characteristics

Non-surgical centre patients underwent CHiP procedures more frequently via radial access compared to patients from SCs (58.2% vs. 41.8%, respectively; $p<0.001$). Moreover, the utilisation of intracoronary imaging techniques, such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), was higher in NSCs compared to SCs (15.1% vs. 10.8%, respectively; $p<0.001$). Regarding the elective use of LV support during CHiP procedures, NSCs exhibited slightly lower utilisation of IABP compared to SCs (0.4% vs. 0.6%, respectively; $p<0.001$). Notably, NSC patients were more frequently treated for two or more lesions compared to SC patients (38.4% vs. 35%, respectively; $p<0.001$), indicating a higher propensity to address multiple lesions in NSCs. Conversely, SCs had a higher percentage of PCI procedures performed on grafts (11% vs. 8.2%) or left main (LMS) arteries (12.6% vs. 11.5%) compared to NSCs ($p<0.001$ for both comparisons).

8.4.4 Clinical outcomes

Significant differences were observed in the crude and adjusted clinical outcomes between patients who underwent CHiP in PCI facilities with onsite surgical cover compared to those with off-site surgical cover. NSC patients exhibited significantly lower crude rates of in-hospital mortality (0.2% vs. 0.3%) and major bleeding events (0.4% vs. 0.6%), respectively (p<0.001). After adjusting for baseline covariates, the odds of both mortality (aOR 0.7, 95% CI 0.5-0.8) and major bleeding events (aOR 0.7, 95% CI 0.6-0.8) were lower in the NSCs cohort compared to SCs.

Propensity score matching (PSM) further supported these findings, demonstrating lower odds of in-hospital mortality (OR 0.6, 95% CI 0.3-0.8) and major bleeding events (OR 0.5, 95% CI 0.2-0.7) in NSCs. However, there were no significant differences in the odds of major cardiovascular and cerebral events (MACCE) between the two groups. Detailed results can be found in Tables 8.2 and 8.3, as well as Figure 8.2.

Table 8-2: Crude and adjusted outcomes of patients with stable angina undergoing CHiP, stratified by type of surgical cover.

Variables	Total, n (%)	On-site, n (%)	Off-site, n (%)	Odd ratio (95% CI), P value
Mortality	396 (0.3%)	300 (0.3%)	96 (0.2%)	0.7 (0.5-0.8), < 0.001
Major bleeding	694 (0.5%)	517 (0.6%)	177 (0.4%)	0.7 (0.6-0.8), < 0.001
MACCE	1,964 (1.5%)	1,332 (1.4%)	632 (1.5%)	1.0 (0.9-1.1), = 0.42

Abbreviation: CHiP, complex high risk percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

Table 8-3: Average treatment effect (ATE) and adjusted odds (aOR) of adverse outcomes post CHiP in patients with stable angina using Propensity Score Matchings (PMS) (reference, on-site surgical cover).

Variables	ATE (95% CI)	aOR (95% CI)	P value
Mortality	-.0013523 (-.0021744 -.0005302)	0.6 (0.3-0.8)	= 0.001
Major bleeding events	-.0028264 (-.0039191 -.0017338)	0.5 (0.2-0.7)	<0.001
MACCE	-.0009283 (-.0028826 .0010259)	0.9 (0.8-1.1)	= 0.351

Abbreviation: ATE, Average Treatment Effect; CAD, coronary artery disease; CHiP, complex high-risk but indicated percutaneous coronary intervention; CI, confidence interval; MACCE, major cardiovascular and cerebral events.

8.5 Discussion

This study represents the first analysis to compare the characteristics and clinical outcomes of CHiP procedures between catheter laboratory PCI facilities with onsite cardiothoracic services (SCs) and those without (NSCs). The key findings of this study are as follows: Firstly, there has been a gradual increase in the number of CHiP procedures performed in NSCs over time, with a rise from 12.5% in 2006 to 42% in 2017. However, SCs continue to be the most common setting for all types of CHiP procedures. Secondly, patients receiving CHiP in NSCs were found to be, on average, 2.4 years older than those in SCs; and exhibited a higher prevalence of cardiometabolic risk factors compared to SCs patients. Thirdly, NSC patients had a higher frequency of CHiP procedures conducted via radial access and were more likely to undergo intracoronary imaging guidance compared to SCs patients. Lastly, the rates of in-hospital mortality, major bleeding events, and the adjusted odds for these outcomes were significantly lower in the NSCs cohort compared to SCs. However, the two groups had no significant differences in the odds of MACCE. These findings highlight the potential benefits of performing CHiP procedures in NSCs and suggest the feasibility and safety of such interventions in these settings in selected cases.

Several factors contributed to the introduction of PCI programs in NSCs. Firstly, the compelling evidence from multiple randomised controlled trials and observational studies emphasised the importance of promptly treating ST-elevation myocardial infarction (STEMI) patients with primary PCI. This evidence-based approach drove the need to establish PCI capabilities in NSCs to ensure timely access to this life-saving intervention[207]. Secondly, there were significant delays in providing evidence-based revascularisation to non-ST-elevation myocardial infarction (NSTEMI) patients within the recommended time frame. This gap in care prompted the expansion of PCI services

to NSCs, enabling more efficient and timely management of NSTEMI patients. [163, 241] Finally, patient-centred factors played a crucial role in advocating for PCI services in close proximity to patients' residential areas.

Recognising the importance of accessibility, the establishment of PCI programs in NSCs aimed to bring revascularisation treatments closer to where patients lived, minimising travel distances and enhancing convenience for patients seeking cardiac care. As the evidence for the safety and effectiveness of PCI procedures grew, the scope of services provided in NSCs naturally expanded to include increasingly higher-risk and complex elective procedures. This evolution in practice reflected the growing confidence in the ability of NSCs to deliver PCI services with comparable safety and outcomes to surgical centres[242]. This expansion of CHiP into NSCs has been backed up by the rapid evolution of multidisciplinary decision-making (Heart Team) meetings. The Heart Team meetings work in a way that facilitates easy access to NSCs PCI operators and can accommodate the increased patients' and procedures' complexity.

Despite the mentioned developments in clinical practice, the most recent AHA/ACC/ESC guidelines on complex and high-risk PCIs in the NSC have taken a more cautious approach towards complex and high-risk PCIs in NSC settings.[163, 207, 208, 243]. For instance, the 2010 ESC guidelines on myocardial revascularisation recommended performing high-risk procedures in SCs specifically those including revascularisation of the distal LMS artery or treating a complex bifurcation atherosclerotic significant disease that involves large side branches[244]. Furthermore, the 2020 SCAI guidelines recommended transferring patients with stable angina to SCs if they required invasive treatment for unprotected left main (LMS) disease or complex cases that necessitate advanced therapies such as calcium modification techniques like rotational or laser atherectomy, which may not be available or feasible to perform safely in NSCs[21]. While RCTs such as CPORT-E (The Cardiovascular Patient Outcomes Research Team)[237] and the MASS COMM

(Massachusetts Hospitals with Cardiac Surgery On-Site and Community Hospitals without Cardiac Surgery On-Site)[238] supported PCI in stable patients in NSCs and have led to guideline recommendations about the same[245], there is still limited knowledge about the outcomes of CHiP specifically in these centres.

This analysis revealed significant differences in baseline characteristics between the two groups. The patients in SCs had a higher prevalence of prior history of MI and current smokers. On the other hand, patients in NSCs had a higher prevalence of stroke and hypertension. This difference can be attributed to the older age of the NSCs cohort, which is associated with a higher incidence of these conditions. It is worth noting that this case mix differs from other studies on PCI outcomes based on the type of facility. For example, a study from the National Cardiovascular Data Registry (NCDR) in 2009 demonstrated a higher burden of cardiovascular risk factors, established cardiometabolic diseases, and diabetes mellitus in patients from surgical centres[246]. Significant differences were observed in the types of CHiP procedures performed based on the presence of cardiothoracic surgical support in the catheter laboratory; consistent with recent guidelines recommendations, left LMS PCI and CTO PCIs were more commonly performed in catheter laboratories with onsite surgical cover[207].

The analysis of clinical outcomes revealed lower odds for mortality and major bleeding events in the NSCs compared to the SCs group, with approximately 30% lower odds in the NSCs. However, the groups had no significant differences in the odds of MACCE. It is important to interpret these findings cautiously, considering the potential impact of unmeasured confounders such as frailty, anaemia, and other co-morbidities that are known to be associated with adverse outcomes, including chronic obstructive pulmonary disease (COPD). [17]. Furthermore, it should be noted that the BCIS dataset used in this analysis does not include specific measurements for CAD severity, such as the extent of vascular calcification or the severity of the disease as determined by the SYNTAX score[30]

and classification of CTOs by disease complexity[247]. These factors could potentially influence the outcomes of CHiP procedures and should be considered when interpreting the results. Additionally, it is important to consider the possibility that the higher odds for worse clinical outcomes observed in SCs could be attributed to the selection of higher-risk cases in those facilities, while lower-risk CHiP cases were more commonly performed in NSCs. Interestingly, CHiP procedures in NSCs were more frequently performed via radial access and guided by intracoronary imaging. The reasons behind this discrepancy are unclear, but it could potentially reflect the presence of newer facilities in NSCs where intracoronary imaging is routinely incorporated into practice.

There is a vast amount of evidence from single-centre experiences [248], RCTs [237, 238], and observational studies [236] that consistently demonstrated no differences in PCI clinical outcomes between NSCs and SCs in general. Building upon this existing knowledge, our current study expands the understanding of CHiP procedures in NSCs. This is particularly relevant because the expansion of CHiP to NSCs offers several advantages. For example, It allows a larger number of patients to receive care in their own communities, close to their families; additionally, it supports the primary PCI service in NSCs by increasing the overall volume of PCI procedures performed at these centres.

To date, no specific studies have investigated the outcomes of CHiP procedures in NSCs. However, there have been analyses that examined the outcomes of LMS PCI based on the type of catheter laboratory facility. For instance, an analysis using data from the Victorian Cardiac Outcome Registry found that undergoing PCI at a SC was not associated with increased in-patient mortality (adjusted odds ratio 0.68, 95% CI 0.32- 1.43, p=0.35), 30-day mortality, or long-term survival at 60 months (hazard ratio 0.88, 95% CI 0.62-1.27, p=0.51). [249] These findings suggest that the type of catheter laboratory facility may not significantly impact these specific outcomes for LMS PCI patients.

Moreover, analyses around PCI to a CTO vessel in NSCs are rare; one prospective analysis in 2009 on 152 patients from 10 NSCs in China showed higher odds for procedure failure (OR 13.023, 95% CI 6.67- 13.69, p=0.002) [250].

8.6 Study strength and limitations

This study represents the first national-level analysis investigating CHiP outcomes based on the type of catheter laboratory facility surgical support in a real-world, unselected setting. The large cohort includes the majority of PCI cases in England and Wales, providing a comprehensive representation of national practice. However, it is important to acknowledge the limitations of the study, primarily its observational nature. Potential sources of bias include errors in reporting and coding, which may lead to under-reporting of co-morbidities and complications without external validation. The dataset also does not capture the severity of coronary artery disease and lesion complexity, which could confound the reported outcomes. Moreover, the Severe Vascular Calcification variable was defined as the use of calcium modification devices such as cutting balloons; this could underestimate the risks as cutting balloons use have other indications other than calcium modifications such as treatment of in-stent restenosis. Other unmeasured confounders, such as anaemia, frailty, and surgical turndown status, may also impact the results. Nevertheless, the study attempted to mitigate confounding by adjusting for multiple variables and conducting propensity score matching. Additionally, while the incidence of periprocedural myocardial infarction is defined in the dataset, the specific definition used is not specified. Lastly, as the BCIS dataset only includes in-hospital outcomes, potential differences in long-term outcomes cannot be ruled out.

8.7 Conclusion

To sum up, this nationwide, real-world study provides valuable insights into the increasing utilisation of CHiP procedures in NSCs. The findings indicate that NSCs tend to attract older patients with a higher prevalence of conditions such as stroke and hypertension. Whereas CHiPs involving treatment for a LMS vessel or graft disease are more commonly performed in SCs.

Our findings suggest that PCI in non-surgical centres may be safe, with no excess mortality demonstrated. Nevertheless, these findings must be interpreted with recognition that given the inherent limitations in observational studies, the possibility of unmeasured confounders influencing the observed trends cannot be excluded.

Overall, this study adds to the growing body of evidence supporting the expansion of CHiP programs in NSCs. It highlights the importance of considering patient characteristics, procedural complexity, and clinical outcomes when evaluating the suitability of NSCs for CHiP procedures. Further research is needed to explore long-term outcomes and identify strategies for optimising patient selection and outcomes in both NSCs and SCs.

Chapter 9

General discussion

9.1 Introduction

This MD thesis investigated complex, high-risk percutaneous coronary intervention trends, differences in patients baseline and procedural characteristics and clinical outcomes in (a) special population (namely females, ethnic groups, and the elderly), (b) according to certain procedural approaches (vascular access) , and (c) according to the type of catheter laboratory facility cardiothoracic cover (onsite and offsite). The results for the same were discussed in detail in the respective chapter of this thesis.

This chapter focuses on providing a brief summary of each research question's key findings and will conclude with identifying future research areas that need to be explored.

9.2 Key findings

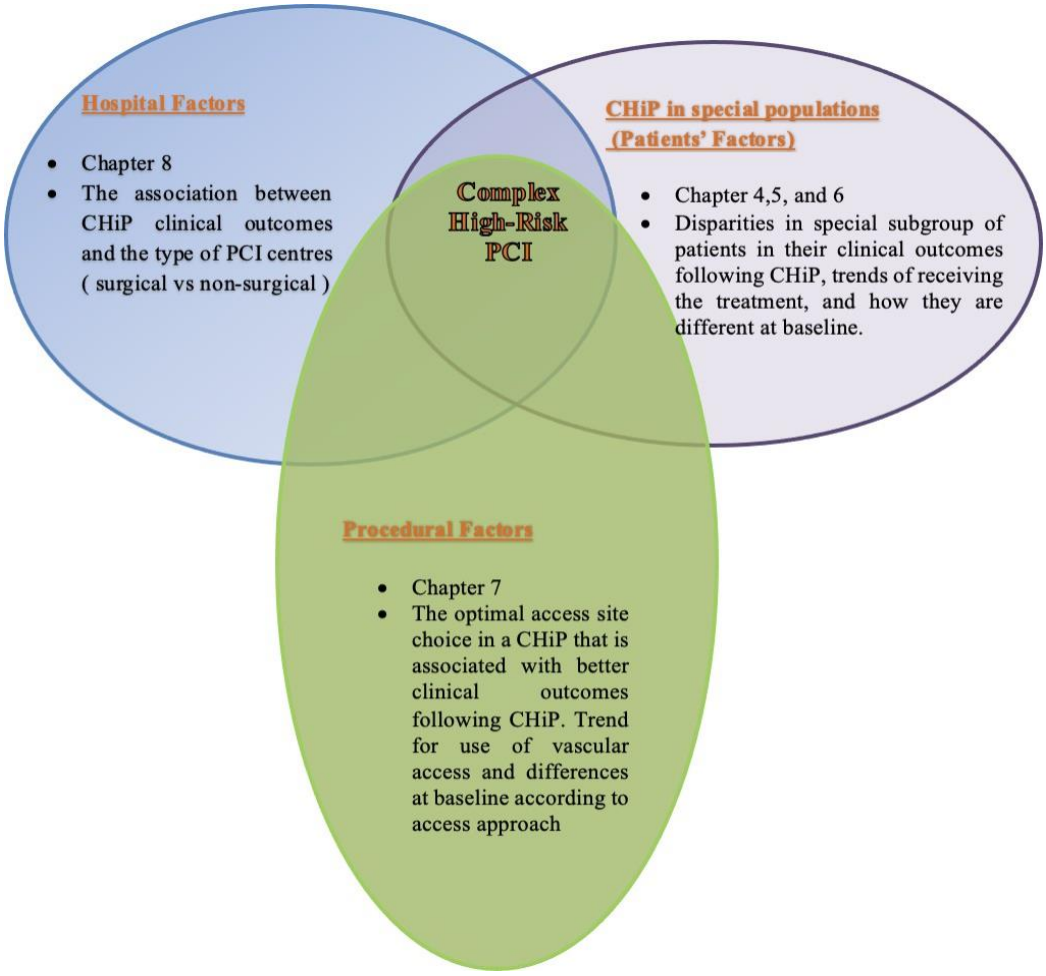
The central focus of this thesis was to comprehensively investigate the association between special populations, procedural aspects, and the type of hospital setting with clinical outcomes in complex, high-risk percutaneous coronary intervention (CHiP). The thesis findings can be summarised as follows:

1) Sex differences: The thesis reveals significant disparities in baseline clinical and procedural characteristics as well as clinical outcomes between male and female patients. Importantly, these differences have remained consistent over time.
2) Ethnic group differences: Significant variations were observed among different ethnic groups in terms of their baseline characteristics. However, the clinical outcomes following a CHiP procedure were found to be similar across these groups, and this pattern has not changed over time.
3) Age as an independent risk factor: The thesis highlights substantial differences in baseline and procedural characteristics associated with increasing age. Moreover, age was identified as an independent risk factor for worse outcomes following a CHiP procedure.

4) Access site selection: Trends in access site use during CHiP procedures were examined, and optimal access site choices associated with better outcomes were identified. Conversely, certain access site choices were linked to poorer CHiP outcomes.
5) Impact of cardiothoracic support: The thesis investigates the association between the type of PCI facility cardiothoracic support (on-site or off-site) and CHiP clinical outcomes. It concluded that certain CHiP types could be safely performed in non-surgical centres.

Overall, this thesis provides valuable insights into the complex interplay between special populations, procedural considerations, hospital settings, and clinical outcomes in CHiP. It serves as a foundation for future research in this field. Figure 9.1 provides a visual representation of the research questions and their corresponding main findings.

Figure 0-1Diagram illustrating the key elements for the thesis.



9.2.1 How CHiP's clinical outcomes is different in special populations and what are the specific patients' factors associated with worse outcomes following CHIPs?

The thesis consists of three chapters investigating complex high-risk percutaneous coronary intervention (CHiP) outcomes in relation to different subgroups of patients (according to sex, ethnicity, and age). The key findings from each chapter are summarised below:

Chapter 4 concluded that females with complex coronary artery disease undergoing high-risk invasive management had higher mortality risks, major bleeding events, and MACCE compared to males. This sex disparity remained consistent over time. The study identified a 'female paradox' where, despite having a lower cardiovascular disease burden and less complex coronary artery disease, females experienced worse adjusted outcomes compared to males. The study uncovered significant differences in patient demographics – for example females were , on average , 5.7 years older and were less likely to receive evidence-based strategies to lower bleeding complications following PCI, such as having their CHiP undertaken via the radial approach. Common CHiP types were different between males and females where age=>80 was commonest among females whereas prior CABG followed by CTO PCI were most common CHiP factors in the male cohort. Notably, CHiP procedures increased over time in both sexes, although the proportion of females undergoing CHiP remained lower than males. In summary, female sex was found to be an independent risk factor for worse odds of in-patient mortality, major bleeding events, and MACCE compared to males counterparts.

Chapter 5 presented a detailed analysis of different ethnic groups undergoing CHiP procedures and revealed significant variations in baseline clinical characteristics.

However, there was no association between ethnicity and worse clinical outcomes, except for a 30% lower odds of major bleeding events in the non-white ethnic group. The Black, Asian, and Other Ethnic minority patients were younger but had a heavier cardiometabolic burden and more frequently received treatment for multiple vessel coronary artery disease. Unadjusted temporal trends in clinical outcomes showed no significant change over time, although major bleeding events rates declined gradually in the non-white group.

The observed lower major bleeding events rates were derived from the "other " ethnic minority patients. Although the white patients were more likely to have their CHiP undertaken via the radial approach, they had higher rates for rotational atherectomy use and used multiple accesses. Also, many white patients met the higher bleeding risk criteria as per the Academic Research Consortium definition, where higher rates of warfarin and glycoprotein IIb IIIa inhibitors prescriptions, octogenarians, and history of stroke were seen among the white patients. Interestingly, the unadjusted temporal trends in clinical outcomes between the ethnic groups demonstrated no change in mortality and major bleeding event rates over time and across all ethnicities, albeit major bleeding event trends in the non-white group showed a gradual decline. The two most common CHiP factors in both groups, the white and BAME, were procedures in patients with a prior history of CABG followed by PCI to a CTO vessel. However, the third most common factor was different with CHiP in those aged =>80 years, common in white patients and treatment for severe vascular calcifications common in the BAME population. Nevertheless, there was a gradual increase in the number of CHiP performed in all CHiP types and across all ethnic groups.

In summary, non-white ethnicity was not found to be a marker for worse outcomes in a CHiP procedure, and Ethnic background should not be considered a negative factor by

interventionists when making decisions around CHiP undertakings in patients with stable angina.

Chapter 6 identified age as an independent risk factor for worse clinical outcomes following CHiP in stable coronary artery disease management, which is even higher than those studies that looked at outcomes of PCI in general according to age. In-hospital mortality was two to three times higher in octogenarians, and this trend remained unchanged over time. The analysis also demonstrated interesting findings in that the risk factor profile changed into lower risk with an increase in patients' age with lower prevalence of diseases like diabetes mellitus and lower rates for current smokers among the elderly population which could indicate that those with heavier co-morbid burden either die before they reach =>80 years or are being turned down for invasive management /managed conservatively.

Procedural characteristics varied significantly among the age groups, possibly reflecting differences in the most common types of CHiP undertaken according to age groups; as the younger age groups had higher rates of PCI to a CTO, treatment for vascular calcifications, and LMS PCI, which probably explains why the femoral approach was more commonly used in the younger age group compared to the octogenarians. This analysis, similar to the trend analysis among the ethnic groups in Chapter 5 and sex groups in Chapter 4 also demonstrated an increase in the number of CHiP undertaken over time. However, outcome trends for mortality across all age groups gradually increased, while major bleeding events trends declined over time.

In summary, this analysis demonstrated that age remains an independent risk factor for worse outcomes in patients undergoing a CHiP procedure.

In conclusion, this thesis provides comprehensive insights into complex, high-risk percutaneous coronary intervention outcomes in relation to sex, ethnicity, and age. The

findings emphasise the higher risks faced by females and older individuals undergoing CHiP procedures while highlighting the absence of ethnicity as a negative factor in clinical outcomes. These findings contribute to the existing knowledge and underscore the importance of considering patient characteristics in decision-making for CHiP procedures. Future research should continue exploring these areas to further enhance clinical practice.

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9.2.2 *How CHiP outcomes can be affected by certain procedural approaches and what is the best approach to get the best procedure's outcomes*?

This question was addressed in Chapter 7, which examined the association between CHiP clinical outcomes and specific procedural approaches using either the femoral or radial access sites. The analysis revealed significant differences between the two access groups in terms of baseline characteristics, procedural characteristics, and clinical outcomes.

The use of radial access was more common in most individual CHiP factors, such as age =>80, chronic renal failure, LMS PCI, poor LV function, and cases requiring calcium modification therapy. On the other hand, femoral access was predominantly utilised in higher-risk procedures, including previous CABG, PCI to CTO, and cases requiring elective use of LV support devices.

Patients with cardiovascular risk factors like hypertension, stroke, and active smoking were more likely to undergo procedures via radial access, while those with heavier co-morbidities and established CAD (e.g., previous MI, previous PCI) tended to have femoral access. This selection bias may be attributed to the perception among interventionists that patients with established CAD and greater cardiometabolic burden

would have more complex disease necessitating larger guides and advanced devices that cannot be accommodated through radial access.

Despite this selection bias, patients in the radial access group exhibited more severe CAD and received treatment accordingly, compared to the femoral access group. Importantly, the adjusted odds for in-hospital mortality, major bleeding events, and MACCE were worse in the transfemoral group compared to the transradial group. These findings suggest that operators should consider adopting the transradial approach in cases with a higher cardiometabolic burden, previous CABG, and PCI to CTO vessels. In summary, wider adoption of transradial access in CHiP procedures could potentially lead to improved outcomes.

9.2.3 Is the type of hospital catheter lab facility an important factor to ensure better outcome in a CHiP?

Chapter 8 was conceptualised to address whether surgical backup onsite is an important factor in ensuring better outcomes following a CHiP and whether it is safe to undertake CHiP in a non-surgical centre. The findings from this analysis did confirm that CHiP is commonly undertaken in a catheter lab facility with in-house surgical backup. However, CHiPs undertaken in non-surgical centres are increasing in number. Moreover, those cases undertaken in Non-surgical canters were, in fact, older by 2.4 years on average and had a higher prevalence of cardiometabolic burdens. There were significant differences in procedural characteristics in CHiP undertaken; for example, CHiPs in non-surgical centres were commonly undertaken via the radial access site and were more guided via imaging than in surgical centres. More importantly, after adjustment in baseline differences between the groups, CHiP clinical outcomes differed. In-hospital mortality and major bleeding events were lower in the non-surgical centres' groups by 30% compared to surgical centres' patients. Although MACCE was not different among the

groups. In summary, this analysis extended the growing body of evidence on the safety of selected types of CHiPs in non-surgical centres.

9.3 Clinical implications

The five studies conducted in this thesis provide crucial insights with profound implications for shaping contemporary clinical practices in the invasive management of stable ischaemic heart disease, particularly in the context of complex and high-risk percutaneous coronary interventions (CHiP). The research reveals distinctive patterns related to sex, ethnicity, age, procedural approaches, and organisational aspects of CHiP, offering valuable guidance for optimising decision-making and enhancing patient outcomes.

Chapter 4 underscores the necessity for sex-tailored approaches in CHiP, addressing disparities observed between male and female patients. By recognising the sex-specific risk profiles and employing strategies such as tailored pharmacotherapies and bleeding avoidance techniques, the study advocates for narrowing the existing sex gap in CHiP outcomes.

Chapter 5 challenges assumptions about ethnicity as a risk factor, emphasising that interventionists need not consider ethnicity as a decisive factor when evaluating the feasibility of CHiP procedures. Attention is directed towards minimising bleeding risks, particularly in white patients, through optimised procedural approaches.

Chapter 6 highlights age as a significant independent risk factor for adverse outcomes post-CHiP, emphasising the need for careful case selection and procedural approaches, especially in octogenarians. Despite an increase in CHiP procedures among octogenarians, mortality trends remained unchanged, showcasing the importance of age-conscious decision-making.

Chapter 7 advocates for the wider adoption of radial access in CHiP, demonstrating its association with improved outcomes, even in cases of more complex coronary artery disease. The study suggests that the benefits of radial access extend to higher-risk patients, potentially contributing to improved CHiP outcomes.

Lastly, Chapter 8 challenges the conventional belief in the necessity of in-house surgical backup for all CHiP procedures. The research indicates that selected CHiP procedures can be safely performed in non-surgical centres, challenging prevailing norms and urging a re-evaluation of international guidance on CHiP procedures.

In summary, the comprehensive findings from this CHiP thesis have far-reaching implications for clinical practice. By adopting sex-specific strategies, recognising age as a critical factor, embracing radial access, and reconsidering the need for in-house surgical backup, clinicians can enhance the overall care and outcomes for patients with stable ischaemic heart disease undergoing CHiP procedures. These insights pave the way for a more nuanced and tailored approach to invasive cardiac interventions, ultimately improving patient care in everyday clinical settings.

9.4 Future area for research

This thesis provides several important findings that can be used in future research. As detailed earlier, the thesis work is derived from a large national PCI registry (BCIS) dataset, which was used to investigate several aspects related to complex, high-risk PCIs undertaken as a part of the invasive management of patients with stable angina in England and Wales. The BCIS dataset is rich with information on patients' demographics, important cardiovascular risk factors and co-morbidities, pharmacological therapies used, and extensive procedural details, including CAD anatomy, which enabled the successful production of these analyses. However, the BCIS dataset lacks information on some important variables such as frailty index, haemoglobin level, and level of control for

certain co-morbidities like diabetes mellitus and hypertension. Moreover, longitudinal outcomes assessment was not possible as the BCIS dataset does not provide information on the same. This issue could be resolved by creating a longitudinal dataset via linking with electronic health records, which would also allow a detailed assessment of patients from admission to discharge from the hospital.

Moreover, sex, ethnicity, and age-stratified differences in characteristics and clinical outcomes were investigated in this thesis retrospectively, and to date, there are no randomised control trials looking at CHiP outcomes among the earlier mentioned groups of patients. These need to be considered, especially when looking at ways to improve and narrow the sex gap in in-hospital outcomes, in-hospital outcomes among octogenarians, and also when looking at long-term outcomes according to ethnicity.

Similarly, outcomes among CHiP undertaken via the radial access versus femoral have not been investigated in a randomised control way before. Addressing this research question may confirm our findings in this thesis, which in turn could offer stronger evidence-based guideline recommendations on the best procedural approach in CHiP, specifically in higher-risk CHiP factors, for example, CTO or left main interventions.

Also, until the date of writing this thesis, there is no clear expert consensus nor guideline recommendations on the types of CHiP that can be safely undertaken in non-surgical centres due to limitations of studies around the same. Therefore, future directions should focus on addressing the aforementioned questions and developing risk models that could facilitate interventionists in choosing the best strategy/procedural approach when undertaking complex, high-risk interventions in patients with stable ischaemic heart disease.

Furthermore, despite addressing a major gap in the evidence around CHiP in heart failure by The REVIVED trial, some questions remain unanswered; for example, can we do CHiP even more safely? Does elective LV unloading have a role in improving outcomes?

The PROTECT [251](Prospective Feasibility Trial Investigating the Use of the IMPELLA RECOVERLP 2.5 System in Patients Undergoing High Risk PCI) I trail investigated the safety and feasibility of use Impella 2.5 system in patients with poor ventricles with encouraging findings that led to the PROTECT II trial [252]that compared the Impella with IABP in CHiP patients with encouraging results favouring Impella use (Impella ,40.6% versus IABP, 49.3%, P=0.066).

