Congenital Heart Disease in Adults: a cost-effectiveness analysis of Public Policies and Interventions

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Francisca, you are the bright light in my days.

List of Abbreviations

6mwt: 6-minute walking test

AHA: American Heart Association

ACHD: Adults with congenital heart disease

AICU: Adult Intensive Care Unit

BNF: British National Formulary

CE: Cost-Effective

CEA: Cost-Effectiveness Analysis

CHD: Congenital Heart Disease

CHF: congestive Heart Failure

DSA: Deterministic Sensitivity Analysis

ESC: European Society of Cardiology

ERS: European Respiratory Society

FDC: Free Dental Care

HF: Heart Failure

IE: Infective Endocarditis

EVBI: Expected Value of Perfect Information

ICER: Incremental Cost Effectiveness Ratio

IHD: Ischemic Heart Disease

FC: Functional Class

LY: life-years

PH: Pulmonary Hypertension

PAH: Pulmonary Arterial Hypertension

PAH-CHD: Pulmonary Arterial Hypertension associated with Congenital Heart Disease

PSA: Probabilistic Sensitivity Analysis

NMB: Net Monetary Benefit

NICE: National Institute for Health and Care Excellence

NYHA: New York Heart Association

QALY: Quality-Adjusted Life Years

RCTs: Randomized Control Trials

UK: United Kingdom

VHD: Valvular Heart Disease

WHO: World Health Organization

WTP: Willingness to pay

y: years

List of Figures

List of Tables

Table of Contents

Abstract

Introduction:

Budget constraints pose significant challenges to countries with free and universal healthcare systems. Therefore, it becomes crucial to allocate resources in the most effective and efficient manner, ensuring optimal value for the population's health and well-being. This process often involves making difficult choices and requires the use of cost-effectiveness studies, which are widely utilized in healthcare economics. These studies allow for a comprehensive comparison of various healthcare policies, drugs, procedures, and new technologies, considering not only their costs but also their impact on patients' quality of life and survival. Additionally, these studies consider the potential consequences of allocating funds to one alternative over another. Among the growing population of patients with Congenital Heart Disease (CHD) transitioning to adulthood (ACHD), there is a substantial burden of anatomical and hemodynamic sequelae. These patients face increased risks of complications such as infective endocarditis (IE), pulmonary hypertension (PH), heart failure, among others, requiring specialized cardiac care throughout their lives. To mitigate the risk of IE, high-risk patients should undergo frequent dental check-ups, but the associated costs are usually not covered or only partially covered by healthcare systems. Consequently, patients often struggle to comply with these clinical recommendations due to economic constraints.

Furthermore, ACHD patients born with cardiac defects and significant shunts are at risk of developing a specific type of pre-capillary PH known as pulmonary arterial hypertension (PAH), even after the cardiac defects have been closed. Unfortunately, the treatment of PAH in this population has been limited due to the lack of randomized controlled trials specifically including CHD patients.

In summary, the limited healthcare budgets in countries with free and universal healthcare require careful resource allocation. Cost-effectiveness studies are useful tools for comparing healthcare options and making informed decisions. Patients with ACHD face unique challenges and require specialized care, including preventive measures for infective endocarditis and consideration of PAH treatment options. Addressing these healthcare needs within budgetary limitations remains an ongoing concern.

Objectives: The first part of thesis aims to evaluate the cost-effectiveness of delivering free dental care for patients considered at high risk of IE within the United Kingdom (UK) National Health Care (NHS) context, using an analytic decision Markov-model. Our main hypothesis is that offering free annual dental checkups to high-risk patients not only allows for early detection of dental infections, but also leads to an improvement in personal dental hygiene and oral care, reducing chronic "low-grade" bacteremia and, consequently, the risk of IE. This free dental care strategy is compared to standard treatment currently in place in the NHS, which involves a co-pay model for patients.

The second part of this work aims to design an analytic decision model to investigate the potential long-term cost-effectiveness of combination therapy in patients with CHD and PAH (PAH-CHD), both repair and unrepaired, using retrospective data from our patient cohort combined with information available in the literature. Our main hypothesis is that combination PAH therapy is cost-effective as a treatment strategy for PAH-CHD, driving an improvement in quality of life and slowing the natural progression of the disease, when compared with monotherapy.

Methodology

For both aims, a decision analytical cost-effectiveness analyses were designed as a Markov Model; the costs were assumed using an NHS perspective and collected from the National Schedule of NHS Costs 2020/21 and the British National Formulary (BNF); the benefits were measured as quality-adjusted life-years (QALY) and life-years (LYs) gained. In the free dental care vs standard policy project, a cohort discrete-time state transition Markov model was constructed, using aggregated data available in the literature. For the project assessing the cost-effectiveness of PAH combination therapy vs PAH monotherapy in PAH-CHD patients, individual data from a tertiary ACHD and PH UK centre was used to populate the model. Therefore, in this case, an individual-level Markov model was constructed using a continuous times state transition model (CTSTM) with inhomogeneous time. A sensitivity analysis for both projects was developed, using determinist sensitivity analysis (DSA) and Probabilistic Sensitivity Analysis (PSA), as appropriate.

Results: Offering free dental care to ACHD patients at high-risk patients of IE yielded a gain of 0,47 quality-adjusted life years (QALYs) and 0,48 life-years per patient, along with a cost reduction of £275,58 per patient for the healthcare system. Consequently, the Incremental Cost-

Effectiveness Ratio (ICER) for this intervention was calculated at £-582,61/QALY, indicating both improved health outcomes and cost savings.

Regarding the PAH therapy models, offering combination therapy compared to monotherapy for PAH-CHD patients resulted in an ICER of £7.446,00/QALY for the entire PAH-CHD population and £5.987,00/QALY for the subgroup of unrepaired PAH-CHD patients. However, for the subgroup of PAH patients after CHD defect correction, the ICER exceeded the current willingness-to-pay (WTP) threshold in the UK, amounting to £82.306,00/QALY.

Conclusion: Offering free dental care to patients at high-risk of IE appears to be cost-effective and cost-saving, using the current UK WTP thresholds. Moreover, combination therapy in patients with PAH-CHD is also cost-effective, especially for patients with unrepaired CHD defects.

In order to bridge the gap between patients and healthcare management, policy decisions regarding new drugs, procedures, and technologies should actively involve clinical practitioners such as medical professionals and nurses. Their unique position allows them to provide valuable insights and expertise. Equipping clinicians with fundamental skills and tools in cost-effectiveness studies and data analysis is crucial to develop cost-effectiveness studies that accurately mirror the clinical impact of diseases, both for patients and for the healthcare system. By doing so, clinicians can play a vital role in shaping the future of national health systems and influencing budget allocation to ensure optimal patient care.

Resumen

Introducción: Las restricciones presupuestarias plantean desafíos significativos para los países con sistemas de atención médica gratuita y universal. Por lo tanto, resulta crucial asignar los recursos de la manera más efectiva y eficiente, garantizando un valor óptimo para la salud y el bienestar de la población. Este proceso a menudo implica tomar decisiones difíciles y requiere el uso de estudios de costo-efectividad, que se utilizan ampliamente en el ámbito de la economía de la salud. Estos estudios permiten una comparación exhaustiva de diversas políticas sanitarias, nuevos medicamentos, procedimientos u otras tecnologías, considerando no solo sus costes, sino también su impacto en la calidad de vida y la supervivencia de los pacientes. Además, estos estudios consideran las posibles consecuencias de asignar fondos a una alternativa en lugar de otra.

La población de pacientes con enfermedades cardíaca congénitas (ECC) está en aumento, y estos pacientes llegan a adultos con una carga sustancial de secuelas anatómicas y hemodinámicas. Este grupo de enfermos enfrentan un mayor riesgo de complicaciones como la endocarditis infecciosa (EI), la hipertensión pulmonar (HP) y la insuficiencia cardíaca, lo que requiere atención cardíaca especializada a lo largo de sus vidas. Para mitigar el riesgo de EI, los pacientes de alto riesgo son aconsejados a tener frecuentes revisiones dentales, pero los sistemas sanitarios no suelen cubrir los costes asociados, o solo lo cubren parcialmente. En consecuencia, los pacientes a menudo tienen dificultades para cumplir esta recomendación debido a limitaciones económicas.

Además, los pacientes adultos con ECC que nacieron con defectos cardíacos y cortocircuitos significativos corren el riesgo de desarrollar un tipo específico de HP precapilar conocida como hipertensión arterial pulmonar (HAP), incluso después de que los defectos cardíacos hayan sido corregidos. Desafortunadamente, el tratamiento de la HAP en esta población ha sido limitado debido a la falta de ensayos controlados aleatorios que incluyan específicamente a pacientes con ECC.

En resumen, los presupuestos sanitarios limitados en países con sistemas de atención médica gratuita y universal requieren una cuidadosa asignación de recursos. Los estudios de costo-efectividad son herramientas muy útiles para comparar opciones de atención médica y tomar decisiones informadas. Los pacientes adultos con ECC enfrentan desafíos únicos y requieren atención especializada, incluyendo medidas preventivas para la IE y la consideración de

opciones de tratamiento para la HAP. Abordar estas necesidades dentro de las limitaciones presupuestarias del sistema sanitario sigue siendo un desafío continuo.

Objetivos: La primera parte de la tesis tiene como objetivo evaluar la relación costo-efectividad de ofrecer cuidado dental gratuito a pacientes considerados de alto riesgo EI en el contexto del Servicio Nacional de Salud (NHS) del Reino Unido, utilizando un modelo analítico de decisión de Markov. La hipótesis principal es que ofrecer revisiones dentales gratuitas anuales conduce a una detección precoz de infecciones bucales y mejora en la higiene dental y el cuidado oral personal, reduciendo la bacteriemia crónica "de baja intensidad" y, en consecuencia, el riesgo de IE. Esta estrategia de cuidado dental gratuito se compara con el tratamiento estándar en vigor en el NHS, que supone un modelo de copago para los pacientes.

La segunda parte de este trabajo tiene como objetivo diseñar un modelo analítico de decisión para investigar la relación costo-efectividad a largo plazo de la terapia combinada de HP en pacientes con ECC y HAP (ECC-HAP), tanto reparados como no reparados. Para este objetivo se han utilizado datos retrospectivos de una cohorte de pacientes con ECC-HAP combinados con información disponible en la literatura. La hipótesis principal es que la terapia combinada para la HAP es coste-efectiva como estrategia de tratamiento para ECC-HAP, mejorando la calidad de vida y desacelerando la progresión natural de la enfermedad, cuando comparada con la monoterapia.

Metodología: Para ambos objetivos, se diseñaron análisis de coste-efectividad basados en modelos analíticos de decisión, llamados Modelos de Markov. Los costes se asumieron desde la perspectiva del NHS y se obtuvieron de la Programación Nacional de Costos del NHS 2020/21 y el Formulario Nacional Británico (BNF, por sus siglas en inglés). Los beneficios se midieron en años de vida ajustados por calidad (AVACs) y años de vida ganados. Para el proyecto de análisis de atención dental gratuita versus política estándar, se construyó un modelo de Markov de transición de estados con tiempo discreto, utilizando datos agregados disponibles en la literatura. Para el proyecto que evaluó la relación coste-efectividad de la terapia de HAP combinada versus monoterapia en pacientes con ECC-HAP, se utilizaron datos individuales de un centro terciario de adultos con ECC-HAP en el Reino Unido para poblar el modelo. Por lo tanto, en este caso, se construyó un modelo de Markov a nivel individual utilizando un modelo de transición de estados con tiempo continuo y no homogéneo. Se desarrolló un análisis de

sensibilidad para ambos proyectos, utilizando análisis de sensibilidad determinista y análisis de sensibilidad probabilístico.