Finally , future research around the use of intravascular imaging in the CHiP cohort could better inform operators about the safety and short- and long-term effectiveness of the same.

9.5 Ongoing RCT around CHiP

There are several ongoing trials that could greatly assist in answering many of the questions raised earlier; they are summarised here.

1- Controlled trial of High-risk coronary Intervention with Percutaneous left ventricular unloading (CHIP trial). This trial examines MACCE outcomes at 12 months between those patients with stable angina and complex CAD (un-protected LMS PCI, extensive calcifications, CTO lesion with planned retrograde approach). The cohort will be randomised to have PCI with or without LV mechanical support.

2- PROTECT [253] 3 and 4 trials that investigate the use of different types of LV mechanical assist device (Impella (R) 2.5, and Impella CP) in high-risk patients in complex CAD.

3- Many trials investigating IVUS-guided PCI versus angiography alone in CHIP patients such as the IMPROVE [254](Impact on revascularization outcomes of IVUS-guided treatment of complex lesions and economic impact) trial is a multicentre, single blinded ; the IVUS-CHIP [254]trial (Intravascular ultrasound guidance for complex high-risk indicated procedures) is an RCT, multicentre, international , event-driven trial; the OPTIMAL[254, 255] (Optimization of left main PCI with intravascular ultrasound), and the DK CRUSH VIII trial [256]that aims to assess the superiority of IVUS-guided PCI in bifurcation lesions. Similarly, the OCOBER trial [257](the European trial on optical coherence tomography optimized bifurcation event reduction) aims to assess the superiority of OCT guided PCI in treating LMS and non LMS bifurcation lesions.

9.6 Overall strength

This thesis provided a significant contribution to understanding various aspects related to complex high-risk indicated patients who need percutaneous coronary intervention to treat stable ischemic heart disease. Specifically, the thesis focused on investigating different aspects of PCI in special populations that are often underrepresented in randomised control trials and observational studies, as well as important procedural approaches that should have been systematically investigated in this patient cohort. The thesis also examined these aspects in different hospital settings.

The thesis reported on patients' demographic characteristics, cardiovascular risk factors, and important co-morbidities, as well as a variety of procedural approaches and their association with clinical outcomes in the context of PCI. Additionally, it highlighted how information obtained from a large national PCI registry dataset can be valuable in examining temporal trends in different aspects of PCI.

One of the strengths of this work lies in the extensive data derived from a national registry that covers nearly 95-99% of all PCI centres in the United Kingdom. The large size and inclusiveness of the dataset allowed for a comprehensive examination of PCI in real-world settings, particularly among populations that were less represented in prospective trials.

The results of this thesis confirmed existing evidence-based knowledge of PCIs in general and expanded it to include specific aspects of PCI in females, non-white ethnicities, and octogenarians. It provided insights into the baseline risk profiles and their association with clinical outcomes in these populations. Furthermore, the thesis explored the role of access approaches in CHiP's clinical outcomes and presented temporal trends in the utilisation of radial and femoral access sites. Lastly, the work's exploration of CHiPs undertaken in non-surgical centres is of interest to policymakers, as it provided novel information in an area that has been insufficiently covered by research studies and is therefore, not extensively addressed in the most current cardiology society guidelines on intervention.

9.7 Study limitations

The five studies' limitations were discussed in their respective chapters. However, this section will address the overall limitations that should be considered when interpreting each study's results.

As mentioned in Chapter 3, the five studies utilised prospectively collected data from the BCIS dataset, which made them observational in nature and resulted in retrospective cohort studies. While this design allowed for the examination of various factors that could impact CHiP outcomes, such as patients' characteristics, procedural factors, type of hospital facility, and trend analyses, the retrospective nature of the research made it

challenging to account for all unmeasured confounders when analysing primary and secondary clinical outcomes in each study. Therefore, we could not conclude a strict causal relationship between the gender type, age, ethnicity, access site used, and type of hospital facility and mortality, MACCE, and major bleeding events. The findings from the five studies should be considered as hypothesis-generating and serve as a foundation for future clinical trials.

Additionally, as mentioned in the limitations of each study, the measured clinical outcomes were limited to in-hospital events only. Long-term outcomes may differ from the observed in-hospital outcomes and could provide a more comprehensive assessment of the effects of certain factors on specific clinical outcomes. Moreover, the in-hospital complications were self-reported, and the results were not validated formally. This could potentially lead to underestimation or underreporting of the actual event rates. Lastly, considering the nature of data collection as part of a national audit rather than under strict observation in prospective controlled trials, the prospectively collected data in the dataset may be susceptible to reporting and coding errors. Consequently, the possibility of unmeasured confounders cannot be entirely ruled out.

In conclusion, while the five studies in this thesis have provided valuable insights, it is important to acknowledge these overall limitations and exercise caution when interpreting the results. Future research, including prospective clinical trials, is necessary to further validate and expand upon these findings.

9.8 Conclusion

In summary, this thesis has focused on a specific type of invasive management for stable ischaemic heart disease, namely complex, high-risk percutaneous coronary interventions.

It has examined trends, procedural characteristics, risk profiles, and associated clinical outcomes in special subsets of patients and according to specific procedural and hospital settings. The studies conducted within this thesis have revealed significant disparities in baseline clinical and procedural characteristics, risk profiles, and trends of CHiP in these unique circumstances.

The findings have demonstrated that females and the elderly population tend to experience worse clinical outcomes in the context of CHiP. However, ethnicity has shown no significant effect on clinical outcomes. Additionally, the use of transradial access has been associated with improved outcomes compared to femoral access. Moreover, the thesis has shown that performing CHiP in selected cases is safe when undertaken in non-surgical centres.

Overall, these results have important clinical implications for risk assessment and management strategies in specific patient populations. Furthermore, they emphasise the necessity for future research endeavours aimed at developing guidelines for the management of complex, high-risk PCI in patients with stable ischaemic heart disease.

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Chapter 10

10.1 Appendix 1: Acronyms

ACRONYM	FULL TEXT
ACS	Acute coronary syndrome
ATE	Average treatment effect
ACC	American College of Cardiology
BCIS	British Cardiovascular Interventional Society
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CHiP	Complex high risk percutaneous coronary interventions
CVA	Cerebrovascular accidents
CI	Confidence interval
DM	Diabetes mellitus
HTN	Hypertension
IABP	Intra-aortic Balloon pump
IHD	Ischaemic heart disease
IQR	Interquartile range
LV	Left ventricle
LMS	Left main stem artery
LAD	Left anterior descending artery
LCX	Left circumflex artery
MI	Myocardial infarction
MACCE	Major adverse cardiac and cerebrovascular events
NICOR	National Institute for Cardiovascular Research Outcomes
PVD	Peripheral vascular disease
PSM	Propensity score matching
PCI	Percutaneous coronary intervention
RCT	Randomised controlled trial
RCA	Right coronary artery
TRA	Trans radial access
TFA	Trans femoral access

10.2 Appendix 2 : Supplemental Tables

Supplemental Table 4.1
Missing data information of each variable included in the study

	Missing data, n	Percent missing, %
Age	0	0%
Sex	0	0%
Bleeding	0	0%
Death	0	0%
MACCE	0	0%
Prior CABG	3,111	2.2
Chronic Renal Failure	6,065	4.3
LV function	58,134	41
LMS PCI	2,507	1.8
CTO PCI	7,745	5.4
Severe coronary calcifications	25,563	18
Use of LV support	6,561	4.6
Hypertension	8,507	6
Dyslipidaemia	8,507	6
Diabetes	6,664	4.7
Smoking	18,507	13
Family history of CAD	19,987	14.1
History of MI	9,434	6.7
Previous PCI	3,872	2.7
Previous stroke	8,507	6
History of PVD	8,507	6
Warfarin	14,105	9.9
GPIIbIIIa inhibitors	10,412	7.4
Clopidogrel	14,105	9.9
Prasugrel	14,105	9.9
Ticagrelor	14,105	9.9
Vascular access	3,825	2.7
Number of treated lesions	1,463	1
Procedural devices	25,563	18
Number of stents used	1,253	0.8
Target Vessel PCI	2,507	1.7
Number of target vessel PCI	1,627	1.2

Variables with missing observations. Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CTO, chronic total occlusion; GPIIbIIIa, glycoprotein IIaIIIb; LV, left ventricle; LMS, left main stem; LCX, left circumflex; MACCE, major cardiovascular and cerebral events.; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery.

Supplemental Table 5.1

Missing observations of baseline clinical and procedural characteristics of patients who underwent CHiP for stable CAD.

Variable's name	Missing data, n	Percent missing, %
Ethnicity	0	0%
Age	0	0%
Sex	0	0%
Bleeding	0	0%
Death	0	0%
MACCE	0	0%
Prior CABG	1,797	1.7
Chronic Renal Failure	3,852	3.6
LV function	43,746	41.3
LMS PCI	1,949	1.8
CTO PCI	5,764	5.4
Severe vascular calcifications	16,418	15.5
Use of LV support	4,332	4.1
Hypertension	5,574	5.3
Hypercholesterolaemia	5,574	5.3
Diabetes mellitus	4,882	4.2
Smoking history	13,307	12.7
Family history of CAD	12,955	12.3
History of MI	5,579	5.3
Previous PCI	2,229	2.1
Previous stroke	5,574	5.3
History of PVD	5,574	5.3
Warfarin	11,032	10.4
GPIIbIIIa inhibitors	7,778	7.3
Clopidogrel	11,032	10.4
Prasugrel	11,032	10.4
Ticagrelor	11,032	10.4
Vascular access	2,516	2.4
Number of treated coronary narrowing	1,196	1.1
Procedural devices	16,418	16
Number of stents used	943	0.9
Target Vessel PCI	1,949	1.8
Number of target vessel PCI	911	0.9

Variables with missing observations. Abbreviations: CHiP, complex high risk percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease; CTO, chronic total occlusion; GPIIbIIIa, glycoprotein IIaIIIb; LV, left ventricle; LMS, left main stem; MACCE, major cardiovascular and cerebral events.; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

Supplemental Table 6.1:

Variables with missing observations of stable angina cases who underwent a CHiP procedure.

Variable name	*Number of observations*	*Missing observations*	*Percent of missing observations*
Age	*138,831*	*0*	*0%*
sex	*138,831*	*0*	*0%*
Death	*138,831*	*0*	*0%*
MACCE	*138,831*	*0*	*0%*
Major bleeding	*138,831*	*0*	*0%*
Race	*103,543*	*35,288*	*25.4%*
BMI	*97,697*	*41,134*	*42.1%*
Prior CABG	*135,746*	*3,085*	*2.2%*
Chronic Renal Failure	*132,830*	*6,001*	*4.3%*
Poor LV function	*83,015*	*55,816*	*40.2%*
LMS PCI	*136,508*	*2,323*	*1.6%*
CTO PCI	*131,142*	*7,689*	*5.5%*
Severe vascular calcifications	*113,333*	*25,498*	*18.4%*
Use of LV support	*132,319*	*6,512*	*4.7%*
Hypertension	*130,406*	*8,425*	*6.1%*
Hypercholesterolaemia	*130,406*	*8,425*	*6.1%*
Diabetes	*132,248*	*6,583*	*4.7%*
Smoking	*120,463*	*18,368*	*13.2%*
Family history of CAD	*118,997*	*19,834*	*14.2%*
History of MI	*129,468*	*9,363*	*6.7%*
Previous PCI	*135,035*	*3,796*	*2.7%*
Previous stroke	*130,406*	*8,425*	*6.7*
History of PVD	*130,406*	*8,425*	*6.7*
Warfarin	*124,818*	*14,013*	*10.1%*
GPIIbIIIa inhibitors	*128,499*	*10,332*	*7.4%*
Clopidogrel	*124,818*	*14,013*	*10.1%*
Prasugrel	*124,818*	*14,013*	*10.1%*
Ticagrelor	*124,818*	*14,013*	*10.1%*
Vascular access	*135,229*	*3,602*	*2.5%*
Number of successful treated lesions	*108,003*	*30,828*	*22.2%*
Procedural devices	*113,333*	*25,498*	*18.3%*
Number of stents used	*137,601*	*1,230*	*0.9%*
LAD	*136,508*	*2,323*	*1.7%*

LCX	*136,508*	*2,323*	*1.7%*
RCA	*136,508*	*2,323*	*1.7%*
Graft	*136,508*	*2,323*	*1.7%*
Number of target vessel PCI	*137,368*	*1,463*	*1.1%*

Abbreviations: CHiP, complex high risk percutaneous coronary intervention; CABG, coronary artery bypass graft; CTO, chronic total occlusion; CAD, coronary artery disease; GPIIbIIIa, glycoprotein IIaIIIb; LV, left ventricle; LMS, left main stem; LCX, left circumflex; MI, myocardial infarction; MACCE, major cardiovascular and cerebral events; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery.

Supplemental Table 7.1
Missing observations of baseline clinical and procedural characteristics of patients who underwent CHiP for stable CAD.

Variable's name	Missing data, n	Percent missing, %
Access	0	0%
Age	0	0%
Sex	0	0%
Bleeding	0	0%
Death	0	0%
MACCE	0	0%
Race	30,612	24.4
Prior CABG	2,780	2.2
Chronic Renal Failure	5,441	4.3
LV function	52,465	41.7
LMS PCI	2,280	1.8
CTO PCI	7,159	5.7
Severe coronary calcifications	21,837	15.5
Use of LV support	4,332	4.41
Hypertension	7,550	6.0
Hypercholesterolaemia	7,550	6.0
Diabetes	6,133	4.9
Smoking	16,717	12.7
Family history of CAD	12,955	13.3
History of MI	8,850	7.0
Previous PCI	3,479	2.7
Previous stroke	7,550	6.0
History of PVD	7,550	6.0
Warfarin	12,210	9.7
GPIIbIIIa inhibitors	9,083	7.2
Clopidogrel	12,210	9.7

Prasugrel	12,210	9.7
Ticagrelor	12,210	9.7
Number of treated lesions	1,298	1.0
Vascular imaging	21,214	16.9
Stent size	25,883	20.6
Stent length	23,162	18.4
Procedural devices	21,837	17.4
Number of stents used	686	0.6
Target Vessel PCI	2,280	1.8
Number of target vessel PCI	3,696	2.9

Abbreviations: CHiP, complex high risk percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease; CTO, chronic total occlusion; GPIIbIIIa, glycoprotein IIaIIIb; LV, left ventricle; LMS, left main stem; LCX, left circumflex; MACCE, major cardiovascular and cerebral events.; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery.

Supplemental table 8.1

Missing observations of baseline clinical and procedural characteristics of patients who underwent CHiP for stable CAD.

Variable's name	Missing data, n	Percent missing, %
Type of surgical cover	0	0%
Age	0	0%
Sex	0	0%
Bleeding	0	0%
Death	0	0%
MACCE	0	0%
access	3,637	2.8%
Race	32,346	25.2%
Prior CABG	3,108	2.2%
Chronic Renal Failure	6,059	4.3%
LV function	58,112	41.8%
LMS PCI	2,507	1.7%
CTO PCI	7,745	5.5%

Severe coronary calcifications	25,428	17.9%
Use of LV support	6,555	4.6%
Hypertension	8,492	6.0%
Hypercholesterolaemia	8,492	6.0%
Diabetes	6,652	4.7%
Smoking	18,503	13.8%
Family history of CAD	19,981	14.1%
History of MI	9,430	6.7%
Previous PCI	3,867	2.7%
Previous stroke	8,492	6.0%
History of PVD	8,492	6.0%
Warfarin	13,984	9.9%
GPIIbIIIa inhibitors	10,412	7.4%
Clopidogrel	13,984	9.9%
Prasugrel	13,984	9.9%
Ticagrelor	13,984	9.9%
Number of treated lesions	1,627	1.2%
Vascular imaging	23,288	16.5%
Stent size	30,199	21.3%
Stent length	27,342	19.3%
Procedural devices	25,428	17.9%
Number of stents used	1,253	0.8%
Target Vessel PCI	1,461	1.3%
Number of target vessel PCI	3,696	2.9

Variables with missing observations. Abbreviations: CHiP, complex high risk percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease; CTO, chronic total occlusion; GPIIbIIIa, glycoprotein IIaIIIb; LV, left ventricle; LMS, left main stem; LCX, left circumflex; MACCE, major cardiovascular and cerebral events.; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery.

10.3 Appendix 3: Thesis related publications and certificates of abstract presentations

CERTIFICATE FOR TCT 2021

ABSTRACT PRESENTER

We hereby certify that

Warkaa Shamkhani

has presented the Abstract entitled

Is There a Difference in the Types of Complex High-risk but Indicated Percutaneous Coronary Interventions (CHIP) Undertaken and Their Outcomes Among Different Racial Groups? Insights From a National Cohort.

Transcatheter Cardiovascular Therapeutics (TCT) 2021

at the Orange County Convention Center on November 4–6, 2021.

Juan F. Granada, MD
President and Chief Executive Officer
Cardiovascular Research Foundation
on Behalf of the Program Leadership

Course Directors
George D. Dangas, MD, PhD
Juan F. Granada, MD
Ajay J. Kirtane, MD
Martin B. Leon, MD
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Gary S. Mintz, MD
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Gregg W. Stone, MD

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was used in 905 cases (45.2%), subintimal tracking and re-entry (STAR) in 333 cases (16.6%), and contrast-guided STAR in 29 cases (1.4%). The mean patient age was 64.2 ± 10 years, 86% were men, and 34.9% had prior coronary artery bypass graft surgery. Cases in which LAST was used were less complex with a lower J-CTO score (2.50 ± 1.32 vs. 2.95 ± 1.10, $P < 0.001$). There was no difference in technical (75.0% vs 78.4%, $P = 0.337$) and procedural success (72.2% vs 75.5%, $P = 0.384$) and major cardiac adverse events (MACEs) (2.08% vs 3.55%, $P = 0.352$) between LAST and non-LAST cases. However, cases in which the LAST technique was used required less procedure and fluoroscopy time (Figure 1A). A primary LAST technique was associated with higher technical and procedural success rates and a similar MACE rate compared with a secondary LAST technique (Figure 1B).

CONCLUSION LAST is used in 7.2% of ADR CTO PCI cases and is associated with similar technical and procedural success rates and major complication rates but lower procedural and fluoroscopy time compared with ADR cases that did not use LAST.

CATEGORIES CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

TCT-320

Pharmacokinetic and Pharmacodynamic Profile of PL-ASA, a Novel Phospholipid-Aspirin Complex Liquid Formulation, Compared to Enteric-Coated Aspirin at an 81-mg Dose – Results From a Prospective, Randomized, Crossover Study

Francesco Franchi,[1] David Schneider,[2] Jayne Prats,[3] Weihong Fan,[4] Fabiana Rollini,[1] Lanonya Been,[5] Heidi Taatjes-Sommer,[6] Efthymios Deliargyris,[7] Dominick Angiolillo[6]
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BACKGROUND Immediate-release (IR) aspirin (ASA) is associated with a risk of mucosal damage in the upper gastrointestinal (GI) tract. Enteric-coated (EC) ASA was designed to reduce GI discomfort and bleeding and is the established standard of care in secondary prevention. However, there is evidence that EC-ASA results in greater variability in absorption and antiplatelet effect than IR-ASA. PL-ASA, a novel Food and Drug Administration-approved, liquid-filled phospholipid ASA capsule, is an IR formulation designed to release aspirin in the duodenum, thus limiting GI toxicity, while still providing fast and complete drug absorption and potent and reliable cyclo-oxygenase-1 inhibition. Previous studies have compared the 325-mg dose of PL-ASA with IR-ASA and EC-ASA, and the current study is the first to investigate the 81-mg dose, which is most commonly used in clinical practice.

METHODS The current study is a randomized, open-label, crossover study assessing the comparative pharmacodynamic (PD) and pharmacokinetic (PK) profiles following treatment with a single 81-mg dose of PL-ASA versus EC-ASA under fasting conditions in subjects (n = 36) between 50 and 75 years of age. Subjects are randomly assigned at a 1:1 ratio to either PL-ASA followed by EC-ASA or EC-ASA followed by PL-ASA with a 14-day washout period between the 2 study drugs. Following each study drug administration, blood draws for PK and PD, including thromboxane B2 (TxB2), and platelet aggregation assessments are performed at multiple time points up to 24 hours. PK parameters of acetylsalicylic acid and salicylic acid will be compared. PD assessments will include the comparison between PL-ASA and EC aspirin of the time to 99% inhibition of serum TxB2, incidence of ≥99% inhibition of TxB2, and platelet aggregation following arachidonic acid and collagen stimuli.

RESULTS The study is currently recruiting, and results will be presented at the meeting.

CONCLUSION The current study will provide data on the comparative PK and PD profiles of PL-ASA, a novel IR-ASA capsule formulation, versus commonly used EC-ASA at an 81-mg dose.

CATEGORIES CORONARY: Pharmacology/Pharmacotherapy

TCT-321

Abstract Withdrawn

TCT-322

Prevention of Radial Artery Occlusion After Transradial Access Using Nitroglycerin (Patens Trial)

Roberto Léo da Silva,[1] Rodrigo Joaquim,[1] Pedro Beraldo,[2] Alexandre Abizaid,[3] Ramiro Vieira,[1] Vanderlei Pereira, Jr.,[2] Renata Viana,[3] Amanda Sousa,[3] Fausto Feres,[3] Jose Costa, Jr.[3]
[1]Instituto de Cardiologia de Santa Catarina, São José, Santa Catarina, Brazil; [2]Santa Casa de Misericórdia, Marilia, São Paulo, Brazil; [3]Instituto Dante Pazzanese de Cardiologia, São Paulo, São Paulo, Brazil

BACKGROUND The use of transradial access (TRA) for coronary catheterization has increased over the years because of the reduced rates of vascular complications and easier postprocedural management. Radial artery occlusion (RAO) remains the Achilles heel of TRA. Intra-arterial nitroglycerin could result in a significant reduction of RAO. The vasodilation may enhance antegrade flow in the artery that reduces stasis-induced thrombosis, but it could also minimize endothelial trauma when used early in the procedure. The main objective of this study is to evaluate whether nitroglycerin at the beginning or end of TRA may preserve the patency of the artery.

METHODS We conducted a prospective, multicenter, randomized, 2 × 2 factorial, placebo-controlled, 2-blinded study and enrolled patients submitted to catheterization by TRA. Patients received either 500 µg nitroglycerin or placebo given intra-arterially through the sheath at 2 moments: early, after sheath insertion, and late, at the end of the radial procedure. All patients received at least 5,000 UI heparin, sheaths were removed immediately after the catheterization, and a radial pneumatic wristband was applied intending patent or minimum pressure hemostasis. The primary outcome was the incidence of RAO, verified by Doppler evaluation within the first 24 hours, and every patient with confirmed RAO was further evaluated 30 days later.

RESULTS A total of 1,894 patients were enrolled, with a mean age of 61.7 ± 10.3 years. The majority (61.6%) were male, and 36.5% had diabetes. The clinical indication was ACS in 47.9%. RAO occurred in 49 patients (2.6%) by Doppler evaluation. Fifteen patients (30.6%) showed re-establishment of flow at 30-day Doppler assessment. Nitroglycerin, as compared with placebo, did not reduce the risk of RAO in either of the 2 moments used (early: 2.4% vs 2.8%, $P = 0.65$ or late: 2.8% vs 2.4%, $P = 0.65$, respectively). In the multivariate analysis, the size of the radial artery, obtaining access with a single puncture, operator inexperience, and the presence of spasm were associated with RAO.

CONCLUSION In the present study, the use of nitroglycerin is not associated with a reduced incidence of RAO regardless of the administration time.

CATEGORIES OTHER: Vascular Access: Coronary

TCT-323

Is There a Difference in the Types of Complex High-Risk but Indicated Percutaneous Coronary Interventions (CHIP) Undertaken and Their Outcomes Among Different Racial Groups? Insights From a National Cohort

Warkaa Shamkhani,[1] Tim Kinnaird,[2] Harindra Wijeysundera,[3] Peter Ludman,[4] Muhammad Rashid,[5] Mamas Mamas[1]
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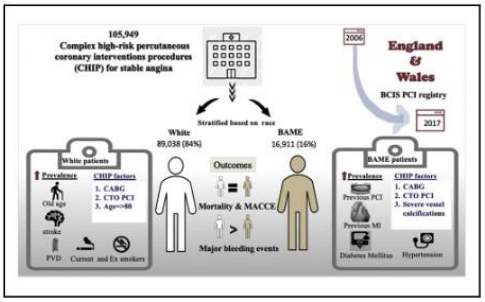
BACKGROUND In contemporary practice, complex high-risk but indicated percutaneous coronary intervention (CHIP) is increasingly common. Data on race-based differences in the nature of CHIP and their clinical outcomes in patients with stable coronary artery disease (CAD) are limited.

METHODS We obtained data on percutaneous coronary intervention (PCI) for stable CAD performed in England and Wales from January 1, 2006, to December 31, 2017, from the British Cardiovascular Intervention Society (BCIS) registry. The collected data were retrospectively analyzed and stratified by race. Multivariate regression analysis was performed to assess the relationship between CHIP, race, and outcomes.

RESULTS Of a total of 424,290 procedure records in the BCIS registry, 105,949 (24.97%) were CHIP; 89,038 (84%) were performed in White and 16,911 (16%) in Black, Asian, and minority ethnic (BAME) patients (Figure 1). BAME patients were younger (median: 68.1 years vs 70.6 years). A previous coronary artery bypass graft was the commonest CHIP factor in both White and BAME patients (33.4% vs 38.3%, respectively; $P < 0.001$) followed by chronic total occlusion (CTO) PCI (31.9% vs 32%, respectively; $P = 0.769$). The third common CHIP factor was age above 80 (23.6%) in the Whites and severe vessel calcification in BAME patients (18.8%). BAME patients had significantly higher rates of diabetes (41.1% vs 23.6%, respectively; $P < 0.001$), hypertension (68% vs 66.5%, $P < 0.001$), previous PCI (43.7% vs 37.6%, $P < 0.001$), and previous myocardial infarction (44.9% vs 42.5%, $P < 0.001$) compared with White patients. Mortality (adjusted odds ratio [aOR]: 1.07; 95% confidence interval [CI]: 0.8-1.5; $P = 0.659$) and major adverse cardiovascular and cerebral event (MACCE) (aOR: 0.9; 95% CI: 0.8-1.1; $P = 0.564$) risks were similar among races, although the bleeding risk (aOR: 0.69; 95% CI: 0.6-0.9; $P = 0.002$) was lower.



CONCLUSION In this large national analysis of CHIP procedures, BAME patients were younger and had worse cardiometabolic risk profiles. There were race-based differences in the type of CHIP procedures. BAME patients had 30% fewer odds for bleeding and similar odds of death and MACCEs to those of their White counterparts.

CATEGORIES CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

TCT-324

Features and Outcomes of Transcatheter Aortic Valve Replacements for Small Aortic Valve Annuli

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BACKGROUND Transcatheter aortic valve replacement (TAVR) in a small annulus may cause patient prosthesis mismatch (PPM), and data on the outcomes of small annulus TAVR are limited. This study aimed to 1) report the prevalence, features, and outcomes of small annulus TAVR and 2) compare the efficacy and safety of the 2 widely used TAVR valves in this patient population.

METHODS All patients treated with TAVR between June 2015 and June 2018 at 21 TAVR centers in Korea were analyzed from the Korean TAVR registry. The primary outcome was procedure-related complications and the major adverse cardiac outcome. The secondary outcome was aortic regurgitation (AR), paravalvular AR, effective orifice area (EOA) index, and PPM. We compared outcomes of 1) small annulus (annular diameter < 20 mm) and nonsmall annulus valves and 2) balloon-expandable valves (BEVs) and self-expandable valves (SEVs) among patients with small annulus valves.

RESULTS Among the total 660 patients, 70 patients had a small annulus with a mean annular diameter of 18.7 mm, whereas the mean diameter of the nonsmall annulus was 23.4 mm (Table 1). Both groups had similar complication rates (8.6% vs 6.6%, $P = 0.71$) and similar clinical outcomes at 1 year with 10.0% and 14.4% MACEs, respectively ($P = 0.41$). The small annulus group showed lower EOA index at 1 month than the nonsmall annulus group (0.99 cm^2/m^2 vs 1.11 cm^2/m^2, $P < 0.01$) and a higher PPM rate (moderate 25.0%, severe 8.2% vs moderate 17.3%, severe 1.9%, $P < 0.01$), whereas the gap narrowed at 1 year. BEVs and SEVs had similar complication rates (7.4% vs 9.8%, $P = 1.00$) and similar 1-year MACEs (18.5% vs 4.9%, $P = 0.16$). The EOA index was significantly greater with SEVs at 1 month, but the difference was not significant at 1 year. The risk of PPM also did not differ significantly. AR or paravalvular AR showed no difference.

	Small Annulus (n = 70)	Nonsmall Annulus (n = 590)	*P* Value
Mean annular diameter	18.7 mm	23.4 mm	0.00
Age, years	78.3 ± 5.3	78.6 ± 6.8	0.63
Sex, female	56 (80.0%)	276 (46.8%)	**0.00**
Procedure-related complications	6 (8.6%)	39 (6.6%)	0.71
1-month EOA index (cm^2/m^2)	0.99 ± 0.25	1.11 ± 0.32	**0.01**
1-month moderate to severe PPM rate	33.3%	19.2%	**0.01**
1-year EOA index (cm2/m2)	1.04 ± 0.24	1.09 ± 0.03	0.27
1 year moderate to severe PPM rate	22.9%	19.9%	0.72
1 year MACE	7 (10.0%)	85 (14.4%)	0.41

CONCLUSION Small annulus TAVR with an annulus diameter less than 20 mm had favorable short-term clinical outcomes. BEVs and SEVs showed similar complication rates and clinical outcomes during at least the 1-year follow-up period.

CATEGORIES STRUCTURAL: Valvular Disease: Aortic

TCT-325

Ultra-Short-Term Evaluation of Coronary Vessel Wall Changes in Reference Segments Adjacent to Culprit Lesions in ST-Segment Elevation Myocardial Infarction

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BACKGROUND Culprit lesions of ST-segment elevation myocardial infarction (STEMI) patients are friable, soft, and prone to disruption during primary percutaneous coronary intervention (pPCI). The presence of dissections in the reference vessel segment (RVS), adjacent to stented culprit lesions, and dynamic luminal changes in proximal or distal RVS have not yet been investigated. Therefore, we sought to assess the healing patterns of edge dissections and the changes of the lumen area at the RVS within 1 week after stent implantation in patients with STEMI.

METHODS In the MATRIX trial (ClinicalTrials.gov, NCT01433627), optical coherence tomography (OCT) was performed at the end of pPCI and within 1 week during staged PCI. The dissection in RVS was defined as follows: type 1, flap; type 2, cavity; type 3, double barrel; and type 4, fissure. We compared separately the fate of residual dissection and luminal area/dimension by OCT in the target vessel between primary and staged PCI, including 1-year clinical outcomes.

RESULTS Of 151 patients, 46 patients had dissections in 50 RVSs and did not experience a worse clinical outcome. Forty-four percent of dissections were type 1, 28% type 2, 16% type 4, and 12% type 3. Overall, 18% of the dissections healed. The mean lumen area of the RVS enlarged in 82 patients (59%) from pPCI to staged PCI. Compared with the proximal RVS, there was a significant increase in the lumen diameter at the distal RVS (0.06 ± 0.25 mm vs −0.01 ± 0.21 mm, $P = 0.01$).

CONCLUSION Dissections occur frequently after pPCI in STEMI, one fifth of them heal within 1 week and do not seem to negatively impact on clinical outcomes. The distal RVS lumen area increased compared with the proximal RVS, likely reflecting a different vasoconstriction pattern over time.

CATEGORIES CORONARY: Acute Myocardial Infarction

ACC.23 TOGETHER WITH WCC

1041
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Volume 81, Issue 8, suppl A

Interventional and Structural

COMPLEX HIGH-RISK PERCUTANEOUS CORONARY INTERVENTION TYPES, TRENDS, AND OUTCOMES IN NON-SURGICAL CENTRES

Poster Contributions
Poster Hall_Hall F
Sunday, March 5, 2023, 2:45 p.m.-3:30 p.m.

Session Title: Interventional and Structural: Complex Coronary Interventions, including CTO 13
Abstract Category: 17. Interventional and Structural: Complex Coronary Interventions, including CTO
Presentation Number: 1623-010

Authors: Warkaa Shamkhani, Muhammad Rashid, Saadiq Moledina, Peter Ludman, Nick Curzen, Harindra Wijeysundera, Cindy L. Grines, Mamas A. Mamas, Keele University, Stoke-on-Trent, United Kingdom, Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom

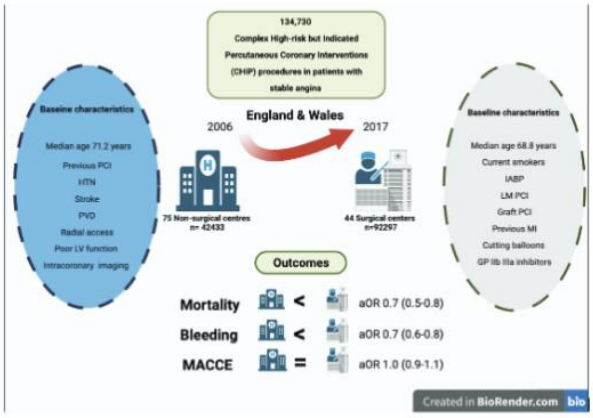
Background: Data on Complex, High-risk Percutaneous coronary intervention (CHiP) trends and outcomes in non-surgical centres (NSC) are limited.

Methods: This is a retrospective cohort study using data from a national PCI registry on all records of CHiP undertaken in patients with stable angina (2006-2017), according to the presence or absence of on-site surgical cover.

Results: Out of 134,730 CHiP procedures, 42,433 (31.5 %) were undertaken in NSCs, increasing from 12.5% in 2006 to 42% in 2017. Compared with onsite surgical centres (SCs), NSCs patients were 2.4 years older, and had a greater prevalence of cardiovascular risks. CHiP procedures least commonly performed in the NSCs included those required the elective use of circulatory support devices (23.9%), treatment for severe vascular calcifications (24.8%), and left main PCI (29.7%). CHiPs undertaken in NSCs were commonly performed via radial access (58%), and used intracoronary imaging guidance more than SCs (15.1 vs 10.8 %, respectively; p<0.001). CHiP undertaken in NSCs independently associated with lower odds for mortality (aOR: 0.7 (0.5-0.8)) and major bleeding (aOR: 0.7 (0.6-0.8)). MACCE odds were similar between the groups (aOR: 1.0 (0.9-1.1).

Conclusion: CHiP numbers in NSCs have gradually increased. NSCs patients were older and had a higher prevalence of cardiovascular risks. Mortality and major bleeding odds were significantly lower in those cases undertaken in NSCs, although MACCE odds were not different between the groups.

Graphical Abstract summarises the CHiP analysis's key findings according to the type of surgical cover.



Abbreviations: CHiP, complex high-risk but indicated percutaneous coronary interventions; GP, glycoprotein; HTN, hypertension; IABP; intra-aortic balloon pump; LM, left main; LV, left ventricle; MI, myocardial infarction; PCI percutaneous coronary intervention; PVD, peripheral vascular disease.

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ORIGINAL STUDIES

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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 percutaneous coronary intervention (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 January 1, 2006, and December 31, 2017, were included. All procedures were stratified by sex. Multivariate logistic regression analyses were performed to investigate the sex-specific adjusted 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 vs. 69.1 years). Males had a higher prevalence of previous myocardial infarction (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 >BO (35.4%), followed by prior coronary artery bypass graft (CABG) (24.3%) and severe coronary calcification (22.6%). In contrast, the most common variable in male patients was prior CABG (36%), followed by chronic thrombus occlusion (CTO) PCI (34.4%) and severe coronary calcification (22%). Females had higher odds (aOR) for mortality (aOR: 1.78, 95% CI: (1.4, 2.21), 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.

KEYWORDS

complex PCI, high-risk PCI, sex, stable angina

Abbreviilltiom;: BOS, British Cardiovascular Intervention Sacicty| CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CHiP, complex high·risk but indicated pcrcu·taneous coron.11ry interventioos: LMS, left m.11in stem; MACCE, major .advcrse cardiovascular and cerebral cvenU; NICOR. National Institute of Cardiovascular Outcomcs and Research: PCI, perculaneoul.i.coronary intervention.

Muhammad Rashid and Mamas A. Mamas are joint senior authors.

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1 | 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 left ventricle (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 hemodynamic 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 noncomplex-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-center 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 among 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.

2 | METHODS

2.1 | Data source

Data were obtained and analyzed from the 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% of 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 data set 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 have been previously ascertained.[16]

2.2 | Study design and definitions

We analyzed all patients who underwent PCI for stable angina in England and Wales between January 1, 2006, to December 31, 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 data set. 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 intra-aortic balloon pump (IABP) or Impella.

2.3 | Study endpoints

The primary outcome of interest was in-hospital all-cause mortality. The secondary outcomes included (a) in-hospital major cardiovascular and cerebral events (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 (MI), non-Q-wave MI, 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]

2.4 | 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 χ^2 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 Table S1. 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 was used in the multiple imputation framework. The variables included in the model were age, body mass index (BMI), history of dyslipidemia, smoking history, previous acute MI, previous CABG, previous ischemic heart disease, previous PCI, 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 data set, and results were pooled using Rubin's rule.[21] Finally, multivariable logistic regression analyses were used to determine the adjusted odds ratios (aORs [95% confidence interval {CI}]) 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 the 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.[23–25] All models included the same variables as used in the multiple imputation framework.

3 | RESULTS

3.1 | 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

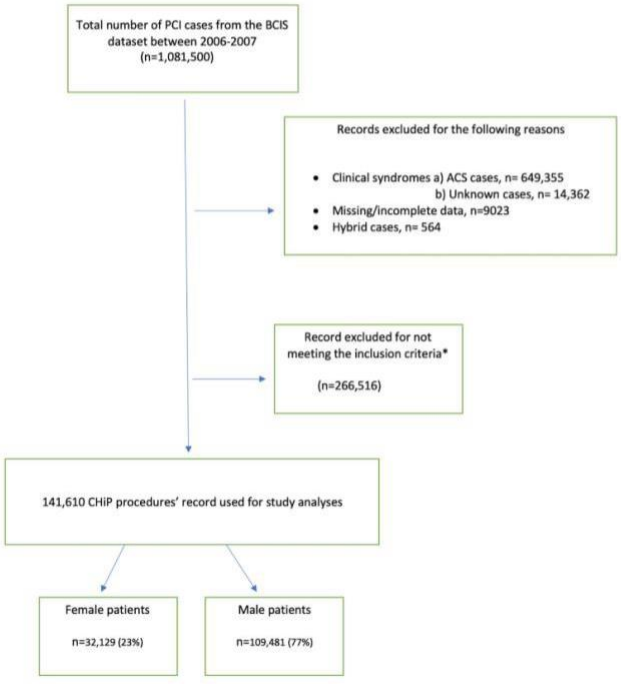

FIGURE 1 Flow diagram illustrating the process of patients' inclusion and exclusion for the complex high-risk but indicated percutaneous coronary interventions (CHiP) analysis Color figure can be viewed at wileyonlinelibrary.com]

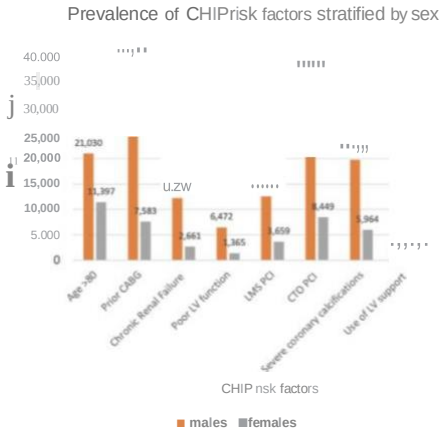

FIGURE 2 Prevalence of complex high-risk but indicated percutaneous coronary interventions (CHiP) factors in patients with stable angina, stratified by sex Color figure can be viewed at wileyonlinelibrary.com)

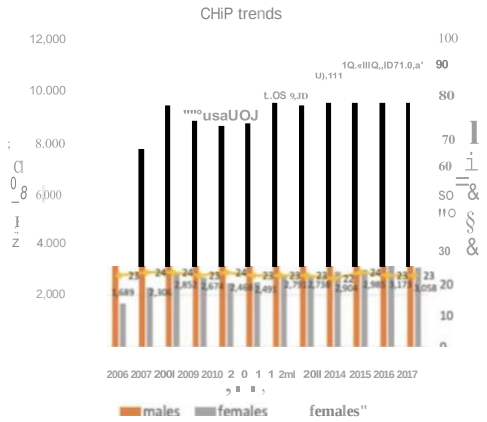

FIGURE 3 Temporal changes in complex high-risk but indicated percutaneous coronary interventions (CHiP) procedures prevalence in patient with stable angina and percent changes over time. stratified by sex Color figure can be viewed at wileyonlinelibrary.com)

cases prevalence are illustrated in Figure 3, where CHiP increased from 7525 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.

3.2 Clinical characteristics

Table 1 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 fac**tors, hypertension was more prevalent in females than males (69 vs**. 64.4%, respectively, $p < 0.001$) and females were more likely to be nonsmokers (56 vs. 37%, respectively, $p < 0.001$). Males. compared to females. had a higher prevalence of previous history of 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.

3.3 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%). While in males. they were prior CABG (36%), CTO PCI (34.4%), and severe coronary calcification (22%) (Table 1, Figure 3). More females than males were 80 years of age or older (35.4 vs. 19.2%, respectively, $p < 0.001$); In contras 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 left main stem (LMS) PCI and use of LV support were observed in the two groups.

Figure S1 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 remains unchanged except of those cases with LMS PCI and CTO PCI. There was a gradual increase in the percentage of females undergoing LMS PCI (2006: 10% vs. 2017: 15%; and a gra**dual decrease in the percentage of cases undergoing PCI to a CTO** vessel (2006: 42% vs. 2017; 29%).

3.4 Procedural characteristics

Differences in procedural characteristics were observed between the sexes. Females, compared to males, had higher rates of left anterior descending artery PCI (44 vs. 40%, respectively, $p < 0.001$) and RCA

TABLE 1 Baseline clinical and procedural characteristics of patients with stable angina undergoing CHiP, stratified by sex

	Total, *n*	Males, *n* (%)	Females, *n* (%)	*p* value
Number of participants	141,610	109,481 (77)	32,129 (23)	
Age median, (IQR)	70.5 (61.9–79.6)	69.1 (60.7–77.5)	75.1 (65.8–81.8)	
BMI median, (IQR)		28 (25.4–31.34)	27(24.7–32)	
Weight <60 kg) *n*, (%)		1580 (1.4%)	4515 (14.1%)	
CHiP risk factors				
(a) Patients' factors				
• Age >80	32,427 (23)	21,030 (19.2)	11,397 (35.4)	<0.001
• Prior CABG	46,299 (33.4)	38,716 (36)	7583 (24.3)	<0.001
• Chronic renal failure	14,895 (11)	12,234 (11.7)	2661 (9)	<0.001
• Poor LV function	7837 (9.4)	6472 (10)	1365 (7.3)	<0.001
(b) Procedural factors				
• LMS PCI	16,220 (12.4)	12,561 (11,7)	3659 (11.6)	0.694
• CTO PCI	44,184 (33)	35,735 (34.4)	8449 (21.1)	<0.001
• Severe coronary calcifications	25,743 (22.2)	19,779 (22)	5964 (22.6)	0.035
• Use of LV support	768 (0.57)	573 (0.55)	195 (0.64)	0.064
Cardiovascular risk factors				
• Hypertension	87,128 (65.5)	66,206 (64.4)	20,922 (69)	<0.001
• Dyslipidaemia	85,949 (64.6)	66,547 (64.7)	19,402 (64)	0.081
• Diabetes	35,091 (26)	27,409 (26.3)	7682 (25)	<0.001
• Smoking				<0.001
Never	51,224 (41.6)	35,492 (37)	15,732 (56)	
Ex-smokers	60,046 (48.8)	50,254 (52.8)	9792 (35)	
Current smokers	11,833 (9.6)	9401 (9.9)	2432 (8.7)	
• Family history of CAD	52,183 (46.7)	43,784 (46.6)	13,040 (47.2)	0.054
• History of MI	56,294 (42.6)	45,602 (44.6)	10,692 (35.6)	<0.001
• Previous PCI	48,763 (38.2)	39,201 (40)	9562 (32.5)	<0.001
• Previous stroke	6300 (4.7)	4820 (4.7)	1480 (4.9)	0.135
• History of PVD	9175 (6.9)	7244 (7)	1931 (6.4)	<0.001
• LV systolic function				<0.001
Normal (EF > 50)	58,589 (70.2)	44,366 (68.6)	14,223 (76)	
Impaired (EF: 30–50)	17,050 (20.4)	13,845 (21.4)	3205 (17)	
Severe (EF < 30)	7837 (9.4)	6472 (10)	1365 (7)	
Pharmacology				
• Warfarin	2742 (2.2)	2201 (2.3)	541 (1.9)	<0.001
• GPIIbIIIa inhibitors	9935 (7.8)	9935 (8)	2014 (7)	<0.001
• Prasugrel	1144 (0.9)	929 (0.9)	215 (0.7)	0.002
• Ticagrelor	4488 (3.5)	3548 (3.6)	940 (3.3)	0.005

(Continues)

TABLE 1 (Continued)

	Total, *n*	Males, *n* (%)	Females, *n* (%)	*p* value
Vascular access				<0.001
• Radial	61,825 (45)	48,525 (46)	13,300 (43)	
• Femoral	63,837 (46)	48,261 (45)	15,576 (49)	
• Multiple accesses	12,123 (9)	9754 (9)	2369 (8)	
Circulatory support				
• No support	134,281 (99.43)	103,953 (99.46)	30,328 (99.37)	0.564
• IABP	714 (0.53)	528 (0.5)	186 (0.6)	0.027
• Impella	57 (0.04)	47 (0.04)	10 (0.03)	0.361
Number of treated lesions				<0.001
• One	90,039 (64.4)	69,167 (63.8)	20,872 (65.9)	
• Two	35,136 (25)	27,387 (25.3)	7749 (24.5)	
• Three	14,808 (10.6)	11,760 (10.9)	3048 (9.6)	
Procedural devices				
• None	90,520 (77.2)	69,947 (77)	20,357 (76.1)	0.034
• Cutting Balloon	15,268 (13)	11,889 (13.2)	3379 (13.2)	0.082
• Rotational atherectomy	10,542 (9)	7937 (9)	2605 (10)	<0.001
• Laser atherectomy	86 8 (0.8)	692 (0.8)	176 (0.7)	0.089
Number of stents used				<0.001
• None	19,842 (14)	15,677(14)	4165 (13)	
• One stent	56,884 (40.5)	42,947 (39)	13,937 (44.5)	
• Two stents	35,736 (25.5)	27,721 (25)	8015 (24.5)	
• Three or more stents	27,895 (20)	22,180 (22)	5715 (18)	
Target vessel PCI				
• LMS	16,220 (12.4)	12,561(11,7)	3659(11.6)	0.694
• LAD	56,879 (41)	42,996 (40)	13,883 (44)	<0.001
• LCX	35,588 (26)	28,655 (27)	6933 (22)	<0.001
• RCA	49,570 (35)	37,660 (35)	11,910 (38)	<0.001
• Graft	13,415 (9.6)	11,178 (10.4)	2237 (7)	<0.001
Number of target vessel PCI				<0.001
• One	102,583 (75)	79,075 (74.3)	23,508 (75.7)	
• Two	27,582 (20)	21,583 (20.3)	5999 (19.3)	
• Three	7203 (5)	5680 (5.4)	1523 (5)	

Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; CHiP, complex high-risk percutaneous coronary intervention; CTO, chronic thrombus occlusion; GPIIbIIIa, glycoprotein IIaIIIb; IABP, intra-aortic balloon pump; LAD, left anterior descending artery; LCX, left circumflex; LMS, left main stem; LV, left ventricle; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery.

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 the sexes.

3.5 | 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 (Table S2).

Table 4 shows trends of crude outcomes among sexes according to study year (Group 1, 2006–2009; Group 2, 2010–2013; Group 3, 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%–0.3% vs. females: 0.4%–0.5% (Groups 1–3, 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%–0.5% vs. females: 1.76%–1.3% [Groups 1–3, 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%–2.1% vs. females: 2.1%–1.6% [Groups 1–3, respectively, for both]; $p < 0.001$ for both).

TABLE 2 Crude outcomes of patients with stable angina undergoing CHiP, stratified by sex

Variables	*n* (%)	Males, *n* (%)	Females, *n* (%)	*p* value
Mortality	421 (0.3)	275 (0.25)	146 (0.45)	0.001
Bleeding	1140 (0.81)	685 (0.63)	455 (1.42)	0.001
MACCE	2101 (1.5)	1534 (1.4)	567 (1.76)	0.001

Abbreviations: CHiP, complex high-risk percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

TABLE 3 Adjusted odds of adverse outcomes post CHiP in patients with stable angina (reference, males)

	Odd ratio	95% confidence interval	*p* value
Death	1.78	1.4–2.2	0.001
Bleeding	1.99	1.72–2.30	0.001
MACCE	1.23	1.09–1.38	0.001

Abbreviations: CHiP, complex high-risk but indicated percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

4 | 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 favorable 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 hypertension 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 favorable 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% to 23%.[31–33] 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 multivessel 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

TABLE 4 Temporal trends of outcomes of patients with stable CAD undergoing CHiP, stratified by sex

Variables	Group 1 Males, n (%)	(2006–2009) Females, n (%)	p value	Group 2 Males, n (%)	(2010–2013) Females, n (%)	p value	Group 3 Males, n (%)	(2014–2017) Females, n (%)	p value
Mortality	83 (0.3)	37 (0.4)	$p = 0.047$	85 (0.2)	46 (0.4)	$p = 0.001$	107 (0.3)	63 (0.5)	$p < 0.001$
Bleeding	189 (0.6)	159 (1.7)	$p < 0.001$	270 (0.8	139 (1.3)	$p < 0.001$	226 (0.5)	157 (1.3)	$p < 0.001$
MACCE	539 (1.7)	196 (2.1)	$p = 0.024$	538 (1.5)	183 (1.7)	$p = 0.071$	457 (1.1)	188 (1.6)	$p < 0.001$

Abbreviations: CAD, coronary artery disease; CHiP, complex high-risk but indicated percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

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: 0.48–0.72).[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 over time has decreased is of interest and suggests that females are perhaps more likely to be managed medically due to either age, comorbidities, and a higher perception of complications.[31,32,39] In contrast, trends of LMS PCI rates in females showed a gradual increase. This may reflect that female patient 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 (hazard ratio [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 noncomplex PCI, our analysis suggests that the increased risk of death in females (compared to males) was even higher than that seen with noncomplex PCIs.[11,26] 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 twofold 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.

5 | 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 data set, including anemia, frailty, which is likely to be more prevalent in the females who were on average 6 years older than males. Second, 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 data set, there data set fails to specify this diagnosis was based on which definition (e.g., the third or fourth universal MI definitions or society for cardiovascular angiography and interventions). 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.

6 | 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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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available from NICOR. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of NICOR.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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ORIGINAL ARTICLE - CLINICAL SCIENCE

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Complex, high-risk percutaneous coronary intervention types, trends, and in-hospital outcomes among different age groups: An insight from a national registry

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Abstract

Background: Complex, high-risk percutaneous coronary intervention (PCI) (CHiP) is increasingly being undertaken in octogenarians. However, limited data exist on CHiP types, trends, and outcomes in the octogenarian.

Methods: This is a retrospective cohort study from a national registry dataset on CHiP undertaken in patients with stable angina in England and Wales (January 2006 and December 2017) according to three age groups (group 1 [G1]: < 65 years; group 2 [G2]: 65–79 years; and group 3 [G3]: ≥80 years).

Results: Of 424,290 elective PCI procedures, 138,831 (33.0%) were CHiP [G1: 46,832 (33.7%); G2: 59,544 (42.9%); G3: 32,455 (23.4%)]. Among CHiP types, chronic total occlusion (CTO) (49.2%), prior coronary artery bypass graft (CABG) (30.4%), and severe vascular calcification (21.8%) were common in G1; prior CABG (42.9%), CTO (32.9%), and severe vascular calcifications (27%) were common in G2; prior CABG (15.8%), severe vascular calcification (15.5%), and chronic renal failure (11.1%) were common CHiP among the octogenarians. The older age groups had higher adjusted odds (aOR) for adverse outcomes [G2: mortality, aOR 1.7, 95% confidence interval (CI): (1.3–2.3); major bleeding, aOR 1.3, 95% CI (1.1–1.5); MACCE, aOR 1.2, 95% CI (1.0–1.3); G3: mortality, aOR 2.6, 95%CI (1.9–3.6); major bleeding, aOR 1.4, 95% CI (1.1–1.7); MACCE, aOR 1.3, 95% CI (1.1–1.5)].

Conclusion: There were significant differences in the types of CHiP cases undertaken and clinical outcomes across age groups.

KEYWORDS

age disparity, complex PCI, high-risk PCI, stable angina

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1 | INTRODUCTION

The elderly population has steadily increased over the past few decades and is expected to grow further. With the aging population comes the increased prevalence of diseases such as coronary arter disease (CAD), which remains the second leading cause of disability among the elderly and accounts for more than half of all deaths related to cardiovascular disease.[1]

Complex, high-risk percutaneous coronary intervention (PCI) (CHiP) is increasingly undertaken in the older age groups; it refers to a subset of patients with specific criteria associated with increased procedural complexity and risks.[2] Age is one of the accepted criteria of how CHiP is defined, and is known to be an important predictor of worse PCI outcomes.[3] While there are no specific studies that have looked explicitly at CHiP outcomes according to age in the real-world setting, prior studies that have focused on individual CHiP components have suggested worse outcomes associated with older age in chronic renal failure (CRF),[4] PCI in chronic total occlusions (CTOs)[5,6] left main (LM) PCI,[7] or severe vascular calcification.[8]

There have been no previous studies focused on whether the type of CHiP cases undertaken in different age groups varies by age, and whether the growth of CHiP and the types of cases undertaken has changed differentially among different age groups. Furthermore, there is no previous data on whether there are differences in CHiP outcomes stratified by age. In this national analysis derived from the United Kingdom, we sought to study age-stratified baseline characteristics, trends, and clinical outcomes of CHiP's undertaken in patients with stable angina over 12 years, using data from a national PCI registry.

2 | METHODS

2.1 | Data source

We obtained the data from the British Cardiovascular Intervention Society (BCIS) registry. The BCIS is managed by the National Institute of Cardiovascular Outcomes and Research (NICOR). The BCIS data includes a wide range of clinical characteristics, interventional and pharmacological treatments, important cardiovascular comorbidities, and in-hospital procedural complications and mortality. Healthcare professionals collect data from over 95% (112 out of the 117 PCI centers in the United Kingdom) of PCI procedures undertaken in England and Wales. Data are collected prospectively and encrypted before transferring to database services as part of a NICOR national audit initiative. Also, data have Section 251 approval of NHS Act 2006, which allows the dataset to be used for audit purposes and research without seeking patients' consent. Hence, ethical approval was not required for this study.[9] The BCIS data entry is mandated as part of the professional revalidation. Data are entered by interventional operators performing the procedures, with almost 100,000 procedures records added to the BCIS registry every year.[10] The BCIS data accuracy and quality have been previously ascertained.[11]

2.2 | Study design and definitions

We retrospectively analyzed records of patients who underwent PCI for stable angina in England and Wales between January 1, 2006 to December 31, 2017 in the BCIS data set. Based on our previously published work,[12–16] CHiP was defined as any procedure with at least one clinical or procedural high-risk feature. Clinical high-risk features were defined as any patient with a previous history of coronary artery bypass graft (CABG), CRF, or severely impaired left ventricular (LV) function. The procedural (anatomical) high-risk factor was defined as cases including LM PCI, severe vascular calcification treatment, CTO PCI, or the need for LV support. All CHiP procedures were then categorized into three groups (group 1 [G1]: <65; group 2 [G2]: 65–79; group 3 [G3]: ≥80 years old).

CRF was defined as any case that met any of the following: renal transplant history, chronic dialysis, or chronic creatinine elevation of more than 200 μmol/L, all predefined in the BICS data. Severe vascular calcifications were defined as any PCI that required using rotational or laser atherectomy devices or cutting balloons. Severe LV impairment was defined as LV function with an estimated ejection fraction of 30% or less. The need for LV support was defined as the use of intraaortic balloon pump (IABP) or Impella.

2.3 | Study endpoints

In-hospital all-cause mortality was the primary outcome of interest. The secondary outcomes included (a) In-hospital major adverse cardiovascular and cerebral events (MACCE). (b) In-hospital major bleeding complications.

MACCE was defined as the cumulative incidence of in-hospital death, periprocedural stroke, or myocardial infarction (MI). Periprocedural myocardial infarction was defined as a composite of non-Q-wave and Q-wave myocardial infarctions, reinfarction, and reintervention (emergency PCI or CABG) defined within the BCIS registry.

Major bleeding events were defined as any case that meets the Bleeding Academic Research Consortium's definition for Bleeding Type 2 and above[17]; this may include clinically evident gastrointestinal bleeding, radiological evidence of intracranial bleed, retroperitoneal bleed/hematoma, any transfusion of blood or blood products, and access site bleeding complications requiring intervention. Access site complications are defined as a composite of a false aneurysm, arterial dissection, retroperitoneal hematoma, or hemorrhage.