Resultados: Ofrecer atención dental gratuita a pacientes adultos con ECC considerados de alto riesgo de EI produjo una ganancia de 0,47 años de vida ajustados por calidad y 0,48 años de vida por paciente, junto con una reducción de costos de £275,58 por paciente para el sistema sanitario. La ratio de Coste-Efectividad Incremental (RCEI) para esta intervención fue de £-582,61/AVAC, lo que indica una mejora tanto en los resultados de salud como a nivel de ahorro de costes.

En cuanto a los modelos de terapia para HAP, ofrecer terapia combinada en comparación con monoterapia para pacientes con ECC-HAP resultó en una RCEI de £7.446,00/AVAC para la población de ECC-HAP en su conjunto y £5.987,00/AVAC para el subgrupo de pacientes con ECC-HAP no reparados. Sin embargo, para el subgrupo de pacientes con HAP después de la corrección del defecto cardíaco, la RCEI superó el umbral actual de disposición a pagar en el Reino Unido, ascendiendo a £82.306,00/AVAC.

Conclusión: Ofrecer atención dental gratuita a pacientes de alto riesgo de EI es coste-efectivo y permite ahorrar costes, utilizando los umbrales actuales de disposición a pagar en el Reino Unido. Además, la terapia combinada en pacientes con ECC-HAP también es coste-efectiva, especialmente para aquellos pacientes con ECC no reparadas.

Con el fin de cerrar la brecha entre los pacientes y la gestión sanitaria, las decisiones de política con respecto a los nuevos fármacos, procedimientos y tecnologías deben involucrar activamente a profesionales clínicos, como los profesionales médicos y de enfermería. Su posición única les permite proporcionar conocimientos y experiencia valiosos. Dotar a los clínicos de habilidades y herramientas fundamentales en estudios de coste-efectividad y análisis de datos es crucial para desarrollar estudios económicos en la salud que reflejen con precisión el impacto clínico de las enfermedades, tanto para los pacientes como para el sistema sanitario. De esta manera, los clínicos pueden desempeñar un papel vital en la configuración del futuro de los sistemas de salud nacionales e influir en la asignación presupuestaria que garantice una atención óptima a sus pacientes.

1. Introduction

1. Introduction

1.1 The Adult Congenital Heart Population

Congenital heart disease (CHD) is the most frequent congenital defect in the world, affecting 9,1 per 1.000 live births worldwide and 8,2 in Europe (1). Advances in early surgery and percutaneous procedures in the last 70 years have greatly transformed the natural disease progression of most CHD types, and currently 97% of congenital children are expected to survive to adulthood, with an acceptable quality of life (2). Therefore, the Adult Congenital heart Disease (ACHD) population is in frank expansion, even though it is still considered a relatively new field within modern Adult Cardiology, since it consists of a cohort of patients most of whom until the 1950s were not expected to reach adulthood (3,4). At present, in Europe alone, there are more than 2,3 million adult patients with ACHD who require highly specialized, multidisciplinary healthcare (5). In the UK it is estimated that 4 in 1.000 adults live with a congenital heart condition (6). However, the numbers of ACHD patients are likely to increase in the near future; indeed, Marelli et al. reported an increase in ACHD prevalence of 57% between 2000-2010, reaching 6,12 cases per 1.000 live adults in the Quebec region (4).

The model of care for ACHD patients is unique within the adult cardiology speciality, for the following reasons (5,7):

1) These patients tend to enter ACHD services at a very young age, typically between 16 and 18 years of age, and need lifelong ACHD and multidisciplinary specialist care.

2) For many, the combination of complex cardiac anatomy, multiple previous palliative or reparative procedures, and the frequent long-term sequelae related to an intricate hemodynamic and arrhythmic profile, result in significant morbidity and mortality.

3) A significant proportion of these patients are likely to need further multiple cardiovascular surgical, structural and/or electrophysiology procedures throughout their lives.

4) This population suffers from a high burden of non-cardiac comorbidities e.g., musculoskeletal, endocrinological, or liver diseases.

5) Finally, as they grow older, they are exposed to the same acquired cardiovascular risks and diseases affecting the general population, such as hypertension, diabetes, alcohol/tobacco abuse, sedentarism, coronary heart disease, lung, kidney, and liver disease. For this reason, the term "geriatric" ACHD was recently introduced (8).

1.1.1 The natural evolution of congenital heart disease and its complications

Despite having a higher mortality than their age-matched counterparts in the general population, the survival prospects in the ACHD population are improving **(Figure 1)** (8). The natural progression of congenital heart disease often includes the risk of sudden death, frequent cardiac or pulmonary infections, pulmonary hypertension (PH) and, ultimately, advanced heart failure (HF) (9). Most types of CHD do ultimately culminate in HF, which is progressive and an important cause of morbidity and mortality in adult patients (9,10). HF is the main cause of death in some ACHD registries (responsible for up to 26% of mortality) and the second cause of hospitalizations, after arrhythmias (11).

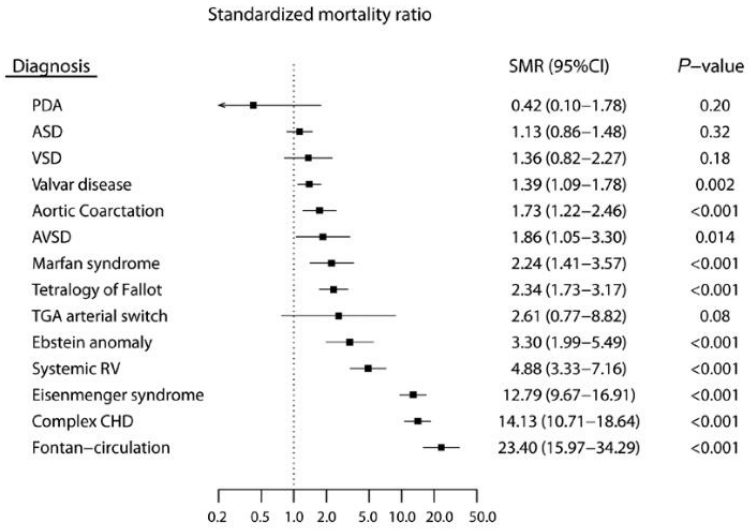


Figure 1: Standardized mortality ratios (SMR) in various CHD groups, from Diller et al. (9). In this graph, an SMR closer to 1 suggests that patients have comparable mortality to that of sex- and age matched sample from the general population.

Acronyms: AVSD, complete atrioventricular septal defect; ASD, atrial septal defect; CHD, congenital heart disease; PDA, Patent ductus arteriosus; RV, right ventricle; TGA, transposition of the great arteries; VSD, ventricular septal defect.

Overall, despite substantial improvements in survival for CHD patients, this population faces multiple short and long-term challenges (12). Therefore, their healthcare involves frequent monitoring and risk stratification to identify those who require intervention or escalation of

therapies and strict control of risk factors for complications relating to the CHD or acquired health conditions.

The need for specialist care is recognized worldwide and guidelines recommend that ACHD patients should be treated in expert high-volume centers. Their care should involve a multidisciplinary team of ACHD cardiologists, specialist nurses, cardiac and congenital cardiac surgeons, electrophysiologists, radiologists, to name a few (13,14). Within the UK National Health System (NHS), the care for ACHD patients is commissioned to a few reference centres who not only provide medical care, but also education to their patients on healthy lifestyle habits, exercise guidance, pregnancy and contraception, and general measures to prevent infective endocarditis (IE) (6). With a few exceptions, almost all of the care recommended by the NHS commissioning guidelines is free-of charge for the patient and paid for by the public healthcare system.

1.1.2 Utilization of healthcare resources and burden for the healthcare system

The ACHD landscape is rapidly changing, with fast expansion of the ACHD population and an increasing number of patients with complex CHD reaching adult life. This is an unprecedented challenge to healthcare providers. In England, it is reported that over 800 pediatric patients are being transitioned to ACHD services every year; this number is based on birth rates estimates, this number should be closer to 2.000 annually (7,15).

This improvement in survival translates into an elevated healthcare usage compared to the general population, in terms of regular outpatient visits with advanced imaging, hospitalizations and surgical or percutaneous procedures (16,17). Burchill et al. reported a 91% increase in HF hospitalizations in patients with CHD in the United States (US) between 1998 to 2008, versus a 21% increase in non-congenital populations (18). Similar trends have been described worldwide over the last 20 years (17,19). Nevertheless, limited research has presented definitive quantification of the actual impact of ACHD on healthcare systems across Europe, and its projected magnitude in the near future remains uncertain. A study carried out in Belgium reported that the health expenditure assigned to adult patients with CHD in 1997 was four times higher than that of age and sex-matched individuals in the general population, with most of the cost concentrated in 12% of the overall CHD population (20). Similarly, the healthcare expenditure related to admissions increased by 158% between 2002 and 2012 in the US in

ACHD patients (21). These numbers most likely reflect, not only the increase in the number of patients treated, but also the higher number of repeat surgeries and other procedures, and the increasing frequency of long/complex hospitalizations. In 2017, Nars et al. from Harvard University reported that CHD patients admitted for cardiac surgery had more in-hospital complications, and a higher mortality compared to patients undergoing coronary bypass surgery, which resulted in more expensive hospitalizations (22).

1.1.3 Economic Analysis in Congenital Heart Disease

The fast-growing ACHD population has an increasing healthcare usage, which is both highly specialized and expensive. To meet these evolving demands, it is important to carefully forecast and plan future ACHD healthcare. Modelling the future of healthcare requires a suitable framework, and cost-effectiveness models are gaining visibility in Medicine and Health Technology Assessment. They are a useful tool for evaluating new health policies, drugs, or procedures, since they are able to take into account both benefits and costs measured in a systematic way (23). Cost-effectiveness models have been used in Health Economics for many years and have also been applied to Cardiology. A most prominent example of this have been the multiple analyses on the cost-effectiveness of the transcatheter percutaneous aortic valve implantations (TAVIs) for patients with degenerative valve disease in different healthcare settings and for patients with different risk-profiles (24–26).

In the ACHD universe, where novel surgical and percutaneous techniques have been instrumental in the modernization of care, such studies are scarce (27). Percutaneous techniques have made it possible for CHD patients, who would otherwise need cardiac surgery, to avoid sternotomy, general anaesthesia and cardiopulmonary bypass (e.g. for closure of atrial septal defects, implantation of pulmonary valves, etc.) and undergo a percutaneous option instead, with a drastic reduction in procedure time, hospitalization length and a faster recovery (28). These new techniques can also impact patients' quality of life (QoL), although research on this field is still limited (29). Studying the ACHD model of care from a health economic perspective, with its chronic nature and high costs, can open the doors for new treatments and procedures, while allocating resources where they are most needed.

In this thesis, we applied Health Economics methods to evaluate new treatment strategies in two main healthcare complications of ACHD, infective endocarditis and pulmonary arterial hypertension associated with CHD.

1.2 Economic Evaluation in Healthcare

Human and economic resources allocated to healthcare systems are finite. In a reality of budgetary constraints, utilization of available resources requires carefully planning and, often, difficult choices need to be made. The economic evaluation of drugs, procedures and health policies are paramount to secure the best possible use of the limited resources. Consequently, new drugs or interventions need to be able to demonstrate, not only their clinical benefit (or "efficacy"), typically in a clinical trial, but also their cost-effectiveness (i.e., that the value added is worth the cost) (30).