2.4 | Data analysis

We expressed the data as median (interquartile range) for continuous data and whole numbers (percentages) for categorical data. Differences between the CHiP groups were assessed using Pearson's χ^2 test for categorical variables and the Kruskal–Wallis or

Wilcoxon–Mann–Whitney tests for continuous data depending on the number of groups being compared. Supporting Information: Table 1 provides information about missing data for each variable included in the study. Multiple imputations with chained equations were used to impute missing data to create 10 data sets, assuming that data were missing at random.[18] In the multiple imputation framework, we used logistic regression for binary variables, multinomial for nominal variables, ordinal logistic regression for ordered variables, and linear regression for continuous variables. We included the following variables in the model: sex, age, and outcomes variables (registered as regular), while we registered the following variables as imputed: ethnicity, history of dyslipidemia, smoking history, previous CABG, previous MI, previous PCI, previous stroke, diabetes mellitus, hypertension, CRF, LV function, peripheral vascular disease (PVD), family history of CAD, clopidogrel, vascular access, LM PCI, circulatory support, number of treated lesions, severe vascular calcification, number of stents used, and body mass index. All the subsequent analyses were performed on the imputed data set, and results were pooled using Rubin's rules.[19] 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 the literature search.[20] 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.[21-23] Finally, multivariable logistic regression analyses were used to determine the adjusted odds ratios (aOR), 95% confidence interval (CI), and p values of outcomes between the age-stratified CHiP groups. All models included the same variables as used in the multiple imputation framework.[20] Stata

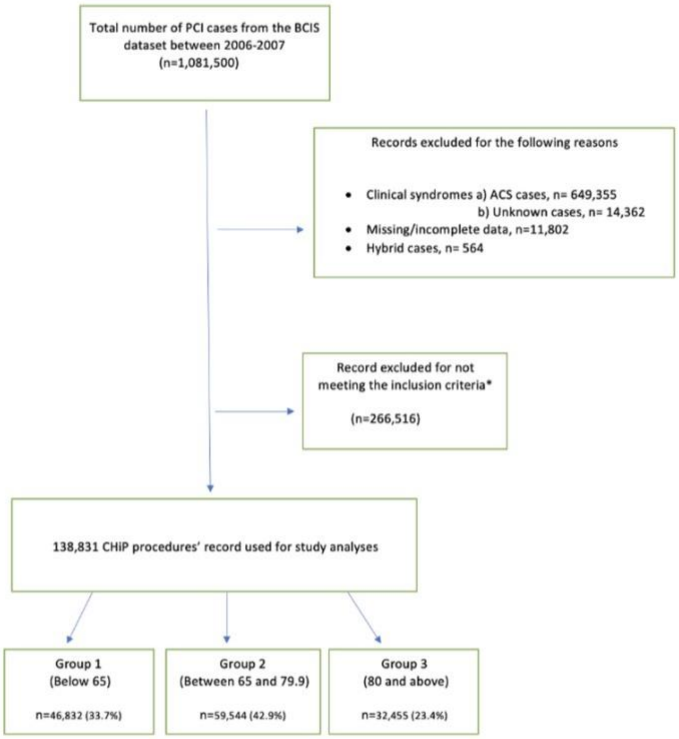

FIGURE 1 Flow diagram illustrating the process of patients' inclusion and exclusion for the CHiP analysis. ACS, acute coronary syndromes; BCIS, British Cardiovascular Intervention Society; CHiP, complex, high-risk percutaneous coronary intervention; PCI, percutaneous coronary intervention *Inclusion criteria: left main PCI, PCT to chronic thrombus occlusion vessel, chronic renal failure, poor left ventricle function, severe vascular calcifications, previous coronary artery bypass graft, age ≥80 years. [Color figure can be viewed at wileyonlinelibrary.com]

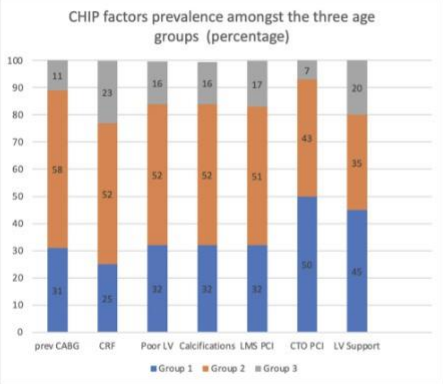

FIGURE 2 Prevalence of CHiP factors in patients with stable angina, stratified by three age groups (group 1, <65 years; group 2, 65–79 years; group 3, 80 and above years). CABG, coronary artery bypass graft; CHiP, complex high-risk percutaneous coronary intervention; CTO, chronic thrombus occlusion; LMS, left main stem; LV, left ventricle; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery. [Color figure can be viewed at wileyonlinelibrary.com]

version 14.1 was used to conduct the analyses (StataCorp). Statistical significance was evaluated at a type I error rate of 0.05.

3 | RESULTS

3.1 | Study cohorts

The study cohort consisted of 138,831 (32.7%) out of 424,290 PCI procedure records undertaken for stable CAD between January 1, 2006 and December 31, 2017 in England and Wales. The process of patients' inclusion and exclusion for this analysis is presented in Figure 1. Figure 2 shows the prevalence of each CHiP factor in the CHiP cohort, stratified by age. CTO PCI was most common in the youngest age group, whereas the most common CHiP factor in the 65 years and above age group was prior CABG.

3.2 | Clinical characteristics

Table 1 provides an overview of CHiP factors distribution, cardiovascular risk factors' prevalence, pharmacology, and procedural characteristics according to three groups (G1: <65 years; G2: 65–79 years; G3, ≥80 years). Overall, most cases (42.9%) were undertaken in patients between 65 and 79 years old. Those aged 80 years and above represented 23.4% of the cases. Male sex represented 64.9% of the patients in G3, 78.5% of the cases in G2, and 84.6% of the cases in G1. Similarly, most patients were White (87.7% in G3 vs. 80.5% in G1).

3.3 | CHiP factors

The most common CHiP indication in G1 was PCI to a CTO vessel (49.2%), followed by prior CABG (30.4%) and severe vascular calcification (21.8%). In contrast, prior CABG was the most common indication in G2 (42.9%) and G3 (15.8%), followed by PCI to a CTO (32.9%) and severe vascular calcification (21.0%) in G2, and severe vascular calcification (15.5%) and chronic renal failure (11.1%) in G3. Except for PCI to a CTO vessel, all other CHiP factors were more prevalent in G2 than in the other groups.

3.4 | Cardiovascular risk factors

Hypertension was common in all groups, with the highest prevalence seen among the octogenarians (70%). A higher prevalence of current smokers (17.9%) and a family history of CAD (55.4%) was seen among G1 compared to other groups. In contrast, the octogenarians had the lowest prevalence of diabetes mellitus (19%), prior PCI (33.8%), and prior MI (36.2%).

3.5 | Procedural characteristics

There were no significant differences in the use of support devices among the groups (Impella, $p = 0.727$ and IABP, $p = 0.154$). Similarly, PCI to a single lesion was commonly observed across all groups (45.5%, 47.1%, 51.7% for G1, G2, and G3, respectively). Cutting balloons were most used in G1 (16%), whereas rotational atherectomy was mostly used in G2 (12%). Octogenarians had the lowest rates of use of calcium modification devices (none used in 84% in G3 compared to 73% in G2% and 78% in G1).

The most common target vessel revascularized in all the three groups was the LAD (G1: 39.4%; G2: 38.2%; G3: 50.9%); $p < 0.001$. PCI to a graft or LM vessel was more common among G2 (graft, 11%; LMS, 14%). Around (51.5%) of CHiP in the octogenarians was undertaken via radial access, which was more common compared to G1 (41.6%) and G2 (43.9%).

Warfarin prescription was more frequent among G3 (3.3%), while G1 had higher prescription rates of ticagrelor (4.0%) and prasugrel (1.3%); $p < 0.001$.

3.6 | Clinical outcomes

Table 2 details the crude outcomes according to three age groups. The octogenarians had the highest in-hospital mortality rates (0.5%)

TABLE 1 Baseline clinical and procedural characteristics of patients who underwent a CHiP procedure for stable angina stratified according to three age groups (group 1: <65 years; group 2: 65–79 years; group 3: 80 and above years)

	Age <65 (%)	Age 65–79 (%)	Age ≥80 (%)	*p* Value
Number of participants	46,832 (33.7)	59,544 (42.9)	32,455 (23.4)	
Age median, *n* (IQR)	58.1 (52.8–61.8)	72.1 (68.6–75.7)	82.9 (81.3–85.2)	<0.001
BMI, *n* (IQR)	29.3 (26.2–32.8)	28.1 (25.3–31.3)	26.5 (24–29.4)	<0.001
Males, *n* (%)	39,610 (84.6)	46,743 (78.5)	21,074 (64.9)	<0.001
Whites, *n* (%)	28,355 (80.5)	37,459 (84.4)	21,012 (87.7)	<0.001
CHiP factors (types)				
Patients' factors				
Prior CABG	13,902 (30.4)	25,094 (42.9)	4975 (15.8)	<0.001
Chronic renal failure	3729 (8.3)	7677 (13.5)	3404 (11.1)	<0.001
Poor LV function	2520 (9.1)	4053 (11.3)	1222 (6.3)	<0.001
Procedural factors				
LMS PCI	5214 (11.3)	8226 (14)	2716 (8.6)	<0.001
CTO PCI	22,103 (49.2)	18,611 (32.9)	3118 (10.5)	<0.001
Severe coronary (vascular) calcifications	8,405 (21.8)	13,273 (27)	3992 (15.5)	<0.001
Use of LV support	255 (0.6)	346 (0.6)	156 (0.5)	0.154
Cardiovascular risk factors				
Hypertension	26,346 (60)	38,341 (68.5)	21,421 (70)	<0.001
Dyslipidemia	29,059 (66.2)	37,081 (66.3)	18,703 (61.2)	<0.001
Diabetes melliti	11,762 (26.4)	16,645 (29.3)	6134 (19)	<0.001
Smoking				<0.001
Never	14,575 (35.6)	21,037 (40.7)	14,141 (50.8)	
Ex-smokers	19,002 (46.4)	27,432 (53.1)	12,954 (46.5)	
Current smokers	7354 (17.9)	3216 (6.2)	752 (2.7)	
Family history of CAD	22,458 (55.4)	24,081 (47.3)	9303 (33.8)	<0.001
History of MI	19,114 (43.8)	25,332 (45.6)	10,978 (36.2)	<0.001
Previous PCI	18,329 (40)	23,501 (40.5)	10,610 (33.8)	<0.001
Previous stroke	1366 (3.1)	2950 (5.3)	1914 (6.2)	<0.001
History of PVD	2260 (5.1)	4502 (8.1)	2324 (7.6)	<0.001
LV systolic function				<0.001
Normal (EF > 50)	20,414 (73.7)	24,070 (67)	13,760 (70.8)	
Impaired (EF 30–50)	4749 (17.2)	7783 (21.7)	4444 (22.9)	
Severely impaired (EF < 30)	2520 (9.1)	4053 (11.3)	1222 (6.3)	
Pharmacology				
Warfarin	411 (0.9)	1338 (2.5)	959 (3.3)	<0.001
GPIIbIIIa inhibitors	3924 (9.1)	3924 (7.8)	1466 (4.9)	<0.001
Clopidogrel	34,242 (81.6)	44,533 (82.9)	24,174 (83.0)	<0.001
Prasugrel	545 (1.3)	493 (0.9)	102 (0.4)	<0.001
Ticagrelor	1688 (4.0)	1805 (3.3)	977 (3.3)	<0.001

(Continues)

TABLE 1 (Continued)

	Age <65 (%)	Age 65–79 (%)	Age ≥80 (%)	*p* Value
Vascular access				<0.001
Radial	18,954 (41.6)	25,500 (43.9)	16,349 (51.5)	
Femoral	21,221 (46.7)	27,361 (47.2)	13,851 (43.7)	
Multiple accesses	5315 (11.7)	5168 (8.9)	1510 (4.8)	
Circulatory support				
No support	44,258 (98.9)	56,560 (99.36)	30,744 (99.46)	0.154
IABP	255 (0.6)	346 (0.6)	156 (0.5)	0.154
Impella	22 (0.5)	23 (0.04)	12 (0.04)	0.727
Number of successfully treated lesions				<0.001
None	5294 (14.8)	5616 (12)	1682 (6.5)	
One	16,193 (45.5)	21,972 (47.1)	13,297 (51.7)	
Two	9921 (27.8)	13,325 (28.6)	7757 (30.2)	
Three or more	4224 (11.9)	5733 (12.3)	2989 (11.6)	
Procedural devices				
None	30,142 (78.0)	35,969 (73.0)	21,766 (84.0)	<0.001
Cutting balloon	6277 (16.0)	7315 (14.1)	1650 (6.2)	<0.001
Rotational atherectomy	2037 (5.3)	6035 (12.0)	2427 (9.3)	<0.001
Laser atherectomy	258 (0.7)	479 (0.9)	128 (0.5)	<0.001
Number of stents used				<0.001
None	7437 (16)	8466 (14.5)	3260 (10.1)	
One stent	17,306 (37.3)	23,473 (39.7)	15,107 (46.9)	
Two stents	11,481 (24.8)	15,116 (25.5)	8533 (26.5)	
Three or more stents	10,165 (21.9)	11,960 (20.3)	5297 (16.5)	
Target vessel PCI				
Left main stem (LMS)	5214 (11.3)	8226 (14)	2716 (8.6)	<0.001
LAD	18,199 (39.4)	22,373 (38.2)	16,152 (50.9)	<0.001
LCX	12,022 (26.0)	15,525 (26.5)	7935 (25)	<0.001
RCA	18,045 (39.1)	20,706 (35.3)	10,626 (33.5)	<0.001
Graft	3406 (7.4)	6446 (11)	1429 (4.5)	<0.001
Number of target vessel PCI				<0.001
One	35,040 (75)	43,869 (74.1)	23,674 (74.1)	
Two	8983 (19)	11,890 (20)	6709 (20.9)	
Three or more	2361 (5.1)	3240 (5.9)	1604 (5.0)	

Abbreviations: BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHiP, complex high-risk percutaneous coronary intervention; CTO, chronic thrombus occlusion; EF, ejection fraction; GPIIbIIIa, glycoprotein IIaIIIb; IABP, intraaortic balloon pump; IQR, interquartile range; LAD, left anterior descending coronary artery; LCX, left circumflex; LMS, left main stem; LV, left ventricle; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery.

compared to the other groups studied (G2, 0.3%; G1, 0.2%); $p < 0.001$. Similarly, major bleeding and MACCE rates were highest in G3 (major bleeding: 1.0%; MACCE: 1.7%) and lowest in G1 (major bleeding: 0.7%; MACCE: 1.3%); $p < 0.001$. Following adjustment for baseline covariates, the odds for mortality increased with increasing age [G2: aOR 1.7, 95% CI (1.3–2.3); G3: aOR 2.6, 95% CI (1.9–3.6) compared to G1]. Similarly, the odds of both major bleeding [G2: aOR 1.3, 95% CI (1.1–1.5), G3: aOR 1.4, 95% CI (1.1–1.7)] and MACCE

TABLE 2 Crude outcomes of CHiP procedures undertaken among patients with stable angina stratified into three age groups (group 1, <65 years; group 2, 65–79 years; group 3, 80, and above years)

Variables	>65, *n* (%)	65–79, *n* (%)	≥80, *n* (%)	*p* Value
Mortality	76 (0.2)	194 (0.3)	147 (0.5)	<0.001
Bleeding	312 (0.7)	519 (0.9)	297 (1.0)	<0.001
MACCE	602 (1.3)	921 (1.6)	556 (1.7)	<0.001

Abbreviations: CHiP, complex high-risk percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

TABLE 3 Adjusted odds of adverse outcomes post CHiP in patients with stable angina according to three age groups (group 1, <65 years; group 2, 65–79 years; group 3, 80 and above years) (comparable, group 1)

Variables	Group 2 aOR	95% CI	*p* Value	Group 3 aOR	95% CI	*p* Value
Mortality	1.7	1.3–2.3	>0.001	2.6	1.9–3.6	>0.001
Bleeding	1.3	1.1–1.5	>0.001	1.4	1.1–1.7	>0.002
MACCE	1.2	1.0–1.3	0.006	1.3	1.1–1.5	>0.001

Abbreviations: aOR, adjusted odd ratio; CHiP, complex high-risk percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

[G2: aOR 1.2, 95% CI (1.0–1.3), G3: aOR 1.3, 95% CI (1.1–1.5)] increased across the age groups (Table 3).

3.7 | Temporal trends

Figure 3 shows the temporal changes in the prevalence of each CHiP factor stratified by age. Over time, there was an expansion of the different types of CHiP cases across all age groups. The greatest increase in the prevalence of prior CABG occurred in octogenarians. Similarly, the greatest expansion of PCI for LM, CTO, and calcific vascular disease occurred in this group.

Supporting Information: Table 2 further details the temporal changes in baseline characteristics and clinical outcomes across three age groups. Overall, the prevalence of cardiovascular risk factors increased across all age groups, except for current smokers in those ≥65 years [G2: 6.5% (≤2011) vs. 6% (>2011); G3: 3% (≤2011) vs. 2.5% (>2011); $p < 0.001$]. There were no changes in the prevalence of dyslipidaemia, prior MI, or previous stroke across all age groups. Radial access trends show an increase in all age groups, and the greatest was seen among the octogenarians (≤2011, 31% vs. >2011, 64%); $p < 0.001$. Interestingly, mortality trends across the three age groups did not change (G1, $p < 0.051$; G2, $p < 0.450$; G3, $p < 0.0.185$). Whereas major bleeding and MACCE events showed significant declines seen across all age groups, with the greatest decline observed in the octogenarians (MACCE: 2.1%, ≤2011 vs. 1.5%, >2011; major bleeding: 1.2%, ≤2011 vs. 0.6%, >2011), $p < 0.001$ for all.

4 | DISCUSSION

This study of a national cohort of 138,831 CHiP procedure' records undertaken in patients with stable angina provided, to the best of our knowledge, the very first insight into the risk profile, trends, nature of CHiP cases undertaken, and their clinical outcomes stratified by age. The findings can be summarized in the following points: (a) The risk factor profile evolved toward a lower cardiometabolic risk profile as patients aged, with a lower prevalence of diabetes mellitus and current smokers in the octogenarians compared to younger age groups; although there was a clear trend toward an increase in the prevalence of cardiovascular risk factors within the same age group; (b) type of CHiP cases varied by age, with CTO, prior CABG, and severe vascular calcification most often encountered in younger patients, while prior CABG, severe vascular calcification, and renal failure were most common in the elderly group; (c) mortality, major bleeding and MACCE risks increased by age, even when differences in baseline risk are adjusted for; (d) mortality trends within the same age group did not change; however, MACCE and major bleeding trends significantly declined, with the greatest decline seen in the octogenarians.

There were significant differences in the baseline clinical characteristics between the study groups, with overall trends toward an increase in the prevalence of cardiovascular risk factors across all age groups. Hypertension was the most prevalent risk factor among the groups, with the highest prevalence seen in octogenarians. Interestingly, the heaviest comorbid burden was observed in those aged 65–79 years (G2), suggesting that those with heavy cardiovascular comorbidities either die before they get to 80 years of age or that elderly patients with multiple comorbidities are more likely to be managed medically. Studies from the USA registries examining outcomes of noncomplex PCI in patients with stable angina according to age groups observed similar findings.[24,25] Procedural characteristics varied too. For example, increased trends and rates for radial artery access use were seen most commonly in the octogenarian cohort compared to other age groups, probably in recognition of higher bleeding risks in the octogenarian group. This may also reflect the case mix, younger patients had higher rates of PCI to a CTO, which could require larger sheaths via femoral access or use of multiple access sites. Similarly, the use of calcium modification devices and LMS PCI was higher in younger patients, which may partly explain the greater propensity toward femoral access in these patient groups.

The most common CHiP variable in octogenarians was prior CABG. A finding that aligns with studies that suggest long-term benefits from CABG, which in turn delays the patients' need for intervention until later in their lives.

There was a gradual increase in all CHiP procedures undertaken across all age groups, particularly octogenarians, over the 12 years.

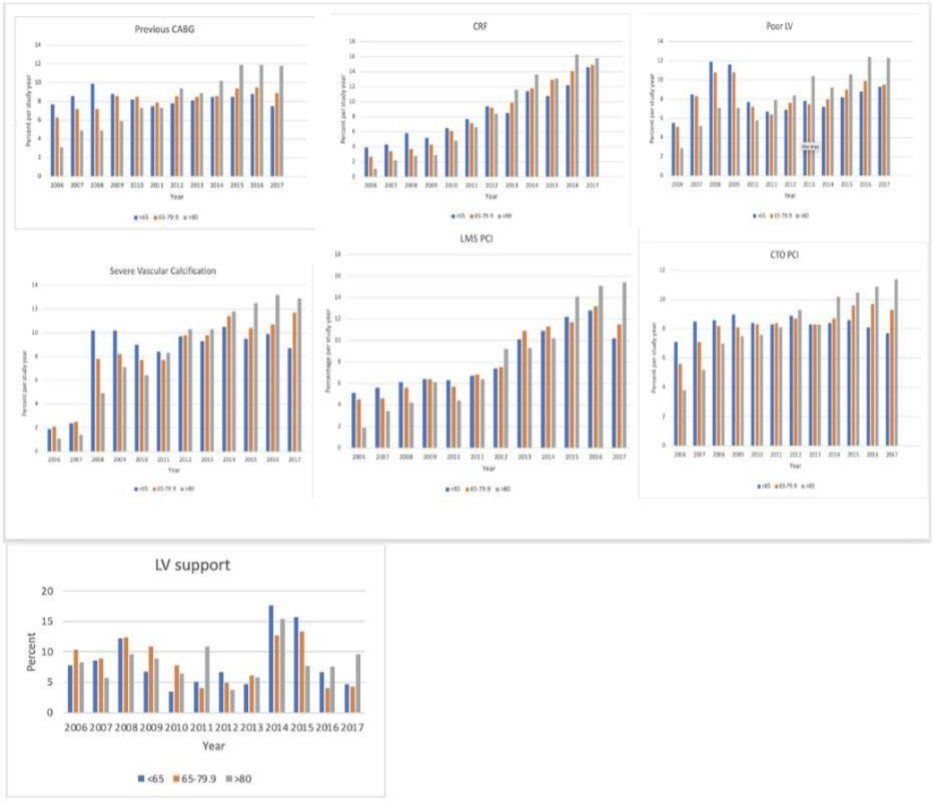

FIGURE 3 Temporal changes in the prevalence of each CHiP factor among patients with stable angina who underwent a CHiP procedure, stratified according to age into three groups: group 1, <65 years; group 2, 65–79 years; group 3, 80 and above years). CABG, coronary artery bypass graft; CHiP, complex high-risk percutaneous coronary intervention; CRF, chronic renal failure; CTO, chronic thrombus occlusion; LMS, left main stem; LV, left ventricle; PCI, percutaneous coronary intervention. [Color figure can be viewed at wileyonlinelibrary.com]

This might be reflective of broader adoption of new management modalities following changes in the guidelines, such as the LMS guidelines,[26,27] or expert consensus in, for example, the management of a CTO vessel[28] using new crossing algorithms[2,3,29,30] as well as the more widespread availability of advanced technologies in managing cases with severe vascular calcification[32] and severe heart failure.[33] Furthermore, the widespread availability of intracoronary imaging[34] has aided better assessment of disease severity, complexity (calcium identification), and helped guide decision making.[35]

The odds for adverse outcomes were worse in the octogenarian cohort despite having a lower comorbidity burden and CAD complexity than in the other two groups. Mortality odds were almost two- to threefolds higher in the octogenarians, and trends suggest no change of the same over time; this may relate to age per se. Age has been consistently shown to be an important predictor of adverse outcomes in all contemporary PCI risk scores studied.[36–40] Moreover, one must not forget the effect of unmeasured confounders in the older ager group, such as age-related physiological changes, frailty, anemia, and poor control of important comorbidities like diabetes that may contribute to the observed high event rates in the octogenarian cohort. Similar mechanisms may account for the higher odds of major bleeding events recorded in the octogenarian population, despite the higher rates of radial access used. Additional mechanisms may, in part, relate to higher rates of warfarin prescriptions and other unmeasured confounders such as frailty.[41]

4.1 | Study limitations

To the best of our knowledge, this is the first study that has examined CHiP outcomes according to different age groups in a real-world, unselected setting at a national level. The BCIS database records over 99% of cases performed in England and Wales. The sample size is sufficiently large to study temporal trends in the type of ChiP cases undertaken in different age groups and determine whether there is a real difference in CHiP outcomes according to age groups. As with all observational studies, this study has a few limitations. First, there is always the risk of reporting and coding errors that could represent a potential bias, such as underreporting other comorbidities and self-reported complications with no external validation. Second, there is the potential for unmeasured confounders in clinical and procedural variables such as socioeconomic status, anemia, frailty,[42] control of cardiovascular risk factors such as diabetes, and lesion complexity that may impact the clinical outcomes we report.

Moreover, the BCIS data set does not provide information on the completeness of revascularization. Although it meets statistical significance due to a large number of patients, many variables presented in the result section have small differences. The clinical significance of these small differences is unclear. Lastly, the BCIS data set only captures in-hospital outcomes. Hence, we cannot rule out significant differences in the longer term.

5 | CONCLUSION

Types of CHiP undertaken for stable angina differ according to age. There was a tendency toward less cardiovascular risk burden and disease complexity in the octogenarians. Age remains an independent risk factor for worse mortality, major bleeding, and MACCE in CHiP. Although trends for death did not change within the same age group, MACCE and major bleeding trends were in decline, with the greatest seen across the octogenarian cohort.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Ethnicity in Complex High-Risk but Indicated Percutaneous Coronary Intervention Types and Outcomes

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Complex High-risk but indicated Percutaneous coronary interventions (CHiPs) is increasingly common in contemporary practice. However, data on ethnic differences in CHiP types, outcomes, and trends in patients with stable angina are limited; this is pertinent given the population of Black, Asian, and other ethnic minorities (BAME) in Europe is increasing. We conducted a retrospective analysis of CHiP procedures undertaken in patients with stable angina using data obtained from the BCIS (British Cardiovascular Intervention Society) registry (2006 to 2017). CHiP cases were identified and categorized by ethnicity into White and BAME groups. We then performed multivariable regression analysis and propensity score matching to determine adjusted odds ratios (aORs) of in-hospital mortality, major bleeding, and major adverse cardiovascular and cerebral events (MACCEs) in BAME compared with Whites. Of 424,290 procedure records, 105,949 were CHiP (25.0%) (White 89,038 [84%], BAME 16,911 [16%]). BAME patients were younger (median 68.1 vs 70.6 years). Previous coronary artery bypass surgery (33.4% vs 38.3%), followed by chronic total occlusion percutaneous coronary intervention (31.9% vs 32%) were common CHiP variables in both groups. The third common variable was age 80 years and above (23.6%) in White patients and severe vascular calcifications in BAME patients (18.8%). BAME patients had higher rates of diabetes (41.1 vs 23.6%), hypertension (68 vs 66.5%), previous percutaneous coronary intervention (43.7 vs 37.6%), and previous myocardial infarction (44.9 vs 42.5%), (p <0.001 for all). Mortality (aOR 1.1, 95% confidence interval [CI] 0.8 to 1.5) and MACCE (aOR 1.0, 95% CI 0.8 to 1.1) odds were similar among the groups. Bleeding odds (aOR 0.7, 95% CI 0.6 to 0.9) were lower in BAME. In conclusion, CHiP procedures differed among the ethnic groups. BAME patients were younger and had worse cardiometabolic profiles. Similar odds of death and MACCE were seen in BAME compared with their White counterparts. Bleeding odds were 30% lower in the BAME group. **© 2022 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2022;175:26−37)**

Introduction

The first reports of racial/ethnic differences in coronary artery disease (CAD) management and clinical outcomes emerged more than 3 decades ago.[1,2] Since then, data derived from trials and observational studies demonstrated that CAD risk profile and outcomes after coronary intervention vary among races.[3−5] Some demonstrated similar outcomes,[3,4] others suggested that Blacks, Asians, and other ethnic minorities (BAMEs) groups have a higher incidence of CAD and poorer clinical outcomes.[5−7] Complex, High-risk but indicated Percutaneous coronary intervention (CHiP) refers to a group subset with specific patient and procedural characteristics that put patients at higher risk for periprocedural complications.[8] Previous studies around CHiP by ethnicity were limited to data that examined outcomes in highly selected cohorts (specific types of CHiP cases only)[8−11] or certain geographical areas.[12] This is of interest given that CHiP cases are growing, and the BAME population, which represents 13% of the population of England and Wales,[13] is expected to increase to 20% by 2050.[14,15] This analysis sought to study the ethnic differences in CHiP undertaken in patients with stable angina over 12 years, using data from a national percutaneous coronary interventions (PCI) registry in the United Kingdom.

Methods

The data were collected from the BCIS (British Cardiovascular Intervention Society) registry. The BCIS is managed by the National Institute of Cardiovascular Outcomes and Research. Data from over 95% (112 of the 117 PCI centers in the United Kingdom) PCI procedures undertaken in

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See page 36 for disclosure information.

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England and Wales are collected annually. The BCIS data include a wide range of clinical characteristics, important cardiovascular co-morbidities, interventional and pharmacologic treatments, in-hospital procedural complications, and mortality.[16] As part of a National Institute of Cardiovascular Outcomes and Research national audit initiative, all data are collected prospectively and encrypted before transferring to database services. Also, all data have Section 251 approval of NHS Act 2006, which allows the dataset to be used for audit purposes and research without seeking patient consent. Hence, ethical approval was not required for this study.[17] The BCIS data entry is mandated as part of the professional revalidation.[16] The accuracy and quality of the BCIS dataset have been previously ascertained.[18]

We analyzed data obtained from all patients who had undergone PCI for CAD in England and Wales between January 1, 2006 and December 31, 2017 on the BCIS registry. On the basis of our previous work,[8,19,20] a CHiP case was defined as any PCI case that has met at least 1 of the following patient characteristics (aged ≥80 years, previous coronary artery bypass graft [CABG], severely impaired left ventricular [LV] function, and chronic renal failure [CRF]) or procedural characteristics (left main [LM] PCI, chronic total occlusion PCI, use of laser atherectomy, use of rotational atherectomy, or need for LV support). The collected CHiP data were then categorized into White and BAME groups. We required a sample size of >13,628 to provide a power of 0.8 at α ($p < 0.05$).

Severe LV impairment was defined as LV function with an estimated ejection fraction of ≤30%, LV support use as cases where Impella or intra-aortic balloon pump (IABP) was used, CRF as any patient with chronic creatinine elevation of more than 200 μmol/L, history of renal transplant, or chronic dialysis, which is predefined in the dataset. Extensive vascular calcification was defined as any PCI that required cutting balloons rotational or laser atherectomy.