Economic Evaluation is defined by Drummond as the "comparison of alternative options in terms of their costs and consequences" (30). In this framework, the concept of *cost opportunity* is a pivotal one, as it recognizes that allocating funds towards one health intervention will undoubtedly lead to a decrease of resources that can be used in a different one (23). In healthcare, this decision can be as simple as choosing between two nonsteroidal anti-inflammatory drugs (for example Ibuprofen vs Naproxen) for pain management in a General Practitioners (GP) consultation. However, health economic decisions are often more complex and might even require comparisons between different fields, for example to decide if a health provider should invest their limited budget in a new knee replacement prosthesis for Orthopedics or a new extracorporeal membrane oxygenation (ECMO) device for the Acute Intensive Care Unit (AICU). The goal of Healthcare Economic Evaluation analysis is to assist these decisions and provide a comprehensive and scientific framework for decision-makers, where both *costs* and *consequences (or outcomes)* of each intervention are carefully appraised (30). Consequently, economic evaluation not only assesses the new technology, but also incorporates the opportunity-cost consequences derived from choosing one option over another.

The final decisions are often made by governments, politicians, healthcare managers and, in some instances, healthcare professionals with the appropriate knowledge to make such evaluations. Doctors and nurses are among those most exposed to a healthcare system's strengths and weaknesses since the beginning of their training, and often act as patients advocates, hence are in a privileged position to understand the different needs across the healthcare system and the challenges associate with each decision; yet they often lack the economic background and tools to participate in these discussions. Therefore, being acquainted with the tools used in Economic Evaluation is paramount for healthcare professionals who want to help improve the healthcare system at a macroscopic scale.

1.2.1 Models for Economic Evaluation in Healthcare

Different economic evaluation models are available in healthcare, which use different approaches on *what to measure* (costs and benefits vs costs alone, for example) and *how to measure* it. These models are summarized in **Figure 2**. Cost-Minimization models, for example, ignore the health benefits/consequences of each intervention to focus only on *monetary* differences between them, with the goal to choose the most inexpensive intervention. Other types of economic analysis, such as Cost-Benefit, Cost-Utility and Cost-Effectiveness, also incorporate the *outcomes* of such interventions into their models, alongside with their cost.

Quantifying the *outcome or benefit* of a new procedure/drug is not straightforward, as it often has multiple layers and dimensions - some quite challenging to calculate. For example, a new costly surgical intervention for pulmonary hypertension associated with chronic thromboembolic disease may benefit the patient, not only in terms of improving their quality of life but may also add a prognostic benefit in terms of survival. Additionally, an extra layer of benefit can be considered if the treatment allows re-incorporation of the patients to their social and workforce roles; in that case, it might be accounted in the model as monetary benefit if the "social" benefit of rejoining the work-force is translated into monetary gains for the country's social security system (31).

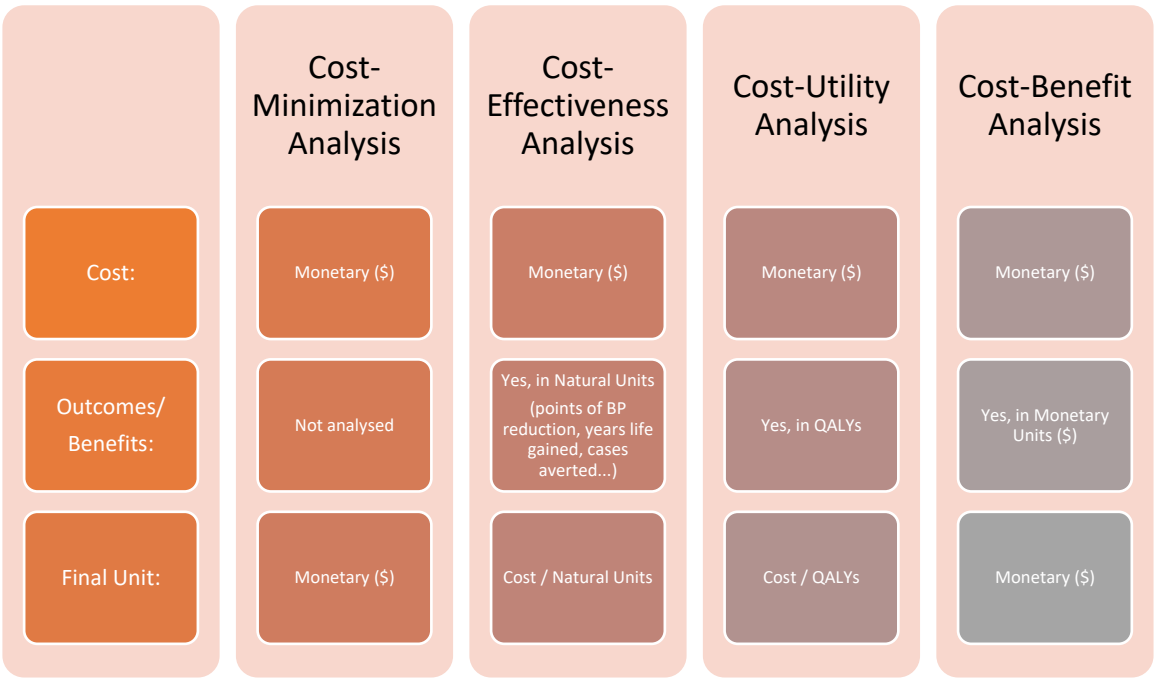


Figure 2: Different economic models in Health Economic Evaluation

Acronyms: BP: Blood pressure. QALY: quality-adjusted life year

1.2.2 Cost-Effectiveness Analysis (CEA)

The most comprehensive evaluation method is Cost-Utility analysis, which is sometimes considered a special type of Cost-Effectiveness Analysis (CEA). Both terms are used interchangeably in the literature and, for simplicity purposes, this thesis will use the term CEA for both methods, specifying the units of measure as appropriate.

In healthcare economic models, it is important to measure not only the benefits of an intervention in terms of years of life gained (or cases adverted, etc.) but also to integrate the life quality of those years (the so called *"utility"*). Its significance is easy to grasp – a new procedure can claim a significant survival improvement when compared with the standard of care (which is usually cheaper), but if quality of life remains severely decreased after the procedure, it may not be a worth-while investment. The most common unit used in Cost-Utility studies to measure the *Benefits or Outcomes* is called the Quality-Adjusted Life Years (or QALYs) and incorporates both the concepts of life extension and utility of the years gained. They have been routinely used in economic evaluation analyses to compare the benefits of different procedures, drugs or healthcare policies, for many decades. In the last few years, their use has been extended to clinical studies and have been used as outcome measures in randomized control trials (RCTs), for example in cardiovascular and oncology studies (32,33). The QALY unit is defined by the National Institute for Health and Care Excellence (NICE) as "a measure of the state of health of a person or group, in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health" (34).

QALYs are calculated by estimating the years of life remaining for a patient following a particular intervention and weighting each year with a quality-of-life score, which usually ranges between 0 to 1. Here 1 equals to a normal life without any day-to-day limitations and 0 corresponds with complete limitation, which is usually attributed to death state (34).

1.2.3 Willingness-to-pay threshold and the incremental cost-effectiveness *ratio*

When appraising a new potential drug and comparing it with the standard option, there are four possible outcomes **(Figure 3):**

1) The new drug is *more effective* and *more expensive* than the standard option.
2) The new drug is *less effective* and *cheaper* than the standard option.
3) The new drug is *more effective* and *cheaper* than the standard option.

4) The new drug is *less effective* and *more expensive* than the standard option.

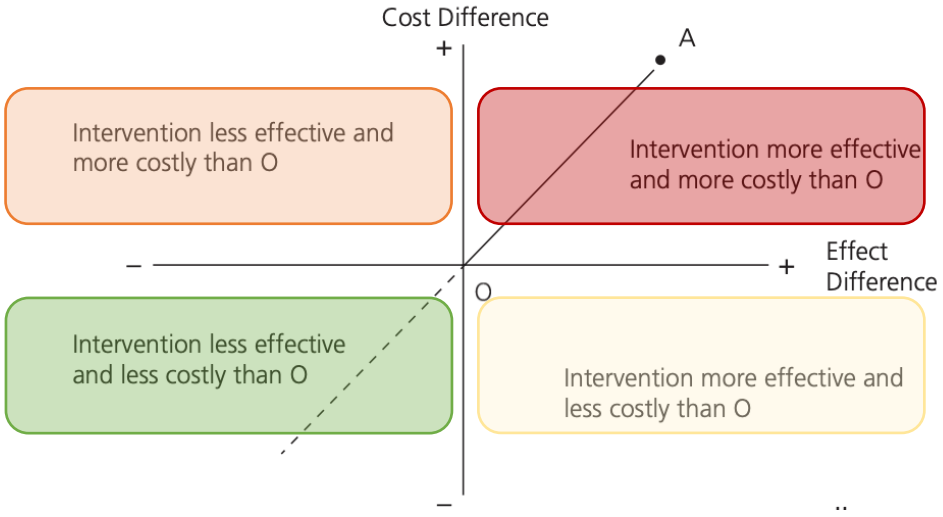


Figure 3: Cost-effectiveness graph, adapted from Drummond et al. (30).

In scenarios 3 and 4 (yellow and orange squares in **Figure 3**, respectively), the results lead to clear decisions: the new drug should replace the standard treatment in scenario 3 (the new drug is more effective and less expensive than the standard option) and should be discarded in scenario 4 (the new drug is costly and less effective). However, the most frequent scenario in healthcare is scenario 1 (i.e., the new drug or procedure is more effective, but also more expensive – red square). Scenario 2 (green square) also raises a similar question for decision-makers: how much of a difference in benefit is enough to offset the increase in cost? In health economics, the ratio between the difference in price and the difference in benefit of two strategies is called the "incremental cost-effectiveness *ratio*", or ICER **(see Formula 1).** The ICER is usually the final product of a cost-effectiveness or cost-utility study. To give a practical example, a CEA study performed by NICE for the drug Sacubitril-Valsartan (used for chronic HF with reduced ejection fraction) reported an ICER of £18.818,00 per QALY gained, versus the standard therapy of Angiotensin-converting enzyme (ACE) inhibitors (35). This result means that an extra £18.818,00 needs to be spend on Sacubitril-Valsartan (vs an ACE-inhibitor) to gain 1 extra QALY. Therefore, in practical terms, the ICER compares the different costs between 2 or more strategies to obtain one QALY, hence a smaller ICER is considered more cost-effective.

Formula 1:

$$ICER = \frac{Cost\ A - Cost\ B}{Benefits\ A - Benefits\ B}$$

Distinct health countries and systems might have different views on how much more they are willing to spend on a new drug/procedure to achieve specific outcomes. The *willingness-to-pay* (WTP) concept derives from a welfarist economic perspective, where individuals are considered better suited to decide on their own health's worth and the (cost) amount they would be willing to spend/not spend on a specific intervention or treatment, while making decisions on alternative options on which to spend their money or budget. Therefore, the monetary value of a procedure/treatment should be strictly linked to the perceived worth attributed by its consumers (in this case, patients) (31). In public healthcare systems, e.g., in Spain, Portugal and the UK, the elected government usually makes these decisions on behalf of its citizens. In theory, the willingness-to-pay thresholds established by each healthcare system/ government should reflect their population's views on how much their health is worth (36). In practice, however, the monetary value allowed to be spent in a new health technology or drug usually also depends on other factors, such as budgetary constraints, the amount of national annual gross domestic product (GDP) per capita, the percentage of GDP spent in healthcare, among many other factors. With this in mind, in 2003 the World Health Organization (WHO) recommended that the WTP threshold should be set to 1-3 times the national annual gross domestic product (GDP) per capita of each country **(Figure 4)** (36). Many countries have identified and published their own WTP thresholds, which may not be in agreement with the WHO recommendations, or the WTP thresholds established by citizen surveys (37–39). These WTP cut-offs vary widely among different countries: for example, a new drug can meet the threshold of WTP in the United States of America (usually cited at approximately $50.000,00 to 100.000,00 per 1 unit of QALY gained) and therefore be considered cost-effective in the American healthcare system, while receiving an opposite judgement in the UK (which has a WTP cut-off that ranges from £20.000,00–£30.000,00 per every QALY gained). Ultimately, if a new therapy is more effective and expensive than its counterparts, these WTP thresholds can be the decisive factor on whether it is adopted from a financial point of view. One example in Cardiology is PCSK9 inhibition drugs, which were introduced in the market in 2015 and showed to be highly potent and effective in reducing cholesterol when compared with the standard treatment (statins); however, due its high cost, many countries decided to finance only specific

subgroups of patients (for example, patients with familiar hypercholesterolemia), where cost-effectiveness analysis showed an acceptable ICER for most healthcare systems (40,41).

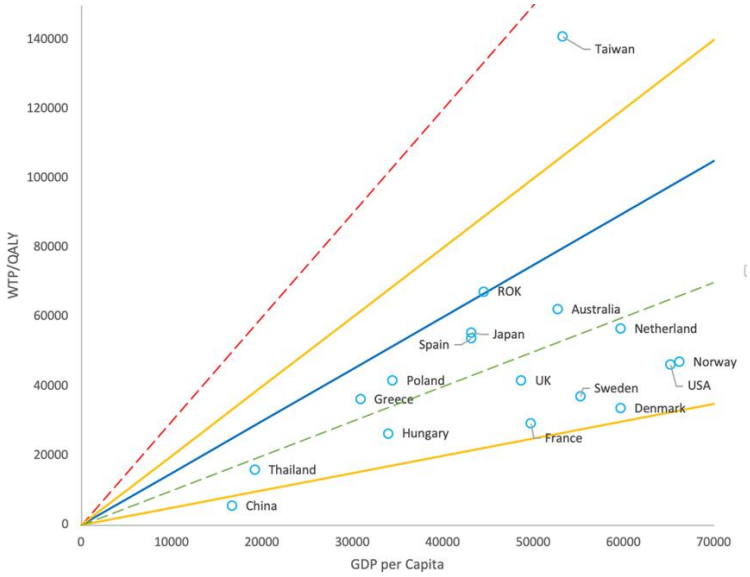


Figure 4: Willingness-to-pay (WTP) thresholds per QALY according to countries' GDP per capita, from (39).

1.2.4 Net Monetary Benefit and the Expected Value of Perfect Information

Net Monetary Benefit (NMB) is an alternative approach to report results in CEA, where benefits and costs have the same unit to facilitate comparison (23). The most frequent case is transforming QALY into a monetary benefit using the WTP threshold. The formula to calculate the NMB is the following **(Formula 2):**

Formula 2:

$$\boldsymbol{NMB = (QALYs * WTP) - Cost}$$

Typically, the NMB is calculated for each strategy and the one with the highest NMB value is considered the most cost-effective option. Another approach is to calculate the incremental NMB difference between alternative interventions, where a positive incremental NMB indicates that the intervention is cost-effective compared with the alternative (at the given WTP threshold).

The results of an economic evaluation suffer from inherent "uncertainty" associated with the parameters used to build the model. CEA uses sensitivity analysis, both deterministic

(deterministic sensitivity analysis or DSA) and probabilistic (probabilistic sensitivity analysis or PSA), to quantify and minimize the uncertainty around the results, but a level of variability will always remain (42). The concept of "expected value of perfect information" (EVPI) tries to capture the price that a healthcare decision maker would be willing to pay to collect the extra information needed to minimize the uncertainty (i.e., to acquire perfect information on all factors that influence the model). If the level of uncertainty is high, the price for the perfect information will increase. The formula to calculate EVPI is displayed in **Formula 3** (23):

Formula 3:

$$EVPI = E_\theta max_j NB(j,\theta) - max_j E_\theta NB(j)$$

where:

Eθ max$_j$ NB (j,θ) is the expected net benefit (NB) from treatment (j), given perfect information theta (θ).

max$_j$ Eθ NB (j,θ) is the expected net befit (NB) from treatment (j), given current information theta (θ).

1.2.5 Assumptions and Limitations of Healthcare Economic Evaluation

Economic evaluation in healthcare has several constraints. The models rely heavily on assumptions and the definitions chosen for costs and outcomes (or benefits), both of which need to be carefully explained. In a universal healthcare system, such as in the UK and Spain, the costs might be calculated from the healthcare perspective (for example using the expenditure related with patient admissions) or go further to incorporate a social perspective (such as lack of productivity for patients and their careers or non-healthcare costs for house adjustments due to mobility impairments, just to name only a few examples). A CEA study in healthcare systems with co-payment or out-of-pocket policies might also incorporate the patients' perspective on their healthcare costs. In this work, for the purpose of simplicity, we use the national healthcare system (NHS) perspective to estimate the healthcare costs of the policies analyzed; social costs (e.g., loss of productivity, need for sick leave payment, etc.) and patient costs (e.g., travelling to and from hospitals) were not included in the analysis.