The primary outcome of interest was in-hospital all-cause mortality. Secondary outcomes included were (1) in-hospital major adverse cardiovascular and cerebral events (MACCEs), defined as the cumulative incidence of in-hospital death, periprocedural myocardial infarction (MI) or cerebrovascular accidents (CVAs), or in-hospital CVA; and (2) in-hospital major bleeding events. We defined periprocedural MI as a composite of Q-wave MI, non-Q-wave MI, reinfarction, and reintervention (emergency PCI or CABG) predefined within the BCIS registry. Major bleeding events are defined as radiologic evidence of intracranial bleed, access site bleeding requiring intervention, clinically evident gastrointestinal tract bleeding, retroperitoneal bleed/hematoma, any transfusion of blood or blood products, or any access site complications requiring intervention or surgery. We defined access site complication as the presence of any of the following: retroperitoneal hematoma, false aneurysm, hemorrhage without hematoma, or arterial dissection.

Patients' variables were summarized as median and interquartile range for continuous variables, and as frequencies and percentages for categoric variables. The patients' baseline and co-morbidity characteristics and procedural details were then compared using chi-square test for categoric and binary 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. We used multiple imputations with chained equations to impute missing data to create 10 datasets, assuming that data were missing at random. We used logistic regression for binary variables, multinomial for nominal, ordinal logistic regression for ordered, and linear regression for continuous variables in our multiple imputation framework. The variables included in our model were: ethnicity, age, body mass index, history of dyslipidemia, previous CABG, previous PCI, previous MI, previous CVA, hypertension, diabetes mellitus, renal failure, peripheral vascular disease (PVD), clopidogrel, family history of CAD, vascular access, LM PCI, IABP, rotational atherectomy, number of treated lesions, and number of stents used. We performed subsequent analyses on the imputed dataset and results were pooled using Rubin rule.[21] Finally, we used multivariable logistic regression analyses to determine the adjusted odds ratios (aORs) of outcomes between White and BAME groups. To control for differences and imbalances in the baseline clinical and procedural characteristics between the groups, we used multiple imputations with propensity score matching (mi estimate:teffects psmatch). We used the propensity score matching to estimate the average treatment effect using all the covariates used in our main regression analysis. We then converted the coefficients to odds ratios to help with better interpretation of the results. To better assess the consistency of the results obtained, we performed a sensitivity analysis on the nonimputed dataset. Stata version 14.1 was used to conduct the analyses (StataCorp, College Station, Texas). Statistical significance was assessed at a type 1 error rate of 0.05.

Results

The study cohort consisted of 105,949 CHiP (24.97%) of 424,290 stable CAD PCI cases performed in England and Wales (January 2006 to December 2017). The process of inclusion and exclusion for this analysis is presented in Figure 1. Figure 2 shows the prevalence of each CHiP factor, stratified by ethnicity. Supplementary Figure 1 demonstrates the temporal changes in the prevalence of CHiP procedures stratified by ethnicity, where CHiP cases increased from 5,073 procedures in 2006 to 9,131 in 2017. Supplementary Figure 1 also shows how the proportion of BAME patients changed throughout the study years, ranging between 13% and 18%. Supplementary Figure 2 shows the absolute number of each CHiP factor.

Table 1 provides an overview of CHiP factors (types), cardiovascular risk factors, pharmacology, and procedural characteristics according to their ethnic background. Overall, 89,038 of the CHiP procedures were performed on White patients (84%), and 16,911 were performed on BAME patients (16%). Whites were, on average, 1.5 years older than BAME patients (median age: Whites, 70.6; BAME, 68.1 years). Among cardiovascular risk factors, BAME patients had a higher prevalence of hypertension, diabetes, and history of both PCI and MI. In contrast, White patients had a higher prevalence of CVA, PVD, and current and former smokers.

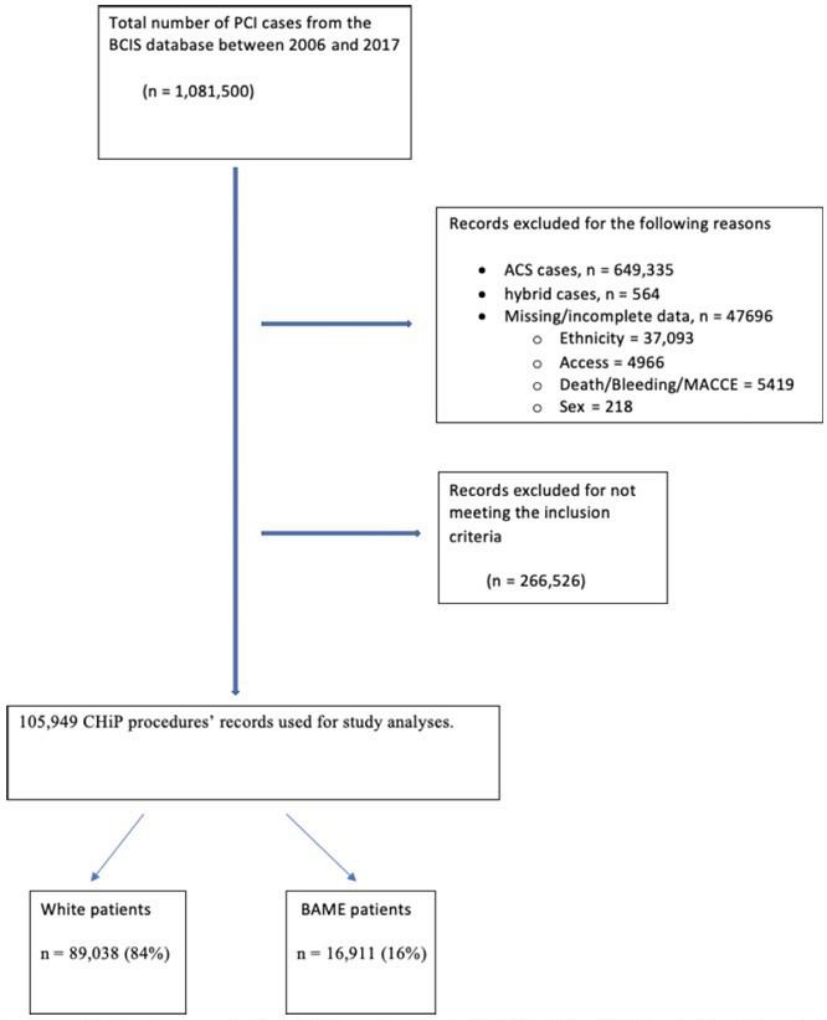


Figure 1. Flow diagram illustrates the process of patients' inclusion and exclusion for the CHiP analysis, stratified by ethnicity. ACS = acute coronary syndrome.

Temporal changes in patients' characteristics and CHiP types by ethnicity are shown in Supplementary Table 2. Supplementary Table 3 details the baseline clinical and procedural characteristics stratified into White, Black, Asian, and other ethnic minorities. Of the BAME, Asian patients represented the majority (7.7%), whereas Black patients represented 0.8% of the cases.

CHiP factors (types) frequencies differed among the groups. The 3 most common CHiP factors in White patients were previous CABG (33.4%), chronic total occlusion percutaneous coronary intervention (CTO PCI) (31.9%), and age 80 years and above (23.6%); whereas in BAME patients, they were previous CABG (38.3%), CTO PCI (32%), and severe vascular calcification (18.8%) (Table 1). Figure 3 shows the temporal trends in each CHiP factor according to ethnicity. Overall, in both groups, the number of procedures undertaken in those 80 years of age and above, history of CRF, poor LV function, LM PCI, and severe vascular calcification which increased gradually (see also Supplementary Table 2). Of the BAME patients, Asians had the highest

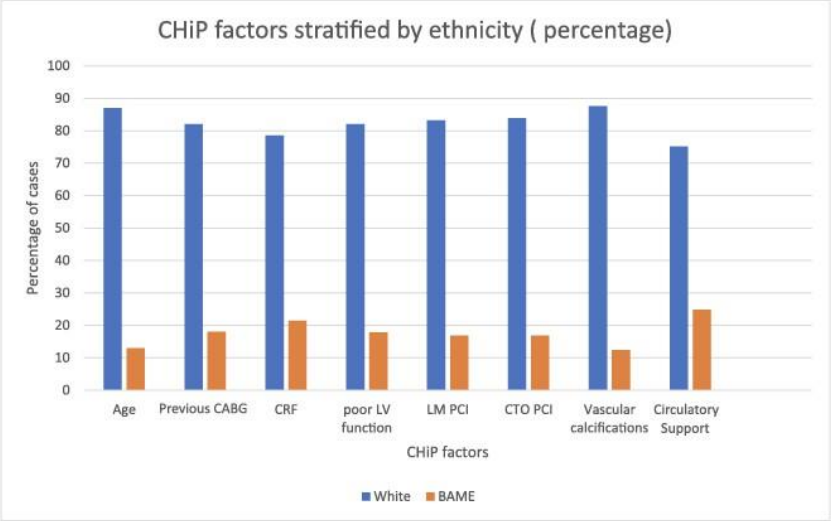


Figure 2. Prevalence of CHiP factors in patients with stable angina, stratified by ethnicity (percentage).

rates of previous CABG (47.5%), followed by PCI to a CTO lesion (31.5%) (Supplementary Table 3).

Procedural characteristics varied as well. BAME patients had higher rates of LM PCI, whereas White patients had higher rates of graft PCI (Table 1). Of the BAME patients, the Asians had the highest rates of LM PCI (15.3%) and PCI to a graft vessel (11.4%) (Supplementary Table 3). Overall, BAME patients had more extensive CAD than Whites. BAME patients were more likely to have more than 1 lesion treated and or multivessel PCI than White patients. However, White patients had more extensive calcific lesions as evidenced by higher rates of rotational atherectomy therapy and cutting balloons use. The radial access was used less frequently in BAME (37.5 vs 46.8%, respectively), with fewer procedures in BAME patients using more than 1 access site. Changes in procedural characteristics over time are shown in Supplementary Table 2.

Variations in pharmacotherapy prescription among ethnic groups were observed. Higher prescription rates of warfarin and glycoprotein 2b/3a inhibitors were observed in the White patients. In contrast, BAME patients were treated more frequently with prasugrel and ticagrelor. Similar findings were seen when stratified into 4 ethnic groups (Supplementary Table 3).

Crude and adjusted outcomes, stratified by ethnicity, are shown in Table 2. Overall, crude inpatient mortality and MACCE did not differ between the groups. However, BAME patients had lower bleeding rates (0.5 vs 0.9%, respectively, p <0.001). Following adjustment for differences in baseline covariates, BAME patients had similar mortality (aOR 1.1, 95% confidence interval [CI] 0.8 to 1.5), p = 0.659) and MACCE odds (aOR 1.0, 95% CI 0.8 to 1.1, p = 0.564) but had 30% lower odds for bleeding compared with White patients. Further stratification into 4 groups (Supplementary Table 4 and 5) showed that the lowest rates and odds of bleeding seen in BAME patients were mainly recorded in the "other" ethnic minorities (aOR 0.5, 95% CI 0.4 to 0.8, p = 0.002). No differences in outcomes between the groups were again confirmed with propensity score matching
analysis (Supplementary Table 6).

The temporal trends of crude outcomes among the ethnic groups demonstrated stable mortality rates with no significant differences among the groups, whereas MACCE rates gradually decreased. Bleeding rates remained unchanged in White patients, whereas a gradual decrease was seen among the BAME patients (Supplementary Table 7). The main study design and findings are summerised in Figure 4

Discussion

This analysis of a national cohort of 105,949 procedural records is the first to examine ethnic differences in the risk profile, procedural characteristics, and clinical outcomes of CHiP procedures undertaken in patients with stable angina. The study findings can be summarized as follows: (1) BAME patients were younger, had a worse cardiometabolic risk profile,and were more likely to have multivessel PCI; (2) common CHiP in BAME patients were previous CABG, PCI to a CTO vessel, and treatment of calcific disease; (3) the adjusted in-hospital mortality and MACCE did not differ among the ethnic groups, although bleeding odds were significantly lower in the BAME patients.

Differences in baseline characteristics between ethnic groups have been reported in previous studies.[22,23] The ethnic case-mix in our study is different from that seen in

Table 1
Baseline and procedural characteristics of patients with stable angina undergone CHiP procedure, stratified by ethnicity

VARIABLES	TOTAL	WHITE	BAME	P-VALUE
NUMBER OF PARTICIPANTS	105,949	89,038 (84%)	16,911 (16%)	
AGE MEDIAN IN YEARS, (IQR)	70.2 (61.5-79)	70.6 (62-79.4)	68.1 (58.9-76.5)	
MALES	81,961 (77.3%)	68,505 (77%)	13,456 (80%)	
BMI IN KG (IQR)	28.1 (25.3-31.4)	28.3 (25.4-31.6)	27.5 (24.7-30.8)	
CHIP FACTORS (TYPES)				
• AGE >80 YEARS	23,948 (22.6%)	21,014 (23.6%)	2,934 (17.4%)	< 0.001
• PRIOR CORONARY ARTERY BYPASS	35,610 (34.2%)	29,266 (33.4%)	6,344 (38.3%)	< 0.001
• CHRONIC RENAL FAILURE	11,545 (11.3%)	9,072 (10.6%)	2,473 (15.2%)	< 0.001
• POOR LV FUNCTION	5,431 (8.7%)	4,459 (8.6%)	972 (9.5%)	= 0.002
• LEFT MAIN INTERVENTION	11,913 (11.4%)	9,908 (11.3%)	2,005 (12%)	= 0.010
• CHRONIC TOTAL OCCLUSION PCI	32,055 (32%)	26,890 (31.9%)	5,165 (32%)	= 0.769
• SEVERE VASCULAR CALCIFICATIONS	20,047 (22.9%)	17,564 (23%)	2,483 (18.8%)	< 0.001
• USE OF LV SUPPORT	617 (0.61%)	464 (0.5%)	153 (1.0%)	< 0.001
CARDIOVASCULAR RISK FACTORS				
• HYPERTENSION	66,943 (66.7%)	55,985 (66.5%)	10,958 (68%)	< 0.001
• DYSLIPIDAEMIA	65,944 (65.7%)	55,294 (65.6%)	10,650 (66%)	= 0.368
• DIABETES MELLITUS	26,689 (26.4%)	20,051 (23.6%)	6,638 (41.1%)	< 0.001
• SMOKER				< 0.001
NEVER	38,827 (42%)	30,753 (40%)	8,074 (54.5%)	
FORMER	45,106 (49%)	39,710 (51%)	5,396 (36.4%)	
CURRENT SMOKER	8,709 (9.4%)	7,354 (9.5%)	1,355 (9.1%)	
• FAMILY HISTORY OF CAD	42,811 (46%)	36,151 (46%)	6,660 (46%)	= 0.946
• HISTORY OF MI	43,056 (43%)	35,831 (42.5%)	7,225 (44.9%)	< 0.001
• PREVIOUS PCI	40,031 (38.6%)	32,838 (37.6%)	7,193 (43.7%)	< 0.001
• PREVIOUS STROKE	4,863 (4.8%)	4,286 (5.1%)	577 (3.6%)	< 0.001
• HISTORY OF PVD	7,279 (7.3%)	6,423 (7.6%)	856 (5.3%)	< 0.001
• LEFT VENTRICLE EJECTION FRACTION				= 0.001
>50	43,989 (70.7%)	36,923 (71%)	7,066 (69.33%)	
30-50	12,783 (20.6%)	10,629 (20.3%)	2,154 (21.13%)	
<30	5,431 (8.7%)	4,459 (8.6%)	972 (9.54%)	
PHARMACOLOGY (IN-LAB)				
• WARFARIN	1,957 (2%)	1,735 (2.1%)	222 (1.5%)	< 0.001
• GPIIBIIIA INHIBITORS	7,116 (7.2%)	6,068 (7.3%)	1,048 (6.8%)	= 0.022
• CLOPIDOGREL	77,787 (81.9%)	65,954 (81.9%)	11,833 (81.8%)	= 0.486
• PRASUGREL	891 (0.94%)	707 (0.88%)	184 (1.27%)	< 0.001
• TICAGRELOR	3,495 (3.6%)	2,871 (3.5%)	624 (4.3%)	< 0.001
VASCULAR ACCESS				< 0.001
• RADIAL	46,846 (45.2%)	40,761 (46.8%)	6,085 (37.5%)	
• FEMORAL	48,204 (46.6%)	39,175 (45%)	9,029 (54%)	
• MULTIPLE ACCESSES	8,383 (8.1%)	7,073 (8.1%)	1,310 (8%)	
CIRCULATORY SUPPORT				
• NO SUPPORT	101,000 (99.3%)	84,965 (99.5%)	16,035 (99%)	< 0.001
• IABP	579 (0.57%)	434 (0.51%)	145 (0.9%)	< 0.001
• IMPELLA	41 (0.04%)	31 (0.04%)	10 (0.06%)	= 0.139
NUMBER OF TREATED CORONARY NARROWING				<0.001
• 1	68,342 (65%)	57,952 (65.8)	10,390 (62.2)	
• 2	26,093 (24.9%)	21,663 (24.6)	4,430 (26.5)	
• 3+	10,318 (9.9%)	8,438 (9.5)	1,880 (11.2)	
PROCEDURAL DEVICES				
• NONE	69,484 (77%)	58,771 (76%)	10,713 (81%)	<0.001
• CUTTING BALLOON	12,540 (14%)	10,917 (14.5%)	1,623 (12.5%)	<0.001
• ROTATIONAL ATHERECTOMY	7,662 (8.4%)	6,808 (8.9%)	854 (6.6%)	<0.001
• LASER ATHERECTOMY	518 (0.6%)	452 (0.6%)	66 (0.5%)	= 0.198
NUMBER OF STENTS USED				< 0.001
• 0	15,058 (14.3%)	12,849 (14.6%)	2,209 (13.1%)	
• 1	43,688 (41.6%)	36,563 (41.4%)	7,125 (42.4%)	
• 2	26,501 (25.3%)	22,265 (25.3%)	4,236 (25.2%)	
• 3+	19,759 (18.8%)	16,517 (18.7%)	3,242 (19.3%)	
TARGET VESSEL PCI				
• LEFT MAIN	11,913 (11.4%)	9,908 (11.3%)	2,005 (12%)	= 0.010
• LEFT ANTERIOR DESCENDING	41,699 (40.1%)	35,091 (40.1%)	6,608 (39.7%)	= 0.225

(*continued*)

Table 1 (***Continued***)

VARIABLES	TOTAL	WHITE	BAME	P-VALUE
• LEFT CIRCUMFLEX	26,365 (25.4%)	21,744 (24.9%)	4,621 (27.7%)	< 0.001
• RIGHT CORONARY	36,774 (35.3%)	31,102 (35.6%)	5,672 (34%)	< 0.001
• GRAFT VESSEL	10,381 (9.9%)	8,790 (10%)	1,591 (9.5%)	= 0.044
NUMBER OF TREATED CORONARY ARTERIES				< 0.001
• 0	2,406 (2.3%)	2,212 (2.5%)	194 (1.2%)	
• 1	78,099 (74.4%)	65,868 (74.7%)	12,231 (72.7%)	
• 2	19,849 (18.9%)	16,326 (18.5%)	3,523 (21%)	
• 3+	4,685 (4.5%)	3,818 (4.3%)	867 (5.2%)	

BAME, Black, Asians, Ethnic Minorities; CHiP = complex high risk percutaneous coronary intervention; CAD = coronary artery disease; GPIIbIIIa = glycoprotein IIaIIIb; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; BMI = body mass index; KG = kilogram.

contemporary PCI studies from the United States, reflecting societal differences, with Asians representing the majority of patients in the United Kingdom, as opposed to Black patients in the United States. Nevertheless, the cardiovascular risk profile of BAME patients in our study was comparable with that generally seen in the United States studies.[24] BAME patients were younger and had worse cardiometabolic profiles, with higher rates of hypertension, diabetes mellitus, CRF, and heart failure. Among BAME patients, Asian patients had the worse cardiometabolic burden.

Previous studies examining outcomes in specific CHiP procedure categories reported no significant differences among ethnic groups in clinical outcomes. For example, observational studies from the Pan-London PCI Registry examining PCI outcomes in patients with a history of CABG, the most common CHiP factor in our study, found that Asian and White patients have comparable mortality risks (multivariable, aOR 1.07 [0.97 to 1.17]).[25]

PCI to a CTO vessel was the second most common CHiP factor in our analysis in both groups. Interestingly, a retrospective analysis from the United States found that Black ethnicity was a predictor for lower success in a CTO PCI (hazard ratio [HR] 0.6, [0.50 to 0.92], p = 0.013).[26] In our analysis, White patients had more extensive vascular calcification than BAME, which may relate to the fact that White patients were older and hence, more likely to have heavier vascular calcifications; this was also seen in a multicenter, retrospective analysis on 12,445 patients from the United States (aOR for vascular calcifications 1.57 [1.42 to 1.73], p <0.001).[27] The same study found that old age (aOR 1.04 [1.03 to 1.04], p <0.001) and history of PVD (aOR 1.32 [1.13 to 1.54], p = 0.0004) were also associated with severe vascular calcification, both of which were more prevalent in White patients in our study. The impact of ethnicity on the angiographic characteristics and clinical outcomes after PCI were examined in 1,863 females with CAD pooled from the PLATINUM Diversity and PROMUS ELEMENT PLUS postapproval studies;[22] the study found differences between African-American women (larger reference vessels diameter and fewer lesion calcifications) and Hispanic women (longer and more calcific disease) compared with White women. Despite these differences, odds for death and MACCE were similar between the groups.[22]

In our study, more BAME patients had PCI to LM than Whites. A previous retrospective analysis from a single center in the United States reported that African-American ethnicity is an independent risk factor for worse outcomes in LM PCI (HR 2.71, 1.44 to 5.10, p = 0.002) for both short- and long-term outcomes.[5] We also observed that a greater proportion of BAME patients had CRF, similar to findings from a retrospective study on 474 chronic dialysis patients from 4 centers in the United States, where ethnicity per se was found to be not associated with worse outcomes (p = 0.069).[12]

Despite the significant differences mentioned earlier among the groups, our study showed that mortality and MACCE odds were comparable, suggesting that ethnicity was not a marker for worse short-term outcomes, similar to findings from many studies around non-CHiP procedures.[3,4,28] We report that bleeding risk was significantly lower in the BAME patients than Whites. This could be related to the fact that BAME patients were younger, had lower rates of severe vascular calcifications, and had lower use of calcium modification devices, meaning their risk of coronary perforation (hence, bleeding complications) was lower. On the contrary, a higher proportion of White patients in our study met some of the criteria for high bleeding risk as per The Academic Research Consortium definition;[29] such as age >80 years, use of anticoagulation (warfarin) and glycoprotein 2b/3a inhibitors, and history of stroke. In support

Table 2
CHiP crude and adjusted outcomes of patients with stable angina, stratified by ethnicity

Variables	Overall	White	BAME	Adjusted odds ratio (95% CI)
Mortality	308 (0.3%)	258 (0.3%)	50 (0.3%)	aOR 1.1 (0.8-1.5), p=0.659
Bleeding	850 (0.9%)	758 (0.9%)	92 (0.5%)	aOR 0.7 (0.6-0.9), p=0.002
MACCE	1,538 (1.5%)	1,312 (1.5%)	226 (1.3%)	aOR 1.0 (0.8-1.1), p=0.564

CHiP = complex high risk percutaneous coronary intervention; MACCE = major cardiovascular and cerebral events.

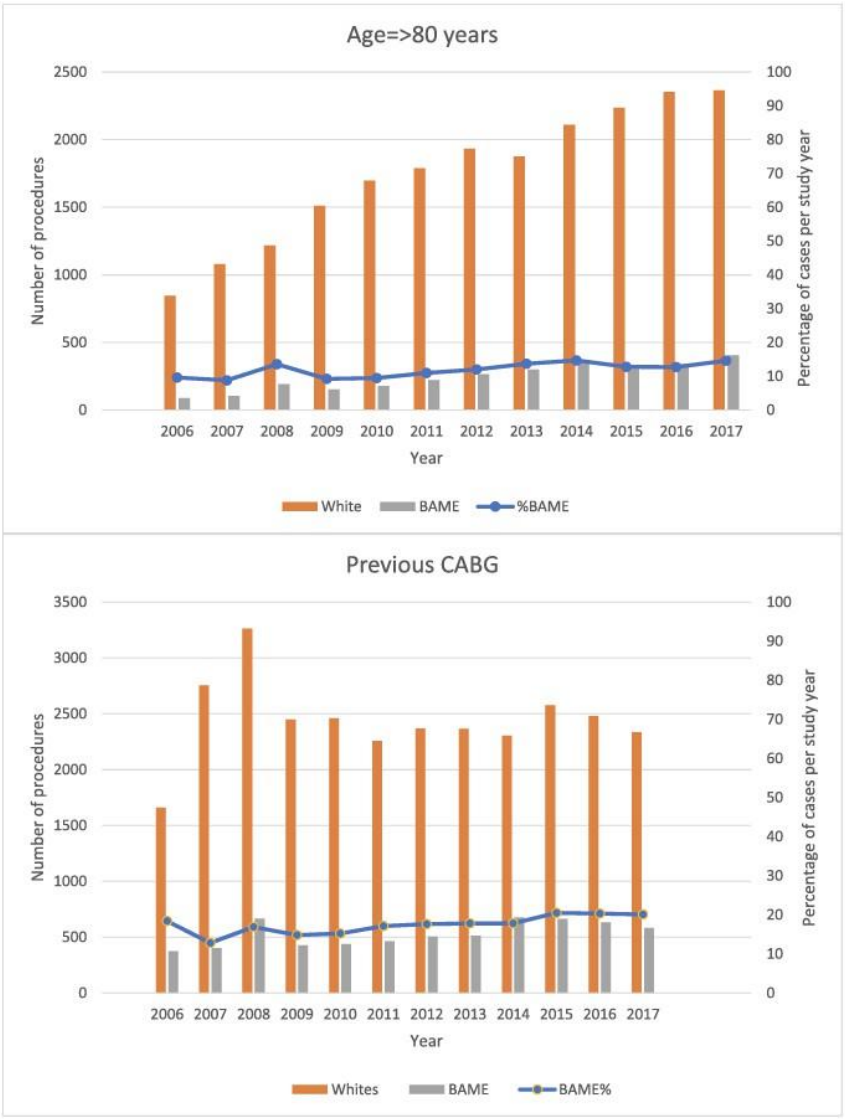


Figure 3. Temporal changes in prevalence of each CHiP factor among patients with stable angina and per cent change over time, stratified by ethnicity.

of this, an analysis on 9,244 patients from a single center in the United States demonstrated a larger proportion of White patients meeting high bleeding risk criteria and experiencing major bleeding events than BAME patients.[30] Nevertheless, the rates for using the femoral access, IABP, and more potent antiplatelets (ticagrelor and prasugrel) were higher among the BAME patients.

The observation in which younger BAME patients with worse cardiometabolic profiles experience similar outcomes to older White patients has been reported in other studies

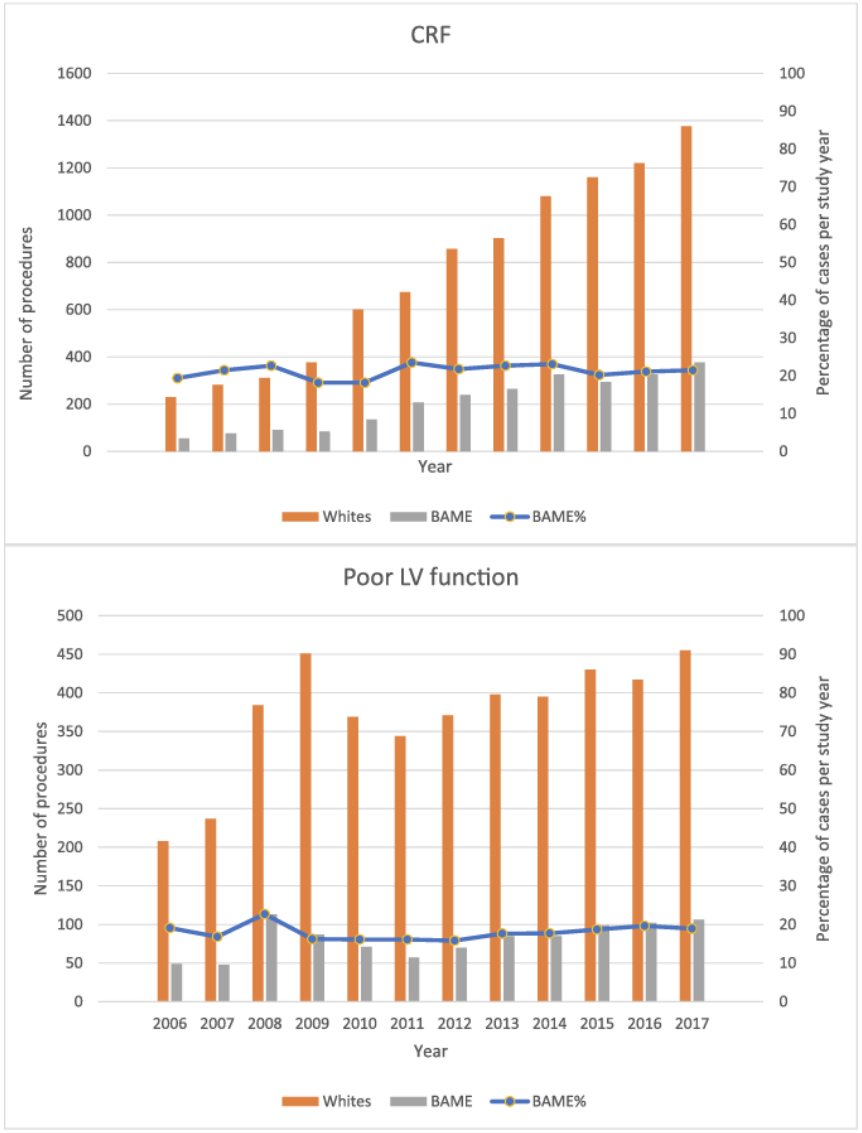


Figure 3. Continued

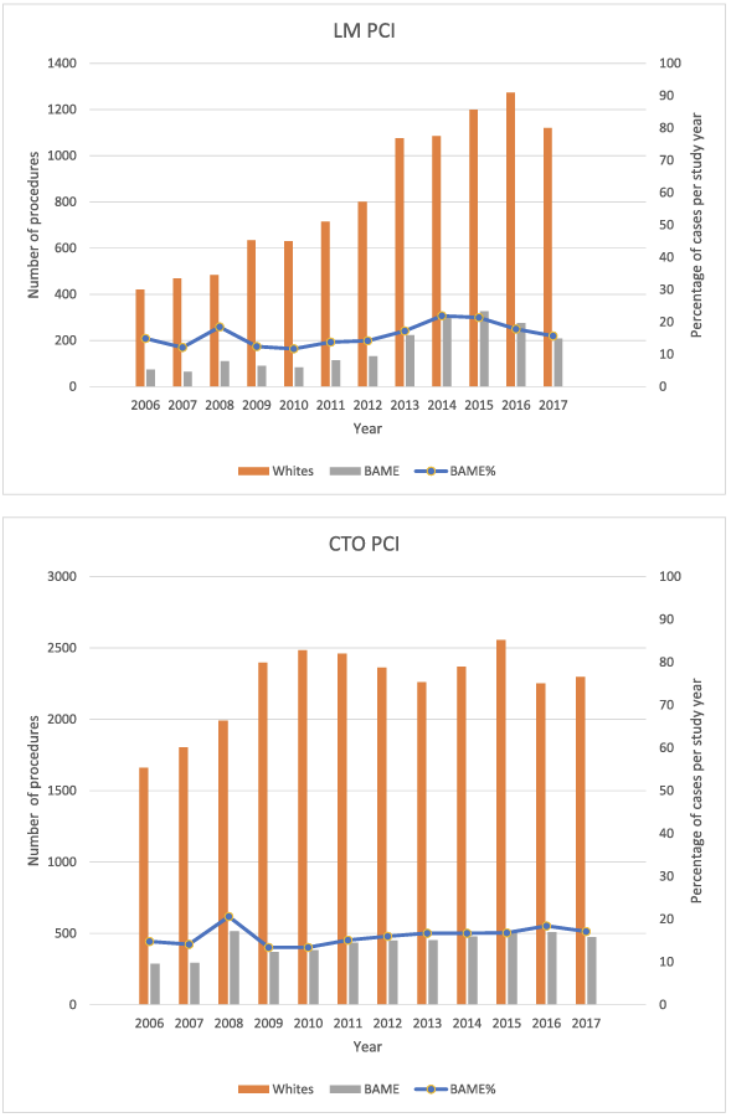
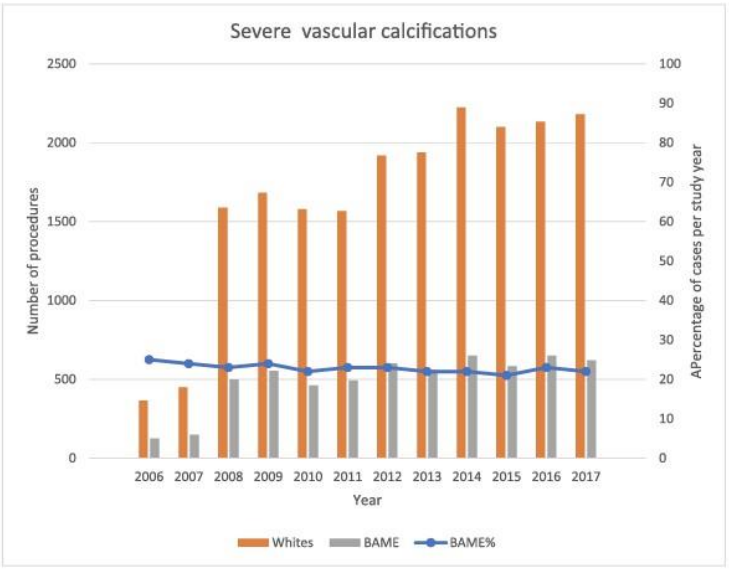
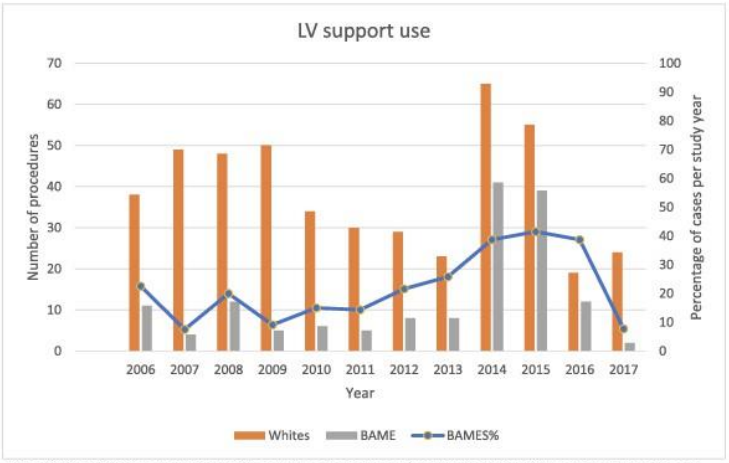


Figure 3. Continued





Abbreviation: CHiP, complex high risk percutaneous coronary interventions; CABG, coronary artery bypass graft; CTO, chronic thrombus occlusion; LV, left ventricle; LM, left main stem; PCI, percutaneous coronary intervention.

Figure 3. Continued

that focused on noncomplex PCI in the short term. However, the same is often not true in comparing longer-term outcomes.[31] For example, a retrospective study from a multicenter complex in the United States comparing outcomes of noncomplex PCI among African-American and White patients demonstrated no significant short-term outcomes, but significant worst outcomes were only seen at 5 years follow-up in the African-American group (adjusted HR 1.44, 95% CI 1.03 to 2.00, p = 0.03).[31] This raises the question of whether longer-term outcomes will be worse in

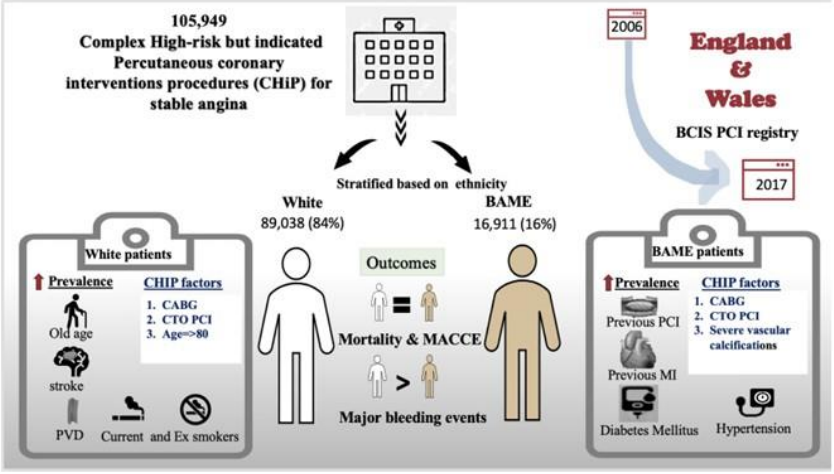


Figure 4. Graphical abstract summarizing the main findings of a retrospective study that looked at CHiP types, baseline patients' characteristics and clinical outcomes of patients with stable angina stratified by White and BAME groups.

BAME patients after CHiP procedures. Nevertheless, our findings are reassuring in that in a universal healthcare system with universal coverage of patients irrespective of ethnicity, complex PCI outcomes are similar. This highlights that disparities observed in other healthcare systems may reflect disparities in healthcare provision.

Our analysis should be considered in light of the following strengths and limitations: to the best of our knowledge, this is the first study that has examined ethnicity-stratified CHiP outcomes in a real world, unselected setting at a national level. Over 99% of cases performed in England and Wales are recorded in the BCIS database. The sample size was large enough to provide sufficient statistical power to determine whether there is a real difference in ethnicity-based CHiP outcomes. As with all observational studies, there are several limitations. First, there is the potential for the presence of unmeasured confounders in both clinical and procedural variables such as socioeconomic status, frailty, control and duration of cardiovascular risk factors such as diabetes, and lesion complexity that may affect the clinical outcomes that we report. Second, there is always the risk of reporting and coding errors that could represent a potential bias, such as the underreporting of other co-morbidities, and complications that are self-reported with no external validation. Third, the BCIS dataset captures ethnicity as Asian, Black, White, and Other, and so the "Other" category is likely to represent a heterogenous racially diverse population. Lastly, the BCIS dataset only captures in-hospital outcomes, and we cannot rule out significant differences in the longer term.

In conclusion, this nationwide analysis has shown significant differences in the types of CHiP procedures undertaken and in the ethnicity case-mix and baseline clinical and procedural characteristics. BAME were younger, with a greater co-morbid burden, and had a more complex coronary disease. Despite these differences, we found no differences in in-hospital mortality and MACCE after CHiP once differences in baseline characteristics were adjusted. Bleeding risk was significantly lower in the BAME patients. Ethnicity should not be considered as a barrier in the decision-making process around CHiP PCI procedure.

Disclosures

An unrestricted educational grant from Abbott supports Dr. Shamkhani salary. The remaining authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.03.056.

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10.4 Appendix 4 – Statistical validation

10.4.1 Sex differences in High Risk but indicated Percutaneous coronary intervention

Manuscript ID: **CCI-21-1600**

Keele Cardiovascular Research Group

Dear Professor Bailey, MD, Editor-in-Chief,

Please find enclosed our revised manuscript "Sex differences in High Risk but indicated Percutaneous coronary interventions (CHiP): national report from British Cardiovascular Intervention Society Registry" for consideration for publication in the *Catheterisation and Cardiovascular Intervention Journal.* We thank the Editorial Committee and Reviewers for their careful appraisal of the paper and their points, to which we have responded below. We feel that these comments have improved the quality of our manuscript. We hope that we have addressed all reviewers' comments sufficiently and hope that these changes will enable the publication of our paper in your esteemed journal.

Yours sincerely,

Professor Mamas A. Mamas

On behalf of submitting authors

Editors comments

Review of your manuscript # CCI-21-1600 entitled "Sex differences in High Risk but indicated Coronary Interventions (CHiP): national report from British Cardiovascular Intervention Society Registry" has been completed. The review process tends to generate candid comments, which at times may seem overly critical. Please accept these criticisms in the positive spirit in which they are intended.

Your manuscript is not acceptable for publication in its present form. The Editors believe that the manuscript would be suitable for publication if the reviewer's comments/questions are addressed and appropriate changes made. Comments will appear either as text at the bottom of this letter or as a separate file in your author center if the reviewer uploaded a separate file.

Response: We thank the Editor for considering our manuscript and acknowledge that all outlined remarks have substantially improved our manuscript. We have responded to each raised point to the best of our efforts and provided a *Response to Reviewers*, indicating changes made to the manuscript.

Reviewer's Comments (1)

General comments:
Comments to the Author:
In this manuscript, authors aimed to investigate the sex-based differences in in-hospital clinical outcomes after complex and high-risk but indicated percutaneous coronary intervention (CHiP), in patients with stable coronary artery disease who underwent PCI and included in the British Cardiovascular Intervention Society Registry.

The study results demonstrated that female patients undergoing CHiP procedures had higher adjusted odds ratio for mortality (OR: 1.78, 95%CI:1.4-2.2), bleeding (OR:1.99, 95%CI: 1.72-3.2), and major adverse cardiovascular and cerebral events (OR:1.23, 95%CI: 1.09-1.38) compared with male patients.

I think that this manuscript is well written, and this study provides some important clinical implications, particularly for the management of patients undergoing CHiP procedures.

The advantages of this study include large sample size from the multicenter nationwide database, sufficient data collection including temporal changes in the prevalence of each CHiP factors, important statistical analyses, and an impressive central figure regarding the summary of key findings of this study (Figure 4). However, there are some important issues that should be addressed in the current manuscript.

Response: We are grateful to the Reviewer for considering our manuscript and providing a critical review of its content. It has undoubtedly improved our manuscript and will help the readers to better understand its results/conclusions.

Major comments:
Comment 1. In general, female patients with coronary artery disease tend to have lower body mass index (BMI) than male patients. Data regarding differences in physique between male and female patients were lacking in the current manuscript. BMI value in Table 1 would be informative to understand the differences in characteristics between genders. Because potential overdosing of antiplatelets or anticoagulants might be a potential explanation of higher incidence of bleeding events in female patients than male patients, differences in BMI between genders would be important in this study.

Response: We thanks the reviewers for pointing out this important remark. We have now included BMI in table 1 and indeed report that BMI was lower in female patients compared to male patients. We agree that potential overdosing of antithrombotic agents may contribute to the higher bleeding event rates in females that we report. We included BMI in our models and

!!1 \l reporteclon the% of males and females with a weight below 60 kg. Analysis for the same was added in Table I (see highlighted Table I). We included **BMI** in our analysis models; adjusted outcomes were updated in Table 3 (see attached table). We also have added the following lines in the following sections (outlined below and marked in the manuscript).

Under *statistical analysis* section: *"The variables included in .the model were age, BMJ, history of dyslipidaemia ...*

Under *clinical charcteristics* section::::: *Hz,igher percentage of females had weight below 60 (males:1.4% vs. females: 14.1%) and lower BMJ readings (males: 28 (25.4-31.34); females: 27 (24.7-32)··*

Table I: Baseline clinical and procedur.al characteristics of patients with stable angina undergoing CHiP, stratified by sex.

	Total, n	**Males, n** (⁷/•)	**Females, n** (o/,)	**P-value**
Number ofpartlelpanfs	141,610	109,481 (77)	32,129 (23)	
Age Median, (IQR)	70.5 (61.9 -79.6)	69.1 (60.7 - 77.5)	75.1 (65.8 -81.&)	
13MI Median, (IQR)		8 (25.4-3134)	7(24.7-32)	
ght<60 kg) !!,_{%)		I 580 11.4%	.lli._(_!A_.!JiJ	
CHlP risk factors				
a) Patients' factors				
Age>80	32,427 (23)	21,030{19.2)	11,397 (35.4)	<0.001
Prii,r CABG	46,299 (33.4)	38,716{36)	7,583 (24.3)	<(1.001
• **Chronic Renal Failure**	14,895 (11)	12,234 {l L7)	2,661 (9)	<0.001
Poor LV function	7,837 (9.4)	6,472(10)	1,365 (7.3)	<(1.001
I>) **Procedural factors**				
LMS PCI	16,220 (12.4)	12,561(11,7)	3,659(11.6)	0.694
CTO PCI	44,184 (33)	35,735{34.4)	8,449 (21.1)	<0.001
• **Severe coronary calcifications**	25,743 (22.2)	19,779 {22)	5,964 (22.6)	*O.o35*
Use of LV support	768 (0.57)	*5n* (0.55)	195 (0.64)	0.064
Cardiovascular risk factors				
• **Hypertension**	87,128 (65.5)	66,206 **{64.4)**	20,922 (69)	<(1.001
• **Dysliplda**emia	85,949 (64.6)	66,547 {64.7)	19,402 (64)	0,081
Diabetes	35,091 (26)	27,409 {26.3)	7,682 (25)	<(1.001
Smoking				<0.001
Never	51,224 (41.6)	35,492 {37)	15,712 (56)	
Ex-fmokuf	60,046 (48.&)	50,254 {52.8)	9,792 (35)	
Current smokt!rS	11,833 (9.6)	9,401 (9.9)	2,432 (8.7)	
Family history of CAD	52,183 (46.7)	43,784(46.6)	I3,040 (47.2)	0.054
History <>f Ml	56,294 (42.6)	45,602 {44.6)	10,692 (35.6)	<0.001
• **Previous PCI**	48,763 (38.2)	39,201{40)	9,562 (32.5)	<(1.001
Previous stroke	6,300 (4.7)	4,820 (4.7)	1,480 (4.9)	0.135
History <>f PVD	9,175 (6.9)	7,244 (7)	1,931 (6.4)	<(1.001
LV systolic functlon				<0.001

Table 3: Adjusted odds of adverse outcomes post CHiP in patients with stable angina (reference, females)

	Odd ratio	95% Confidence Interval	P-value
Death	2.2	1.6-2.8	0.001
Bleeding	2.6	2.1-3.1	0.001
MACCE	1.3	1.2-1.4	0.001

Abbreviation: CHiP, complex high-risk but indicated percutaneous coronary intervention; MACCE, major cardiovascular and cerebral events.

<u>Comment 2.</u> There were large differences in baseline clinical characteristics between male and female patients in this study. In particular, average age was significantly higher in female patients than male patients (75.1 vs. 69.1 years). Although authors tried to adjust some of the baseline characteristics and confounding variables in multivariable analyses, some bias might not have been completely adjusted in this study. Subanalysis in each age group may be an option.

Response: We thank the reviewer for pointing out this interesting remark. We have undertaken a separate paper on the impact of age in CHIP outcomes, by stratifying patients into separate age categories. Nevertheless, for the purpose of this submission, we have conducted an additional internal sensitivity analysis by age groups (<50; 50-79; ≥80 years) to determine whether age was a confounding/ bias in the observed outcome between sexes (*outlined in the Supplemental Table below*). The results generally indicate higher events rates in female patients across age groups, including higher mortality, MACCE and major bleeding events.
We have provided an additional explanation of the same in the *Clinical outcomes* section of the manuscript (outlined below and marked in the manuscript).
Under *Clinical outcomes* section of the manuscript: "*Age stratification of outcomes according to sex suggested again worse outcomes in females (Supplementary Table 2).* "

Supplementary Table 2

Outcome rates of patients with stable angina underwent a CHiP procedure according to three age groups and stratified by sex.

	<50 n (%)	50-79 n (%)	=>80 n (%)	p-value
Death				
Males	5 (0.08)	182 (0.22)	88 (0.41)	0.001
Females	3 (0.25)	84 (0.43)	59 (0.51)	0.336

Bleed				
Males	18 (0.28)	304 (0.37)	99 (0.47)	0.051
Females	3 (0.25)	202 (1.04)	110 (0.96)	0.027
MACCE				
Males	74 (1.14)	1,117 (1.37)	343 (1.61)	0.004
Females	13 (1.01)	341 (1.75)	213 (1.85)	0.164

Comment 3. The baseline haemoglobin level (or presence of anaemia), as well as renal dysfunction and/or diabetes mellitus, may be strongly associated with adverse clinical outcomes such as mortality and/or bleeding in patients undergoing PCI. In general, female patients tend to have higher prevalence of anemia and lower baseline hemoglobin levels than male patients. Therefore, the baseline hemoglobin values or prevalence of anemia, in addition to the prevalence of chronic renal failure, should be included in the Table 1.

Response: We agree with this observation that anaemia tends to be more prevalent in females, and it is associated with worse bleeding and mortality outcomes. Unfortunately, the BCIS database does not capture Haemoglobin. A line has been added in the *manuscript's study limitation* section (outlined below and marked in the manuscript).

Under the *Study limitations* section of the manuscript: "*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, for example, information about anaemia, and frailty, which is likely to be more prevalent in the females is not recorded in the BCIS registry.*

Comment 4. Given the low event rates especially in mortality (0.3%), findings from the multivariable analyses should be cautiously interpreted.

Response: The total number of mortality events in our study was 421. In outcome analysis, the rule of thumb is usually followed (logistic regression and Cox models should be used with a minimum of 10 outcome events per predictor variable (EPV))[1]. However, in the analysis of causal influences in observational data like in our study, control of confounding may require adjustment for more covariates than the rule of 10 or more EPV allows [1]. Before using our model to estimate effects, we evaluated the assumptions implied by the model against both data and prior information obtained from the literature search. This method has been suggested as an effective way of tackling this issue[1]. Additionally, our mortality figures were comparable to other studies, and our sample size was large enough to provide a meaningful conclusion.

We have amended our manuscript to reflect the same (outlined below and listed in the *Methods section* of the manuscript).

Under the *Methods* section of the manuscript: "*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* "(see reference [1]).

Reviewer's Comments (2)

Comment to the author:

In this study, Shamkhani et al report the cardiovascular outcome of patients undergoing CHIP (complex and high-risk intervention in indicated patients) procedures stratified by their sex. It has been previously reported that female have higher risk of adverse outcome after PCI compared to male and they extend this finding to the CHIP population.

The strength of this study is the large number of patients included in the analysis. The clinical question is concisely stated and addressed.

Response: We are thankful to the Reviewer for their interest in our work. The reviewers' thorough analysis of our manuscript with helpful comments and suggestions has improved our manuscript. We have provided a point-by-point response to the best of our efforts.

Specific comments:

Comment 1. The large number of missing data, especially LVEF, one of the inclusion criteria for CHIP (missing in 41% of patients), is a limitation of the study.

Response: Thank you for highlighting this important issue. We agree with the reviewer that there is a large number of missing data in the LVEF variable. Whilst missing variables were imputed, the large number might be considered a limitation of the study. However, studies have shown that the proportion of missing data should not be used to guide decisions about performing multiple imputations or not; rather, the fraction of missing information should guide the choice of auxiliary variables in the imputation analysis[2]. Also, in agreement with previous studies, the recommendation was to use all available data even when variables of interest have extensive (20-80%) missiningness[3]. It is agreed that multiple imputation models that exclude such covariates seem to perform much worse [4]. We have amended the study Methods section

of our manuscript to reflect the same (outlined below and listed in the *Methods section* of the manuscript).

Under *Methods* section: "*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. (Reference 4-6)*

Comment 3. 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.

Response: We are thankful for this remark. Some of the small defferences were statistically significant. For example, Diabetes (26.3 vs 25%). Effect sizes describe the magnitude of a quantitative relationship between variables. The confidence interval CI can be used to determine whether a finding is statistically significant and helpful in determining the clinical significance. Moreover, we have discussed only those variables with clinically meaningful differences in our paper. We have provided some literature-based speculations about the possible clinical significance for these findings (cited below).
Under *Study limitations section*: "*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.* (Reference[5])

Comment 4. The reference section needs to be sorted consistently.

Response: We thank the reviewer for their remark. We have amended the reference section.

Comment 5. The graphs for temporal trend of each CHIP factors is interesting. Consider elaborating further in the discussion.
Response: We thank the reviewer for their comment and acknowledge the importance to elaborate further. We have included additional elaborations in the *Results and Discussion* section (outlined below and listed in the *Results and Discussion section* of the manuscript).

Under *Results section „* *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 except for those cases with LM PCI and CTO PCI. There was a gradual increase in the percentage of females undergoing LM PCI (2006: 10% vs*

2017: 15%; and a gradual decrease in the percentage of cases undergoing PCI to a CTO vessel (2006: 42% vs 2017; 29%. "

Under the *Discussion section*: "*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 be managed medically due to either age, comorbidities, and a higher perception of complications. In contrast, trends of LMS PCI* rates *in the females showed a gradual increase. This may reflect that female patients are less likley to be offered cardiac surgery than male patients, and so may be more likley top 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."—see reference[6] [7, 8]*

1. Greenland, S., *Modeling and variable selection in epidemiologic analysis.* American Journal of Public Health, 1989. **79**(3): p. 340-349.
2. Madley-Dowd, P., et al., *The proportion of missing data should not be used to guide decisions on multiple imputation.* Journal of Clinical Epidemiology, 2019. **110**: p. 63-73.
3. Janssen, K.J., et al., *Missing covariate data in medical research: to impute is better than to ignore.* J Clin Epidemiol, 2010. **63**(7): p. 721-7.
4. Kontopantelis, E., et al., *Outcome-sensitive multiple imputation: a simulation study.* BMC Medical Research Methodology, 2017. **17**(1).
5. Schober, P., S.M. Bossers, and L.A. Schwarte, *Statistical Significance Versus Clinical Importance of Observed Effect Sizes.* Anesthesia & Analgesia, 2018. **126**(3): p. 1068-1072.
6. Patel, B., et al., *Percutaneous coronary intervention and inpatient mortality in patients with advanced chronic kidney disease presenting with acute coronary syndrome.* Proc (Bayl Univ Med Cent), 2017. **30**(4): p. 400-403.
7. Guo, L., et al., *Gender Differences in Long-Term Outcomes of Medical Therapy and Successful Percutaneous Coronary Intervention for Coronary Chronic Total Occlusions.* Journal of Interventional Cardiology, 2019. **2019**: p. 2017958.
8. Akodad, M., et al., *Is sex associated with adverse outcomes after percutaneous coronary intervention for CTO?* Int J Cardiol, 2019. **288**: p. 29-33.

10.4.2 Complex, High-risk Percutaneous Coronary Intervention Types, Trends, and In-hospital Outcomes Among Different Age Group. An Insight from a National Registry.

Manuscript ID: **CCI-21-2141**

Keele Cardiovascular Research Group

Dear Professor Bailey, MD, Editor-in-Chief,

Please find enclosed our revised manuscript " **Complex, High-risk Percutaneous Coronary Intervention Types, Trends and In-hospital Outcomes Among Different Age Groups. An Insight From a National Registry** " for consideration for publication in the *Catheterisation and Cardiovascular Intervention Journal.* We thank the Editorial Committee and Reviewers for their careful appraisal of the paper and their points, to which we have responded below. We feel that these comments have improved the quality of our manuscript. We hope that we have addressed all reviewers' comments sufficiently and hope that these changes will enable the publication of our paper in your esteemed journal.

Yours sincerely,

Professor Mamas A. Mamas

On behalf of submitting authors

Editors comments

The authors report from a database from the registry of British Cardiovascular Intervention Society (BCIS). This database includes in-hospital procedural data from 112 of the 117 PCI centers in the UK. The study population consisted 138,831 patients who underwent PCI with at least one clinical or procedural high-risk (CHIP) feature for stable angina between 2006 and 2017. Clinical high-risk features were defined as any patient with a previous history of CABG, chronic renal failure, or severely impaired left ventricular function. The procedural (anatomical) high-risk factor was defined as any left main PCI, severe vascular calcification, chronic total occlusion PCI, or the need for LV support. In-hospital mortality was the primary outcome of interest and the secondary outcomes included in-hospital MACCE and major bleeding complications The determinant of interest was age stratified as < 65, 65-79, and => 80

years.The statistical analysis of the in-hospital outcomes was straightforward with baseline characteristics and in-hospital rates of mortality, major bleeding, and MACCE for the three age groups. The authors observed small increasing rates by age of in-hospital mortality (0.2%, 0.3%, and 0.5%), bleeding (0.7%, 0.9%, and 1.0%), and MACCE (1.3%, 1.6%, and 1.7%). Because of the large numbers, the P values for these differences were all < 0.001. The authors also presented adjusted Odds Ratios for the 3 outcomes, which were in line with the crude proportions. Please do add the CHIP score that you have developed for the groups. Your manuscript would benefit from presenting the hgb values for these groups. Your table indicates differences in number of vessels, number of non-PCI procedures and stents. Please provide information regarding the degree of complete Revascularization versus incomplete Revascularization.

Response: We thank the Editor for considering our manuscript and acknowledge that all outlined remarks have improved our manuscript. We have responded to each raised point to the best of our efforts and provided a *Response to Reviewers*, indicating changes made to the manuscript.

Regarding the Editor comments :

1) We elected to not use the CHIP score as we have already adjusted for differences in clinical and procedural characteristics and further adjusting by CHIP score would introduce co-linearity into models. Furthermore many readers wont be familiar with a CHIP score that was only recently published and so would prefer to perform adjustment using conventional risk factors that readers will be more familiar with. Finally introduction of the concept of CHIP scores would lose the focus of the manuscript in which we have already added substantial further data as requested by reviewers

2) Unfortunately, BCIS dataset does not provide us with information about hgb/anaemia and this was stated clearly in our study limitation section (outlined below and marked in the manuscript).

Under study limitation section" *Secondly, there is the potential for unmeasured confounders in clinical and procedural variables such as socioeconomic status, anaemia, frailty[1], control of cardiovascular risk factors such as diabetes, and lesion complexity that may impact clinical outcomes that we report"*

3) Our study data were obtained from the BCIS dataset, unfortunately, the dataset does not provide us with information related to the degree of completeness of revascularisation. We have added a line in study limitation (outlined below and marked in the manuscript).

Under study limitation section". *Moreover, BCIS dataset does not provide information on the completeness of revascularisation"*

Reviewer's Comments (1)

General comments:
Comments to the Author:

In the present revised manuscript entitled "Complex, High-risk but Indicated Percutaneous Coronary Interventions (CHiP) Types and Outcomes Amongst different Age Groups. An Insight From a National Registry", the authors reported in-hospital clinical outcomes of CHiPs identified from the British Cardiovascular Intervention Society (BCIS) registry during the years 2006-2017.The study aims were to verify: 1) if patient's age is related to worst outcomes; 2) if there are different CHiPs types according to patient's age.The authors conclude that older age is an independent risk factor for worse in hospital outcomes.The manuscript is well written but some critical consideration must be done

Response: We are grateful to the Reviewer for considering our manuscript and providing a critical review of its content. It has undoubtedly improved our manuscript and will help the readers to better understand its results/conclusions.

Major comments:

Comment 1. Patient age is an inherent risk factor of CHiP definition criteria and it has been demonstrated to be an important predictor of worst outcomes following PCI in the overall population. Moreover, a novel score to predict outcomes in CHiP patients, recently published in 2021 but not cited in the present manuscript, (Brener et al. A Novel Risk Score to Predict One-Year Mortality in Patients Undergoing Complex High-Risk Indicated Percutaneous Coronary Intervention (CHIP-PCI). J Invasive Cardiol. 2021 Apr) has clearly identified the role of each different factor contemplated in the CHiP definition, including age, in affecting the patient's outcome.

Response: We thank the reviewers for their comment. We congratulate the reviewer for publication of their risk score - nevertheless it is not relevant to our manuscript so have chosen not to cite it. Our manuscript's main aim was to show differences in the types of CHIP procedures undertaken in different CHIP groups, aswell as differences in the risk profile of patients. Importantly we highlight that types of CHiP undertaken for stable angina differ according to age. There was a tendency toward less cardiovascular risk burden and lower disease complexity in the older patient groups, suggesting a degree of selection bias at the operator level that we highlight in the discussion.

Comment 2. The authors do not state in the title that the outcome is in-hospital only, while the long term one would have been more interesting. Indeed, especially for the oldest patient, in the context of chronic coronary artery disease, a clear long term outcome benefit after PCI is not still proven; that's why some concern may still exist if to revascularize or not these subsets of patient, especially if a complex procedure is planned with inherent theoretical higher complication rates.

Response: We thank the reviewer for pointing out this remark. We agree in chronic coronary syndrome, RCTs would suggest that the main benefit is symptom control rather than prognosis. Furthermore, this study isn't really structured to look at prognostic benefit of CHIP procedures, particularly in the older patient groups that the reviewer highlights as one would need a matched control group that were managed medically that we don't have. We have declared clearly that the outcomes were in-hospital outcomes in our study definition, results, and study limitation

sections. We have changed the title to reflect the same as outlined below and marked in the manuscript.

Under *Title* of the manuscript: " *Complex, High-risk Percutaneous Coronary Interventions (CHiP) Types, Trends and In-hospital Outcomes Among Different Age Groups. An Insight From a National Registry*. "

Comment 3. In conclusion I believe that the manuscript, in the present form, is not appealing and the authors should rather rearrange the study in a completely new fashion, probably taking in account other different comparison subgroup of patients, treatment trends across the last two decades or in-hospital outcomes related to the operator expertise.

Response: We thank the reviewer for their evaluation and remarks. In- hospital outcomes related to operator experience in CHiP was a research question that has already been answered by us in a previously published paper, hence we could not repeat the same here [4].

The purpose of this investigation was to determine whether there were differences in types of CHiP undertaken in different age groups, whether patient risk factor profile and procedural complexity varies and their outcomes. This is our research question - that is the authors perogative.

Nevertheless we have taken on board the reviewer's suggestion for assessment of temporal trends and that the reviewer for their suggestion- we have run the analysis for the same and added a new paragraph in the results section titled "Temporal Trends " where we discussed the results. We have taken 2011 as the midpoint of the study and compared outcomes before/ after otherwise sample size would be too small when stratifying by age group and year. We added Supplementary Tables 2 as outlined here and mentioned in the manuscript

Under the *Temporal trends of the Results* section of the manuscript: "*Figure 3 shows the temporal changes in the prevalence of each CHiP factor stratified by age. There was an expansion of the different types of CHiP cases across all age groups over time. The greatest increase in the prevalence of prior CABG occurred in octogenarians. Similarly, the greatest expansion of PCI for LM, CTO, and calcific vascular disease occurred in this group.*

Supplement Table 2 further details the temporal changes in baseline characteristics and clinical outcomes across three age groups (G1, <65 years; G2, 65-79 years; G3, =>80 years). Overall, the prevalence of cardiovascular risks increased across all age groups, except for current smokers in those =>65 years (G2: 6.5 % (<2011) vs 6 % (>2011); G3: 3% (<2011) vs 3.5%

(>2011); p<0.001. There were no changes in prevalence of Dyslipidaemia, prior MI, previous stroke, across all age groups. Although radial access trends show increase in all age groups, the greatest was seen among the octogenarians (<2011, 31% vs >2011, 64%); p<0.001. Interestingly, mortality trends across the 3 age groups did not change (G1, p<0.051; G2, p<0.450; G3, p<0.0.185). Whereas major bleeding and MACCE events showed significant declines seen across all age groups with the greatest decline observed in the octogenarians (MACCE: 2.1% before 2011 vs 1.5% after 2011; Major bleeding: 1.2% before 2011 vs 0.6% after 2011), p<0.001 for all."

Supplement Table 2
Temporal trend of baseline and procedural characteristics and clinical outcomes of CHiP undertaken in patients with stable angina stratified according to three age groups (< 65, 65-79, and 80 and above years)

Age group	< 65 years		p-value	65-79 years		p-value	=>80 years		p-value
Year of study	=<2011	>2011		=<2011	>2011		=<2011	>2011	
Total number	22,499	24,333		25,844	33,700		22,499	24,333	
Hypertension	11,816 (56%)	14,530 (63%)	< 0.001	15,521 (64%)	22820 (72%)	< 0.001	7,690 (67%)	13,731 (72%)	< 0.001
Dyslipidemia	13,824 (66%)	15,235 (66%)	0.246	16,089 (67%)	20,992 (66%)	0.224	7,021 (61%)	11,682 (61%)	0.519
DM	5,099 (23%)	6,663 (29%)	< 0.001	13,824 (66%)	15,235 (66.4%)	< 0.001	1,999 (17%)	4,135 (21%)	< 0.001
Current smokers	3,348 (18%)	4,006 (18.4%)	< 0.001	1,414 (6.5%)	1,802 (6%)	0.019	311 (3%)	441 (2.5%)	< 0.001
Previous MI	8,910 (44.5%)	10,204 (43%)	0.008	10,682 (47%)	14,650 (45%)	< 0.001	4,008 (36%)	6,970 (36%)	0.553
Previous PCI	7,499 (35%)	10,830 (45%)	< 0.001	8,753 (35%)	14,748 (45%)	< 0.001	3,275 (28%)	7,335 (37%)	< 0.001
Previous stroke	640 (3%)	726 (3%)	0.490	1,230 (5%)	1,720 (5.5%)	0.088	720 (6%)	1,194 (6%)	0.952
PVD	1,047 (5%)	1,213 (5%)	0.159	1,956 (6%)	1,194 (6%)	0.734	942 (8%)	1,382 (7%)	0.003

Radial access	6,092 (28%)	12,862 (54%)	< 0.001	6,946 (28%)	18,554 (56%)	< 0.001	3,744 (31%)	12,605 (64%)	< 0.001
Mixed access	1,154 (5%)	4,161 (17%)	< 0.001	967 (4%)	4,201 (13%)	< 0.001	304 (2.5%)	1,206 (6%)	< 0.001
Clinical outcomes									
• Death	45 (0.2%)	31 (0.1%)	0.051	79 (0.3%)	115 (0.3%)	0.450	64 (0.5%)	83 (0.4%)	0.185
• Major Bleeding	178 (0.8%)	134 (0.6%)	0.001	233 (0.9%)	286 (0.9%)	0.491	146 (1.2%)	151 (0.6%)	< 0.001
• MACCE	347 (1.5%)	255 (1.1%)	< 0.001	462 (1.8%)	459 (1.4%)	< 0.001	260 (2.1%)	296 (1.5%)	< 0.001

Abbreviations: CHiP, complex high-risk percutaneous coronary intervention; DM, diabetes mellutus; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; MACCE, major adverse cardiovascular and cerebral events.

Reviewer's Comments (2)

Comment to the author:

The analysis provides interesting and potentially useful information regarding CHIP PCI cases.

Response: We are thankful to the Reviewer for their interest in our work. We have provided a point-by-point response to the best of our efforts.

Specific comments:
Comment 1. However, for the information provided the manuscript is too long. For instance the introduction could be shortened as well as the discussion.

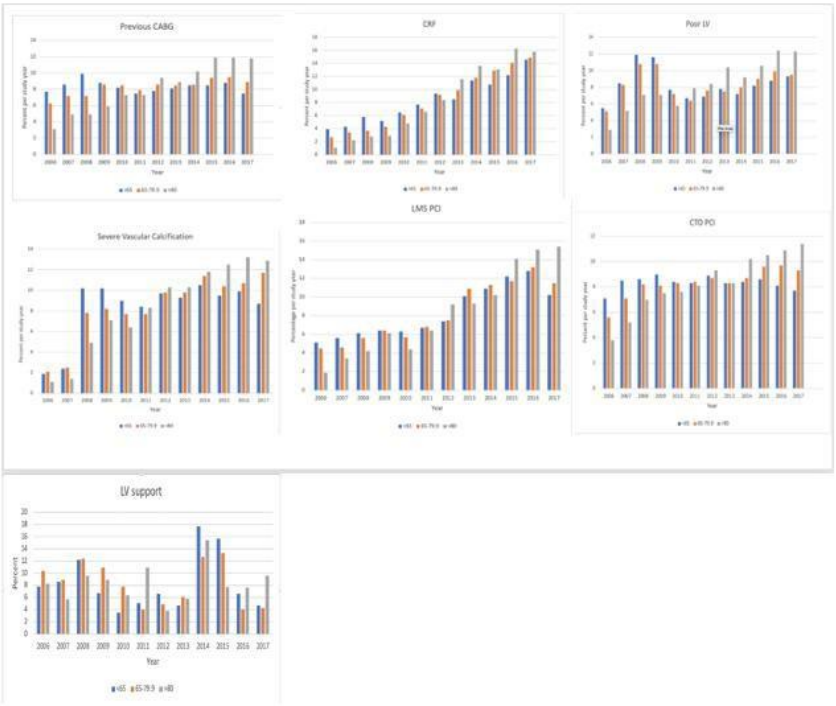
Response: Thank you for highlighting this remark. We agree with the reviewer comment, and we have tried our best to shorten both discussion and introduction sections of the manuscript.

Comment 2. The multiple figures of variables is a bit hard to compare. Perhaps it could be displayed more succinctly.

Response: We thank the reviewer for this remark. We have changed the figures scale and fit them all in one page as outlined below and mentioned in the manuscript.

Figure 3

Temporal changes in prevalence of each CHiP factor amongst patients with stable angina who underwent a CHiP procedure, stratified according to age into three groups Group 1, <65 years; Group 2, 65-79 years; Group 3, 80 and above years).

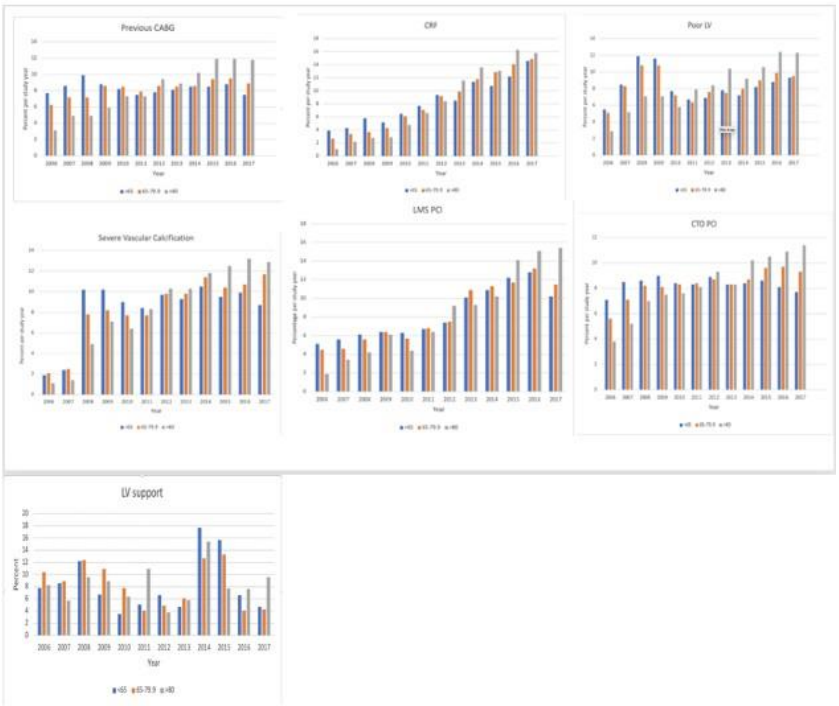


Abbreviation: CHiP, complex high-risk but indicated percutaneous coronary interventions; CABG, coronary artery bypass graft; CTO, chronic thrombus occlusion; LV, left ventricle; LMS, left main stem; PCI, percutaneous coronary intervention.

Comment 3. In addition it would be helpful to show how multiple CHIP characteristics varied by age group. Perhaps you could display by groups of years rather than yearly to minimized grafts. The question is which group has the most adverse characteristics. Thanks for the opportunity to review your work.

Response: We are thankful for this remark. We have changed the scale and were succefully able to display all graphs in one page – see response to comment 2. We have also created two year-groups to illustrate temporal trends in characteristics/ procedure types/ outcomes more succinctly as highlighted in our response to reviewer 1. We have included the results for the same in Supplement Table 2. We have also added a paragraph in our results section outlined below and mentioned in the manuscript.

Temporal changes in prevalence of each CHiP factor amongst patients with stable angina who underwent a CHiP procedure, stratified according to age into three groups Group 1, <65 years; Group 2, 65-79 years; Group 3, 80 and above years).



Abbreviation: CHiP, complex high-risk but indicated percutaneous coronary interventions; CABG, coronary artery bypass graft; CTO, chronic thrombus occlusion; LV, left ventricle; LMS, left main stem; PCI, percutaneous coronary intervention.

Comment 3. In addition it would be helpful to show how multiple CHIP characteristics varied by age group. Perhaps you could display by groups of years rather than yearly to minimized grafts. The question is which group has the most adverse characteristics. Thanks for the opportunity to review your work.

Response: We are thankful for this remark. We have changed the scale and were succefully able to display all graphs in one page – see response to comment 2. We have also created two year-groups to illustrate temporal trends in characteristics/ procedure types/ outcomes more succinctly as highlighted in our response to reviewer 1. We have included the results for the same in Supplement Table 2. We have also added a paragraph in our results section outlined below and mentioned in the manuscript.

Under the *Temporal trends of the Results* section of the manuscript: "*Figure 3 shows the temporal changes in the prevalence of each CHiP factor stratified by age. There was an expansion of the different types of CHiP cases across all age groups over time. The greatest increase in the prevalence of prior CABG occurred in octogenarians. Similarly, the greatest expansion of PCI for LM, CTO, and calcific vascular disease occurred in this group.*

Supplement Table 2 further details the temporal changes in baseline characteristics and clinical outcomes across three age groups (G1, <65 years; G2, 65-79 years; G3, =>80 years). Overall, the prevalence of cardiovascular risks increased across all age groups, except for current smokers in those =>65 years (G2: 6.5 % (<2011) vs 6 % (>2011); G3: 3% (<2011) vs 3.5% (>2011); p<0.001. There were no changes in prevalence of Dyslipidaemia, prior MI, previous stroke, across all age groups. Although radial access trends show increase in all age groups, the greatest was seen among the octogenarians (<2011, 31% vs >2011, 64%); p<0.001. Interestingly, mortality trends across the 3 age groups did not change (G1, p<0.051; G2, p<0.450; G3, p<0.0.185). Whereas major bleeding and MACCE events showed significant declines seen across all age groups with the greatest decline observed in the octogenarians (MACCE: 2.1% before 2011 vs 1.5% after 2011; Major bleeding: 1.2% before 2011 vs 0.6% after 2011), p<0.001 for all."

Supplement Table 2
Temporal trend of baseline and procedural characteristics and clinical outcomes of CHiP undertaken in patients with stable angina stratified according to three age groups (< 65, 65-79, and 80 and above years)

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DM	5,099 (23%)	6,663 (29%)	< 0.001	13,824 (66%)	15,235 (66.4%)	< 0.001	1,999 (17%)	4,135 (21%)	< 0.001
Current smokers	3,348 (18%)	4,006 (18.4%)	< 0.001	1,414 (6.5%)	1,802 (6%)	0.019	311 (3%)	441 (2.5%)	< 0.001
Previous MI	8,910 (44.5%)	10,204 (43%)	0.008	10,682 (47%)	14,650 (45%)	< 0.001	4,008 (36%)	6,970 (36%)	0.553
Previous PCI	7,499 (35%)	10,830 (45%)	< 0.001	8,753 (35%)	14,748 (45%)	< 0.001	3,275 (28%)	7,335 (37%)	< 0.001
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PVD	1,047 (5%)	1,213 (5%)	0.159	1,956 (6%)	1,194 (6%)	0.734	942 (8%)	1,382 (7%)	0.003
Radial access	6,092 (28%)	12,862 (54%)	< 0.001	6,946 (28%)	18,554 (56%)	< 0.001	3,744 (31%)	12,605 (64%)	< 0.001
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Clinical outcomes									
• Death	45 (0.2%)	31 (0.1%)	0.051	79 (0.3%)	115 (0.3%)	0.450	64 (0.5%)	83 (0.4%)	0.185
• Major Bleeding	178 (0.8%)	134 (0.6%)	0.001	233 (0.9%)	286 (0.9%)	0.491	146 (1.2%)	151 (0.6%)	< 0.001
• MACCE	347 (1.5%)	255 (1.1%)	< 0.001	462 (1.8%)	459 (1.4%)	< 0.001	260 (2.1%)	296 (1.5%)	< 0.001

Abbreviations: CHiP, complex high-risk percutaneous coronary intervention; DM, diabetes mellutus; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; MACCE, major adverse cardiovascular and cerebral events.

Manuscript ID: **CCI-21-2141**

1. Singh, M., et al., *Influence of Frailty and Health Status on Outcomes in Patients With Coronary Disease Undergoing Percutaneous Revascularization.* Circulation: Cardiovascular Quality and Outcomes, 2011. **4**(5): p. 496-502.
2. Shamkhani, W., et al., *Sex differences in high-risk but indicated coronary interventions (CHiP): National report from British Cardiovascular Intervention Society Registry.* Catheterization and Cardiovascular Interventions, 2022.
3. Shamkhani, W., et al., *Ethnicity in Complex High-Risk but Indicated Percutaneous Coronary Intervention Types and Outcomes.* Am J Cardiol, 2022.
4. Kinnaird, T., et al., *Complex high-risk and indicated percutaneous coronary intervention for stable angina: Does operator volume influence patient outcome?* Am Heart J, 2020. **222**: p. 15-25.

10.4.3 Ethnicity in Complex High-risk but Indicated Percutanous Cpronary Intervention (CHiP) Types and Outcomes.

Manuscript ID: **AJC-D-22-00139**

Keele Cardiovascular Research Group

10 March 2022

Dear Dr Roberts, Editor-in-Chief,

Please find enclosed our revised manuscript " **Ethnicity in Complex High-risk but Indicated Percutaneous Coronary Intervention (CHiP) Types and Outcomes?** " for consideration for publication in the American Journal of Cardiology. We thank both you and the reviewers for your / their careful appraisal of the paper and their points, to which we have responded below. We feel that these comments have improved the quality of our manuscript. We hope that we have addressed all reviewers' comments sufficiently and hope that these changes will enable the publication of our paper in your esteemed journal.

Yours sincerely,

Professor Mamas A. Mamas

On behalf of submitting authors

Reviewer's Comments (1)

General comments:

Comments to the Author:

This study looks at the association of race on outcomes post complex high-risk but indicated percutaneous coronary interventions (CHiP). This is of particular interest given Europe's population of Black, Asian, and other Ethnic Minorities (BAME). Importantly, this study represents many geographic areas and types of CHiP cases. The data were collected from the British Cardiovascular Intervention Society (BCIS) registry. The BCIS is managed by the National Institute of Cardiovascular Outcomes and Research (NICOR). Data were collected from 112 of the 117 PCI centers in the U.K. from Jan 1, 2006- Dec 31, 2017. The primary outcome of interest was in-hospital all-cause mortality. Secondary outcomes included MACCE and in-hospital major bleeding events. No IRB was required as the data are approved by NHS for audit and research purposes.

Overall, the objectives are presented clearly with methods, results and discussion that are consistent with answering the question of interest. My largest concern is heterogeneity of the BAME cohort. I assume the numbers do not make it possible, but it would be nice if racial groups, Asian and Black be split out. I have a few suggestions which I believe would strengthen the manuscript. As expected, the majority (60%) of exclusions were because the PCI was ACS indicated and 25% did not meet the high-risk inclusion criteria. The consort diagram is nice to include.

Response: We are grateful to the Reviewer for considering our manuscript and providing a critical review of its content. Regarding the racial split, we presented a subgroup analysis of the 4 racial groups (White, Black, Asian, and Ethnic minorities) and presented the finding in a supplemental Table 3. We also have a paragraph to reflect the same in the result section "Supplementary *Table 3 details the baseline clinical and procedural characteristics stratified into White, Black, Asian, and other Ethnic Minorities as captured by the BCIS dataset. Of the BAME, Asian patients represented the majority (7.7%), whereas black patients represented 0.8% of the cases*".

Major comments:

Regarding the study design:

Comment 1. Include a power analysis to ensure the null findings are not caused by being underpowered to detect a difference.

Response: We thanks the reviewers for pointing out this remark. Our analysis had a large sample size of 105,949 and was powered to detect significant differences amongst the groups

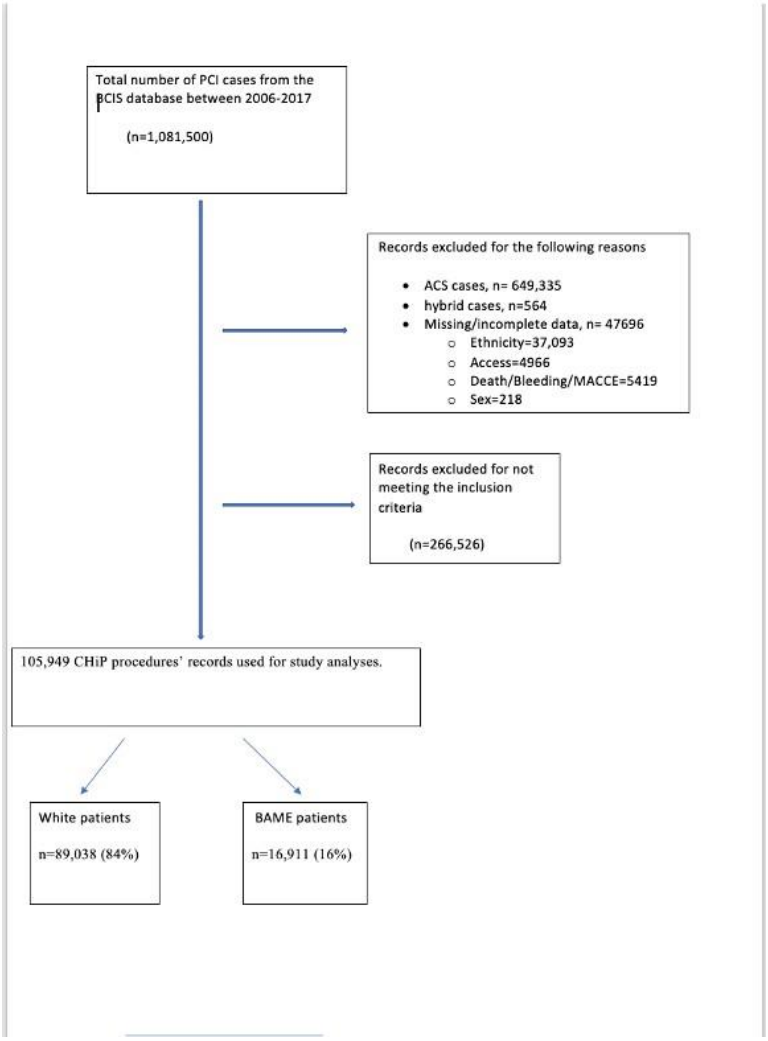
(a sample size of >13,628 would provide a power of 0.8 at alpha ($p<0.05$) and our sample size was seven fold greater) . We have added the following line (outlined below and marked in the manuscript).

Under Methods section:" *We required a sample size of >13628 to provide a power of 0.8 at alpha ($p<0.05$)"*

Comment 2. It appears that cases where race, age, sex, or any of the outcome variables were missing were excluded. Is that correct? If so, a breakdown of the where the majority of missingness was among the 47,696 would be important to report.

Response: We thank the reviewer for this remark. Yes, we have excluded the missing observations in the race/ethnicity, age, sex, and all outcome variables. This is because outcome (predictor) variables must not be imputed as it could affect the accuracy of the analysis. The majority of the missingness were amongst the ethnic groups. We have amended Figure 1 to reflect the same as outlined below and marked in the manuscript.

Figure 1
A flow diagram illustrates the patients' inclusion and exclusion process for the CHiP analysis, stratified by race/ethnicity.


Total number of PCI cases from the BCIS database between 2006-2017
(n=1,081,500)
Records excluded for the following reasons
ACS cases, n= 649,335
hybrid cases, n=564
Missing/incomplete data, n= 47696
Ethnicity=37,093
Access=4966
Death/Bleeding/MACCE=5419
Sex=218
Records excluded for not meeting the inclusion criteria
(n=266,526)
105,949 CHiP procedures' records used for study analyses.
White patients
n=89,038 (84%)
BAME patients
n=16,911 (16%)

Comment 3. How are the history variables defined - how far back did you look for the presence of disease? How did you distinguish between history of disease or new onset?

Response: We thank the reviewer for this remark. Unfortunately, the BCIS dataset is cross sectional and has no defined look back period. Physicians will enter the history variables based on history derived from patients and medical records in which the look back period will vary from hospital to hospital. The BCIS dataset does not provide details about the duration and or control of the disease. Important cardiovascular risk factors such as diabetes, hypertension, etc. are collected on admission in the dataset and provide a measure of comorbidity burden in these patients. We included this as part of our study limitation. We also have added the following line (outlined below and marked in the manuscript)

Under Study strength and limitations section:" variables such as socioeconomic status, frailty, control, and duration of cardiovascular risk factors such as diabetes …"

Comment 4. How are pharmacology variables defined - in-lab, in-hospital, discharge, particularly for clopidogrel which was included in the model.

Response: We thank the reviewer for this remark. Pharmacology is defined as in-lab. We also have added the following line in Table 1 (outlined below and marked in the manuscript)

Under Table 1: " Pharmacology (in-lab) "

Comment 5. Please justify the selection of variables for model inclusion.

Response: We used the forward selection (FS) process [1]; we started with the most significant univariate model and then repeatedly reestimated/evaluated the model each time we added a significant independent variable that was not in the model. We stopped once no significant independent variable was left to include. The variables used in our models were known to

influence the clinical outcomes post PCI. We included all cardiovascular risk variables, pharmacology, and procedural variables in the analysis model, including the dependant variables.

Comment 6. How were in-labs deaths handled?Although the multivariable logistic regression is appropriate to answer the study question, a generalized mixed model would allow for adjustment of patient characteristics, procedural characteristics, and a random intercept for site to account for clustering of patients within site. If possible, it would be nice to include site level variables, e.g., region, urban vs. rural, proportion of all CHiP who are BAME at each site. Additional patient level variable to consider is the hospital length of stay, e.g., dichotomous less than or equal to 3 days versus greater than 3 days.

Response: We thanks the reviewers for pointing out this important remark. In-lab death was regarded as in-hospital death and counted as such. We did not look at site level variables such as region- urban vs rural as we did not have patient identifiable data such as postcode that would enable us to define this from a patient perspective. Furthermore, PCI activity in the UK is regionalised, and as such unlike the US there are no PCI cath labs in rural settings as the UK is relatively small in comparison to the US. The proportion of CHiP who are BAME at each site was not considered as this was not our principal research question. Similarly, length of stay was not considered as there is a significant degree of missingness in this parameter. We recognise the importance of variability in practice at the individual hospital setting as highlighted by the reviewer and are running a separate analysis for a different manuscript that will focus around differences in CHiP activity/ type across different units.

Comment 1: First of all, the authors should provide the reason to justify the use of "racial difference" in the title of manuscript, instead of "ethnic difference". As the authors might fully recognize, the term "Race" refers to a person's physical appearance, such as skin color and eye color, the "Ethnicity", on the other hand, incorporates the differences in culture, language, socioeconomic status, which inevitable contributes to the medical treatment. This issue is also frequently raised in researches comparing the treatment outcomes between women and men, and the "gender difference" is much more favored than "sex difference", considering the significant contribution of socio-economic factors in treatment. In this regard, the authors should clearly state the reason for using the term "race" rather than "ethnicity" in their manuscript. Defining individuals as non-white does not adequately describe the cultural, social, and religious nuances that define ethnicity. Asian and black people are no more homogeneous than white people in their health status, service use, socioeconomic position, or social and cultural experiences. Indeed, the proportion of CRF or severe coronary calcification shows significant differences among the races gathered in the BAME group. As presented in Supplementary Tables, there were significant differences between Asian and Black.

Response: We thank you for your suggestions- we are in agreement with the important points that the reviewer raises. We have changed Race to Ethnicity, as the field in the BCIS dataset that captures this data captures "Patient Ethnic Group". To avoid any confusion, we have amended our manuscript to reflect the same in the following lines under the following section as outlined below and marked in the manuscript:

Under the *Title* section of the manuscript: we added ethnicity „ ***Ethnicity in Complex High-risk but Indicated Percutaneous Coronary Intervention (CHiP) Types and Outcomes*?"**

we are limited with word count, we decided not to include it. For reference, the results of the same are shown below.

variables	*White/Black*	*White/Asians*	*White/Others ME*
Death	258 (0.3%)/ 2 (0.3%) ,p=0.828	258(0.3%)/23(0.3%) , p=0.880	258 (0.3%)/25(0.3%) ,p=0.675
Bleeding	758(0.9%)/8(1%) ,p=0.662	758(0.9%)/45(0.6%) ,p=0.004	758(0.9%)/39(0.5%) ,p=0.001
MACCE	1312(1.5%)/14(1.7%) ,p=0.534	1312(1.5%)/119(1.5%) ,p=0.870	1312(1.5%)/93(1.2%) ,p=0.034

Comment 3: The authors compared the treatment outcome of CHiP-PCI between the White and BAME patients, by utilizing multivariable regression analysis. However, given the significant heterogeneity of baseline characteristic among races, statistical methods to further minimize the remaining bias should be seriously considered. Please consider the use of propensity-score matching or inverse probability of treatment weighting (IPTW) methodology in the comparison of clinical outcomes.

Response: We thank the reviewer for highlighting this important issue and acknowledge the need of considering PSM or IPTW when comparing outcomes between the groups. We have used PSM and generated Supplement Table (6), which confirmed the overall findings of the study. The results of the same are outlined below and marked in the manuscript:

Under the *Methods section* of the manuscript: „ *To control for differences and imbalances in the baseline clinical and procedural characteristics between the groups, we used multiple imputations with propensity score matching PSM (mi estimate:teffects psmatch). We used the*

we are limited with word count, we decided not to include it. For reference, the results of the same are shown below.

variables	*White/Black*	*White/Asians*	*White/Others ME*
Death	258 (0.3%)/ 2 (0.3%) ,p=0.828	258(0.3%)/23(0.3%) , p=0.880	258 (0.3%)/25(0.3%) ,p=0.675
Bleeding	758(0.9%)/8(1%) ,p=0.662	758(0.9%)/45(0.6%) ,p=0.004	758(0.9%)/39(0.5%) ,p=0.001
MACCE	1312(1.5%)/14(1.7%) ,p=0.534	1312(1.5%)/119(1.5%) ,p=0.870	1312(1.5%)/93(1.2%) ,p=0.034

Comment 3: The authors compared the treatment outcome of CHiP-PCI between the White and BAME patients, by utilizing multivariable regression analysis. However, given the significant heterogeneity of baseline characteristic among races, statistical methods to further minimize the remaining bias should be seriously considered. Please consider the use of propensity-score matching or inverse probability of treatment weighting (IPTW) methodology in the comparison of clinical outcomes.

Response: We thank the reviewer for highlighting this important issue and acknowledge the need of considering PSM or IPTW when comparing outcomes between the groups. We have used PSM and generated Supplement Table (6), which confirmed the overall findings of the study. The results of the same are outlined below and marked in the manuscript:

Under the *Methods section* of the manuscript: „ *To control for differences and imbalances in the baseline clinical and procedural characteristics between the groups, we used multiple imputations with propensity score matching PSM (mi estimate:teffects psmatch). We used the*

Under the *Abstract* section of the manuscript: „ *However, data ethnic differences in CHiP types, outcomes, and trends in patients with stable angina are limited.*" AND „ *CHiP cases were identified, categorized by ethnicity into White and BAME groups.*"

Under the *Introduction* section of the manuscript: „ *The first reports of racial/ethnic differences in CAD management and clinical outcomes emerged more than three decades ago"* AND „*Previous studies around CHiP by ethnicity were limited to data that examined outcomes in highly selected*" AND „*In this analysis, we sought to study the ethnic differences in CHiP undertaken.* "

Under the *Results* section of the manuscript: we have replaced race with ethnicity throughout. For example: „*Table 1 provides an overview of CHiP factors (types), cardiovascular risk factors, pharmacology, and procedural characteristics according to their ethnic background.* "

<u>Comment 2:</u> Furthermore, there were very small number of black patients (0.8%) in the study and it would be not sufficient to find any significance compared to the other race. What about comparing the treatment pattern and outcomes between White vs Black, White vs Asian, or White vs Oriental? This would provide more valuable information to identify "racial differences" or "ethnic differences".

Response: We thank the reviewers for their thorough review. Supplement Table 3 provides details about differences in each ethnic group which were compared to the White patients group. Also, Supplement Table 4 provides details of clinical outcomes in each ethnic group compared to the White patients. We have created another table comparing White patients with each of the ethnic groups. However, as the results were similar to the overall finding in our study and

we are limited with word count, we decided not to include it. For reference, the results of the same are shown below.

variables	*White/Black*	*White/Asians*	*White/Others ME*
Death	258 (0.3%)/ 2 (0.3%) ,p=0.828	258(0.3%)/23(0.3%) , p=0.880	258 (0.3%)/25(0.3%) ,p=0.675
Bleeding	758(0.9%)/8(1%) ,p=0.662	758(0.9%)/45(0.6%) ,p=0.004	758(0.9%)/39(0.5%) ,p=0.001
MACCE	1312(1.5%)/14(1.7%) ,p=0.534	1312(1.5%)/119(1.5%) ,p=0.870	1312(1.5%)/93(1.2%) ,p=0.034

Comment 3: **The authors compared the treatment outcome of CHiP-PCI between the White and BAME patients, by utilizing multivariable regression analysis. However, given the significant heterogeneity of baseline characteristic among races, statistical methods to further minimize the remaining bias should be seriously considered. Please consider the use of propensity-score matching or inverse probability of treatment weighting (IPTW) methodology in the comparison of clinical outcomes.**

Response: We thank the reviewer for highlighting this important issue and acknowledge the need of considering PSM or IPTW when comparing outcomes between the groups. We have used PSM and generated Supplement Table (6), which confirmed the overall findings of the study. The results of the same are outlined below and marked in the manuscript:

Under the *Methods section* of the manuscript: „ *To control for differences and imbalances in the baseline clinical and procedural characteristics between the groups, we used multiple imputations with propensity score matching PSM (mi estimate:teffects psmatch). We used the*

PSM to estimate the average treatment effect using all the covariates used in our main regression analysis. We then converted the coefficients to odds ratios to help with better interpretation of the results. To better assess the consistency of the results obtained, we performed a sensitivity analysis on the non-imputed dataset. Stata version 14.1 was used to conduct the analyses (StataCorp, College Station, Texas). Statistical significance was assessed at a type I error rate of 0.05."

Under the *Results section* of the manuscript: „ *No differences between the groups were observed with propensity score matching analysis (Supplement Table 6)* **"**

Supplement Table (6)

VARIABLE	ATE	95% CI	P VALUE
DEATH	-.0002824	-.0018619 .0012972	0.723
BLEEDING	-.0029836	-.0053202 -.000647	0.013
MACCE	-.002438	-.0057853 .0009094	0.153

VARIABLE	AOR	95% CI	P VALUE
DEATH	0.9	0.6 - 1.8	0.723
BLEEDING	0.7	0.6 - 0.9	0.013
MACCE	0.8	0.6 – 1.1	0.153

Comment 4: In my opinion, the most important finding in this data is that non-white

patients are being provided with advanced CHiP-PCI techniques (atherectomy device, cutting balloon, multiple stents implantation, or Impella LV support device) with a frequency similar to that of the White patients. The authors should further emphasize the fact that minority population, which is likely to receive relatively poor treatment, receives the same treatment as the mainstream group (White patients), which could be unique characteristics of British cohort under NHS insurance coverage, and that there is no difference in treatment outcomes in this situation. Please consider about this.

Response: We are thankful for this remark. The management of patients under NHS has been proven by other studies to be unique in providing all comers with the same standard of care, and this study is an extension of all those preceeded. However, rightfully, the frequencies of advanced CHiP-PCI techniques (atherectomy device, cutting balloon, multiple stents implantation) was statistically different except for the use of Impella. In our discussion, we explored reasons why we thought, for example, whites received more advanced therapies (older, more vascular calcification etc.). We have added a line to highlight the point raised by the as outlined below and marked in the manuscript.

Under the Discussion section of the manuscript: "*Nevertheless our findings are reassuring in that in a universal healthcare system with universal coverage of patients irrespective of ethnicity, complex PCI outcomes are similar. This highlights that disparities observed in other healthcare systems may reflect disparities in healthcare provision.*"

Comment 5: Which CHIP-related factors were important for in-hospital outcomes? Were there any differences in the factors related to the outcome according to the race? It would be also interesting to analyze the impact of multiple risk factors on the clinical outcomes in each race.

Response: We thank the reviewer for their comment. We have attached a Table that details differences in outcomes amongst CHiP factors. There were no differences in individual CHiP outcomes amongst Black, Asians, and other ethnic minorities, except in major bleeding events were significant bleeding odds in the Whites seen in those 80> years, left main PCI, previous CABG and severe vascular calcifications as outlined in the tables below. Indeed it is interesting to see the impact of multiple risk factors on the clinical outcomes in each group. However, this was not the question of our paper and also are limited with word count. We are, however, considering answering this question in our future papers. For your reference, please see the Tables below.

Variable	aOR death	aOR bleed	aOR macce	
blacks	0.66, p=0.572	1.1, p=0.743	1.1, p=0.754	
asians	1.1, p=0.827	0.7, p=0.095	1.1, p=0.503	
Other minorities	1.1, p=0.613	0.5, p=0.002	0.8, p=0.088	
Age>80	1.1, p=0.688	0.9, p0.368	1.1, p=0.300	
Previous CABG	1.0, p=0.905	0.6, p<0.001	0.9, p=0.019	
CRF	2.2, p<0.001	1.1, p=0.628	1.4, p<0.001	
Poor LV function	2.2, p<0.001	0.7, p=0.044	0.9, p=0.442	
LM PCI	2.2, p<0.001	1.4, p=0.002	1.4, p<0.001	

CTO PCI	0.9, p=561	1.2, p=0.060	0.7, p<0.001	
Vascular calcifications	1.4, p=0.45	0.8, p=0.070	1.0, p=0.864	
Cic support	20.8, p<0.001	5.9, p<0.001	13.2, p<0.001	

a) Death

Variables	**White**	**BAME**	**P value**
Age >80	105 (0.5%)	10 (0.4%)	0.224
Previous Coronary Artery Bypass	77 (0.3%)	14 (0.2%)	0.544
Chronic renal failure	53 (0.6%)	14 (0.6%)	0.916
Poor left ventricle function	30 (0.7%)	10 (1.0%)	0.240
Left main intervention	71 (0.7%)	11 (0.6%)	0.407
Chronic total occlusion intervention	61 (0.2%)	10 (0.2%)	0.642
Severe vascular calcifications	53 (0.3%)	10 (0.4%)	0.400
Use of circulatory support	45 (9.7%)	15 (9.8%)	0.969

b) Major bleeding events

Variables	**White**	**BAME**	**P value**
Age >80	207 (1%)	17 (0.6%)	0.033
Previous Coronary Artery Bypass	171 (0.6%)	19 (0.3%)	0.005
Chronic renal failure	71 (0.8%)	11 (0.4%)	0.069
Poor left ventricle function	29 (0.7%)	7 (0.7%)	0.808

Left main intervention	101 (1%)	9 (0.5%)	0.015
Chronic total occlusion intervention	338 (1.3%)	49 (1%)	0.063
Severe vascular calcifications	113 (0.6%)	6 (0.2%)	0.015
Use of circulatory support	30 (6.5%)	7 (4.6%)	0.393

c) MACCE

Variables	**White**	**BAME**	**P value**
Age >80	366 (1.7%)	40 (1.4%)	0.137
Previous Coronary Artery Bypass	413 (1.4%)	58 (0.9%)	0.002
Chronic renal failure	115 (0.7%)	54 (2.2%)	0.116
Poor left ventricle function	81 (1.8%)	24 (2.5%)	0.181
Left main intervention	227 (2.3%)	28 (1.4%)	0.012
Chronic total occlusion intervention	381 (1.4%)	62 (1.2%)	0.222
Severe vascular calcifications	238 (1.4%)	31 (1.3%)	0.666
Use of circulatory support	104 (22.4%)	23 (15%)	0.050

Comment 6: It would be better to analyze the proportions of CHIP-related factors in the whole registry population for understanding which CHIP-related factors were important during PCI procedure in each race. Because the study population included only CHIP patients, we could just understand relative importance of each variable among the CHIP patients. However, all CHIP patients were not clearly categorized or recognized before

the procedure. It would be more important to understand prevalence and clinical relevance of CHIP-related factors in overall patients undergoing PCI.

Response: We thank the reviewer for making this point. We have published other papers focussed around CHIP characteristics in the whole cohort from the BCIS registry (several papers by Kinnaird et al) and feel that this would be outside of the remit of the current work and feel that this request would duplicate published data

Minor comments

Comment 1. How was the temporal change of clinical outcomes according to the racial differences?

Response: We thank the reviewer for this remark. The temporal change of clinical outcomes according to race was detailed in supplement Table 7 and mentioned in the Results section in our manuscript . We have copy-pasted the related section herewith „ *The temporal trends of crude outcomes amongst the ethnic groups demonstrated stable mortality rates with no significant differences amongst the groups, whereas MACCE rates gradually decreased. Bleeding rates remained unchanged in White patients, while gradual decline was seen amongst the BAME patients (Supplementary Table 7)*". We haven't included graphs as the message was conveyed more clearly in the overall cohorts and as per quarters (Supplement Table 7). We have, however, generated these figures for temporal outcomes according to ethnicity below for your reference.

Comment 2. There are some comments regarding Figure 2. Is it right that the percentage of each variable >70% for BAME patients? 'CHiP factots' seems to be an error. Some labels were overlapped and poorly visualized (e.g. cut-off of 'age' - over 80 years?).

Response: We thank the reviewer for this remark. We have reviewed Figure 2, and indeed it was a lapse from our side as White and BAME were miss labelled. We have corrected this lapse and checked all other figures and graphs for consistency. We have attached the corrected graph below and also replaced the new one in the manuscript.

Comment 3. It would be interesting to find the proportions and clinical outcomes of patients having multiple CHIP characteristics in each race.

Response: We are thankful for this interesting note. We tried to run an analysis comparing the proportions and clinical outcomes of patients having multiple characteristics in each race. Unfortunately, the numbers were too small to help measure the significance of our findings. We were also limited by other factors: a) this was not our research question b) limited word count.

Comment 4. Please definitions of clinical outcome. Furthermore, the term 'outcomes' should mean more clearly in the study - in-hospital or clinical outcome.

Response: We thank the reviewer for this remark. We defined the clinical outcomes in our Methods section in detail. The outcomes were in-hospital outcomes. We have copy-pasted the

section related to the definition of clinical outcomes herewith" *The primary outcome of interest was in-hospital all-cause mortality. Secondary outcomes included were a) in-hospital major adverse cardiovascular and cerebral events (MACCE); defined as the cumulative incidence of in-hospital death, peri-procedural MI or CVA, or in-hospital CVA; b) In-hospital major bleeding events. We defined peri-procedural MI as a composite of Q-wave myocardial infarction, non-Q-wave myocardial infarction, reinfarction, and reintervention (emergency PCI or CABG) predefined within the BCIS registry. Major bleeding events are defined as radiological evidence of intracranial bleed, access site bleeding requiring intervention, clinically evident gastrointestinal tract bleeding, retroperitoneal bleed/hematoma, any transfusion of blood or blood products, or any access site complications requiring intervention or surgery). We defined access site complication as the presence of any of the following: retroperitoneal hematoma, false aneurysm, haemorrhage without hematoma, arterial dissection "*

Comment 5. Please provide each component of in-hospital MACCE.

Response: We are thankful for his thorough remark. The MACCE was defined in our Methods section as follows "*in-hospital major adverse cardiovascular and cerebral events (MACCE); defined as the cumulative incidence of in-hospital death, peri-procedural MI or in-hospital CVA;* all were predefined in the BCIS dataset.

Comment 6. Which ethnicities were included "Other" ethnic minorities? And how many patients were in each?

Response: We thank the reviewer for their remark. Other ethnic minorities are predefined in the BCIS dataset. They refer to any patient that is not White, Black, or Asian. For example, Arab and Hispanic are classified as other ethnic minorities. Unfortunately, the BCIS dataset

Manuscript ID: **AJC-D-22-00139**

does not distinguish between them. This point is acknowledged as a limitation in our study as outlined here "Thirdly, ***the BCIS dataset captures race as Asian, Black, White and Other, and so the "Other" category is likely to represent a heterogenous racially diverse population."***

1. Heinze, G., C. Wallisch, and D. Dunkler, *Variable selection - A review and recommendations for the practicing statistician.* Biometrical Journal, 2018. **60**(3): p. 431-449.

10.4.4 Complex High-risk Percutanous Coronary Intervention Types, Trends, and Outcomes According to Vascular Access Site

Manuscript ID: **CCI-** 22-1375

Keele Cardiovascular Research Group

Dear Professor Bailey, MD, Editor-in-Chief,

Please find enclosed our revised manuscript **"Complex High-risk Percutaneous Coronary Intervention Types, Trends, and Outcomes According to Vascular Access Site"** for consideration for publication in the *Catheterisation and Cardiovascular Intervention Journal.* We thank the Editorial Committee and Reviewers for their careful appraisal of the paper and their points, to which we have responded below. We feel that these comments have improved the quality of our manuscript. We hope that we have addressed all reviewers' comments sufficiently and hope that these changes will enable the publication of our paper in your esteemed journal.

Yours sincerely,

Professor Mamas A. Mamas

On behalf of submitting authors

Editors comments

Comments to Author:
(There are no comments.)

Reviewer's Comments

General comments:

The authors performed a retrospective analysis of the observational British Cardiovascular Intervention Society BCIS database 2006-2017 comparing outcomes of a subset of high risk PCI patients (CHIP) according to access site.

Response: We are thankful to the Reviewer for their interest in our work. The reviewers' thorough analysis of our manuscript with helpful comments and suggestions has improved our manuscript. We have provided a point-by-point response to the best of our efforts.

Comment 1. CHIP does not have a universally accepted definition. This group has used this definition in prior research. Some patients meet criteria for CHIP for more than one reason. Age >80 or CKD alone can qualify. It would be interesting to see if removing individual criterial influences overall findings.

Response: This is a very interesting question and one we explored and tried to answer. Unfortunately, the number of those with one CHiP factor only was relatively small (<6000 of all 8 CHiP factors with some of the factors <500 cases) – meaning running an underpowered analysis would not provide anything meaningful.

Comment 2. How many of the PCIs were ad hoc vs planned? This could potentially affect access site as diagnostic cath performed via radial and the patient may be brought back for PCI with femoral access.

Response: Unfortunately, the BCIS dataset does not provide details about whether the PCI was performed as planned vs ad hoc, furthermore the dataset does not capture diagnostic procedures. Nevertheless, the access site utilised during a diagnostic procedure is not relevant to our research question around access site utilisation in CHIP cases and its associated outcomes

Comment 3. Would add procedural success rates by access site. This is important in understanding any limitation to one access site vs another.

Response: We thank the reviewer for pointing out this interesting remark. Procedural success rate was mentioned in Table 1 (see highlighted row). Radial access procedural success rates were significantly lower than femoral (8.6 vs 13.2% respectivelly; p<0.001). To highlight this finding, we have added a sentence in the result section about the same (outlined below and marked in the manuscript).

Under the *Results* section of the manuscript: *" Moreover, the TRA was associated with less failed PCI attempts compared to TFA (8.6 vs 13.2% respectivelly; p<0.001)."*

Table 1: Baseline clinical and procedural characteristics of patients with stable angina undergoing CHiP, stratified by access site.

	Total, n	Radial, n (%)	Femoral, n (%)	Multiple, n (%)	P-value
Number of participants	137,785	61,825 (44.9)	63,837 (46.3)	12,123 (8.8)	

Age Median, (IQR)	70.7 (62 -79.6)	71.2 (62.4 – 80.3)	70.2 (61.6 - 78.6)	66.8 (58.3-75)	< 0.001
BMI Median, (IQR)	28.0 (25.2-31.4)	28.1 (25.3-31.6)	27.8 (25.1-31.2)	28.9 (25.9-32.4)	< 0.001
Weight<60 kg) n, (%)	6,592 (5.3)	3,069 (4.9)	3,523 (5.5)	493 (4.1)	< 0.001
CHiP risk factors					
a) Patients' factors					
• **Age >80**	31,659 (23)	16,330 (51.6)	13,834 (43.7)	1,495 (4.7)	< 0.001
• **Prior CABG**	44,970 (33)	16,635 (37.0)	25,319 (56.3)	3,016 (6.7)	< 0.001
• **Chronic Renal Failure**	14,650 (11.1)	7,702 (52.6)	6,138 (42.0)	810 (5.5)	< 0.001
• **Poor LV function**	7,640 (9.4)	3,637 (47.6)	3,446 (45.1)	557 (7.3)	< 0.001
b) Procedural factors					
• **LM PCI**	15,863 (11.7)	7,605 (48.0)	7,247 (45.6)	1,011 (6.4)	< 0.001
• **CTO PCI**	42,576 (32.7)	15,424 (36.2)	17,935 (42.1)	9,217 (21.7)	< 0.001
• **Severe coronary calcifications**	25,464 (22.5)	12,812 (50.3)	11,315 (44.4)	1,337 (5.3)	< 0.001
• **Use of LV support**	746 (0.6)	202 (27.1)	347 (46.5)	197 (26.4)	< 0.001
Cardiovascular risk factors					
• **Hypertension**	85,348 (65.3)	39,314 (67.4)	38,461 (64.4)	7,573 (65.6)	< 0.001
• **Dyslipidaemia**	84,112 (64.9)	37,260 (63.9)	38,974 (65.2)	7,878 (68.2)	< 0.001
• **Diabetes Mellitus**	34,250 (26.1)	15,335 (25.8)	15,980 (26.6)	2,935 (25.0)	< 0.001
• **Smoking**					< 0.001
Never	49,769 (41.5)	22,982 (41.8)	22,764 (42.1)	4,023 (36.7)	
Ex-smokers	58,659 (48.9)	26,652 (48.6)	26,476 (49)	5,531 (50.4)	
Current smokers	11,484 (9.6)	5,257 (9.6)	4,814 (8.9)	1,413 (12.9)	
• **Family history of CAD**	55,473 (46.8)	25,010 (45.3)	25,120 (47.8)	5,343 (49.4)	< 0.001
• **History of MI**	54,780 (42.6)	23,757 (40.2)	25,491 (44.2)	5,532 (46.7)	< 0.001
• **Previous PCI**	51,735 (38.6)	22,522 (37.1)	23,798 (38.7)	5,415 (45.3)	< 0.001
• **Previous stroke**	6,182 (4.8)	3,097 (5.3)	2,593 (4.3)	492 (4.2)	< 0.001
• **History of PVD**	8,994 (6.9)	4,174 (7.2)	3,972 (6.7)	848 (7.3)	= 0.001
• **LV systolic function**					< 0.001
Normal (EF>50)	57,077 (70.1))	27,548 (70.9)	23,518 (68.3)	6,011 (73.4)	
Impaired (EF 30-50)	16,666 (20.5)	7,646 (19.8)	7,402 (21.4)	1,618 (19.8)	
Severe (EF<30)	7,640 (9.4)	3,637 (9.4)	3,446 (10.0)	557 (6.8)	
Pharmacology					
• **Warfarin**	2,689 (2.2)	1,487 (2.7)	1,042 (1.8)	160 (1.4)	< 0.001
• **GPIIb IIIa inhibitors**	9,731 (7.6)	3,658 (6.4)	5,640 (9.6)	433 (3.7)	< 0.001
• **Clopidogrel**	102,388 (82.0)	45,734 (81.6)	47,076 (82.1)	9,578 (83.7)	< 0.001
• **Prasugrel**	1,132 (0.9)	645 (1.2)	346 (0.6)	141 (1.2)	< 0.001
• **Ticagrelor**	4,452 (3.7)	2,940 (5.2)	917 (1.6)	595 (5.2)	< 0.001
Vascular imaging					< 0.001
• **None**	92,495 (88.6)	44,051 (85.5)	48,444 (91.5)	8,614 (82.3)	
• **IVUS or OCT**	13,811 (12.0)	7,459 (14.5)	4,494 (8.5)	1,858 (17.7)	
Circulatory support					

• **No support**	130,960 (99.5)	59,379 (99.7)	60,049 (99.4)	11,532 (98.3)	< 0.001
• **IABP**	694 (0.5)	184 (0.3)	335 (0.6)	175 (1.5)	< 0.001
• **Impella**	55 (0.04)	18 (0.03)	15 (0.02)	22 (0.2)	< 0.001
Number of treated lesions					<0.001
• **One**	87,576 (64.3)	38,452 (62.8)	40,642 (64.3)	8,482 (71.2)	
• **Two**	34,279 (25.2)	16,084 (25.3)	15,865 (25.1)	2,330 (19.6)	
• **Three**	14,421 (10.6)	6,658 (10.9)	6,663 (10.6)	1,100 (9.2)	
Stent size Median, (IQR)	3.5 (3.0-3.75)	3.5 (3.0-4.0)	3.0 (3.0-3.5)	3.5 (3.0-4.0)	< 0.001
Stent length Median, (IQR)	24 (18-38)	24 (18-38)	23 (16-30)	38 (24-60)	< 0.001
Procedural devices					
• **Cutting Balloon**	15,174 (13.4)	8,098 (15.9)	6,305 (11.9)	771 (8.3)	< 0.001
• **Rotational atherectomy**	10,358 (9.2)	4,780 (9.4)	5,049 (9.5)	529 (5.7)	<0.001
• **Laser atherectomy**	861 (0.8)	389 (0.8)	377 (0.7)	95 (1.0)	0.006
Number of stents used					< 0.001
• **One stent**	55,607 (40.6)	25,818 (41.9)	27,417 (43.2)	2,372 (19.7)	
• **Two stents**	34,929 (25.5)	16,120 (26.2)	16,103 (25.3)	2,706 (22.5)	
• **Three or more stents**	27,280 (19.9)	11,718 (19.1)	11,600 (18.3)	3,962 (32.9)	
Target Vessel PCI					
• **LM PCI**	15,863 (11.7)	7,605 (48.0)	7,247 (45.6)	1,011 (6.4)	< 0.001
• **LAD**	55,510 (41.0)	27,763 (45.6)	23,794 (38.1)	3,953 (32.9)	< 0.001
• **LCX**	34,710 (25.6)	16,460 (27.0)	16,376 (26.2)	1,874 (15.6)	< 0.001
• **RCA**	48,135 (33.6)	20,123 (33.0)	21,250 (34.0)	6,762 (56.3)	< 0.001
• **Graft**	12,917 (9.5)	4,494 (7.3)	7,839 (12.6)	584 (4.9)	< 0.001
Failed PCI attempts	12,575 (11.8)	4,574 (8.6)	5,587 (13.2)	2,414 (22.1)	< 0.001
Number of target vessel PCI					< 0.001
• **One**	100,000 (74.7)	43,660 (72.7)	46,994 (75.9)	9,346 (78.4)	
• **Two**	26,853 (20.1)	12,804 (21.3)	12,065 (19.5)	1,984 (16.6)	
• **Three**	7,033 (5.3)	3,560 (5.9)	2,883 (4.7)	590 (4.9)	

Abbreviations: CHiP, complex high risk percutaneous coronary intervention; CABG, coronary artery bypass graft; CTO, chronic thrombus occlusion; CAD, coronary artery disease; GPIIbIIIa, glycoprotein IIaIIIb; LV, left ventricle; LMS, left main stem; LCX, left circumflex; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RCA, right coronary artery.

Comment 4. Clarify the meaning of deleted in the following sentence whether "All missing

Comments to the Author The authors present an important analysis of BCIS dataset comparing outcomes of patients undergoing PCI for complex disease via radial vs femoral access with appropriate methodology and adjustment. The findings of higher risk for mortality, bleeding, MACE in TFI support continued use and uptake of TRI for complex disease.

Response: We are thankful to the Reviewer for their interest in our work. We have provided a point-by-point response to the best of our efforts.

Comment 1. The authors should clarify whether multiple access sites includes patients with access site cross over (due to failure to obtain intended access) or only those with planned dual access sites such as for CTO or MCS?

Response: This is a very interesting question and one we explored and tried to answer. Unfortunately, our data source, BCIS, does not provide information on the indication for using multiple access. Since the research question was to compare radial vs. femoral outcomes – we reported on only femoral vs. radial cases, nevertheless we kept the multiple access analyses for interested readers.

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Response: We thank the reviewer for this important remark. As mentioned earlier, we have added the p value. We chose to report on the failed attempt rather than successful attempts as total cases performed = falied + successful attempts.

Comment 8. Figure 4 not additive could remove.

Response: We thank the reviewer. Figure 4 details the prevalence of CHiP factors according to access site ; results of the same already mentioned in Table 1. We thought that graphs would be more appealing to the readers hence added Figure 4. We have , however, considered the reviewer remarks and deleted it.

observations in the access, age, sex, and outcomes variables were deleted." Does this mean the patients were excluded from the analysis?

Response: We thank the Reviewer for this remark. What was meant was that all cases where access site, age , sex or outcomes were missing were excluded from the analysis. To avoid misunderstanding, we have added a sentence (outlined below and marked in the manuscript).

Under the *Study analysis* section of the manuscript: " *All cases where there was missing data in the access, age, sex, and outcomes variables were excluded from the analysis"*

Comment 5. CHIP procedures accounted for 29.6% of PCIs. For the interpretation of trends in access, comparison to non-CHIP patients is of interest. Would add non-CHIP category data to table 1 and Figure 3. I suspect the trends in CHIP are similar to non-CHIP, which raises the question of how operators are viewing access in relation to procedural complexity.

Response: We thank the reviewer for his thorough review. We agree, it would be of interest to compare CHiP vs non-CHiP, however, this is another research question and it is outside the scope of this analysis.

Comment 6. Absolute rates of mortality, major bleeding and MACCE are low – what is the number of radial compared to femoral access needed to potentially avoid 1 adverse outcome?

Response: We thank the reviewer for pointing out this important remark. We have calculated the overall NNT and the trends for the same. We created a new table to reflect the same (outlined below and marked in the manuscript).

Table 3
The number of Radial compared to Femoral access needed to potentially avoid one adverse outcome in the overall CHIP cohort and in those cases performed between 2010 and 2017.

	Overall NNT (2006-2017)	NNT (2014-2017)
Death	928	579
Major bleeding events	263	244
MACCE	491	403

Abbreviations, CHiP, complex high-risk per cutaneous coronary interventions

Under the *Results* section of the manuscript: " *Table 3 depicts the overall number of radial access procedures needed to potentially avoid one death, major bleeding event, or MACCE and the number needed in those cases performed in the last 4 years of the study. (2014-2017, NNT: mortality, 579; Major bleeding events, 244; MACCE, 403"*

Comment 7. Failed attempts in table 1 – no p value and requires explaination of definition.