The CEA frequently uses *utilities* to incorporate quality of life in the models, usually based on the table of utilities collected from the general population (by age and sex). This assumes that

patients value their life utility in a homogenous way. Moreover, in a perfect market, the consumers would be well informed and perfectly able to make choices regarding the value of a good or a service which, in turn, will translate on the cost they were willing to accept to acquire such a good or service for the utility perceived. This is not the case in healthcare, where health consumers (i.e., patients) have asymmetric information on their health status, treatment options and prognosis. Therefore, the healthcare market relies on "agents" who work on patients' behalf, usually the clinical staff (i.e., doctors or nurses), to advise on the best course of action; although this "indirect" market model makes it difficult to ascertain the true treatment value for patients, CEA models are still a powerful tool to incorporate both life expectancy (survival) and quality of live in economic healthcare models.

Cost-effectiveness analyses use a variety of parameters captured in different types of literature, from RCTs to retrospective small studies, to national scheduler costs for healthcare service. This lends both variability and uncertainty to the model, therefore the source of these variables needs to be disclosed and justified (34).

1.2.6 Decision Analysis Models in Cost-effectiveness Studies

There are different types of models used to analyse the impact of a certain procedure, drug or policies in healthcare, but two of the more frequently used are Decision Trees and State-Decision Models (or Markov Models). The most basic one is a "Decision Tree" model, which is typically used to compare two competing strategies in a short-term impact, or in situations where the procedure/drug is used once (for example, cost effectiveness between open vs laparoscopic cholecystectomy)(42). In the example below **(Figure 5),** an atrial shunt device implantation is tested against the standard treatment (a combination of heart-failure [HF] drugs) for patients with end-stage left-sided HF. As this procedure is usually only performed once and is only indicated for end-stage patients, it is reasonable to analyse its impact (costs and benefits) using a short-term scenario. In this Decision Tree example, after being treated with either treatment option, patients can improve or suffer a deterioration of their HF condition. Both conditions are linked to a specific utility, cost, and future survival probabilities. The model horizon ends when patients reach the absorbing state, i.e., the last state (in this case death or survival at 1 year, for example).

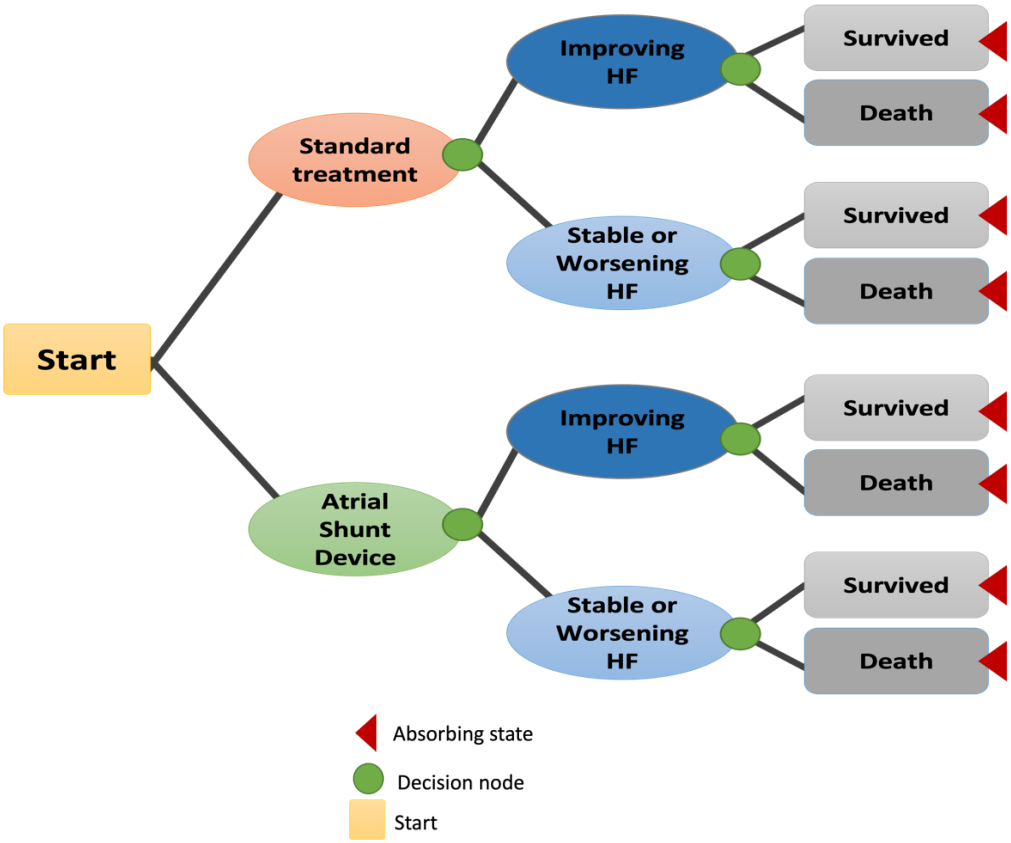


Figure 5: Schematic Example of a Transition Tree exploring the benefits of an atrial shunt device.

To assess the long-term impact of a new procedure/drug or policy, particularly in chronic diseases, a state transition model, such as "Markov Model", is more appropriate. The Markov model is a cyclic discrete model, which uses pre-specified disease/health states and time cycles, with the aim to "mimic" the natural progression of a disease (42). Therefore, a hypothetical population enters the model and transitions between health and disease states depending on the probability of developing the disease and the time spent on the model (cycle-length). In the example below, patients start in the "well" state (where utility is high and healthcare costs are low) and, according to underlying probabilities (which reflect their cardiovascular risk factors, age, etc), can either progress to an "ischemic heart disease" (IHD) state or a "valvular heart disease" (VHD) state, or remain in the "well" state **(Figure 6).** With the passage of time, patients can stay in the first three states or advance to heart failure. Once in the state of IHD, VHD or HF it is not possible to move back to the "well state" (i.e., in this example, the disease cannot be cured). Individuals in the HF stage may remain in the same state or advance to "death". When two competing treatment strategies are being assessed (for example, the use of

statins for IHD primary prevention), the probabilities of transition to the next stages are adjusted based on the efficacy of the treatment vs the standard (or no treatment).

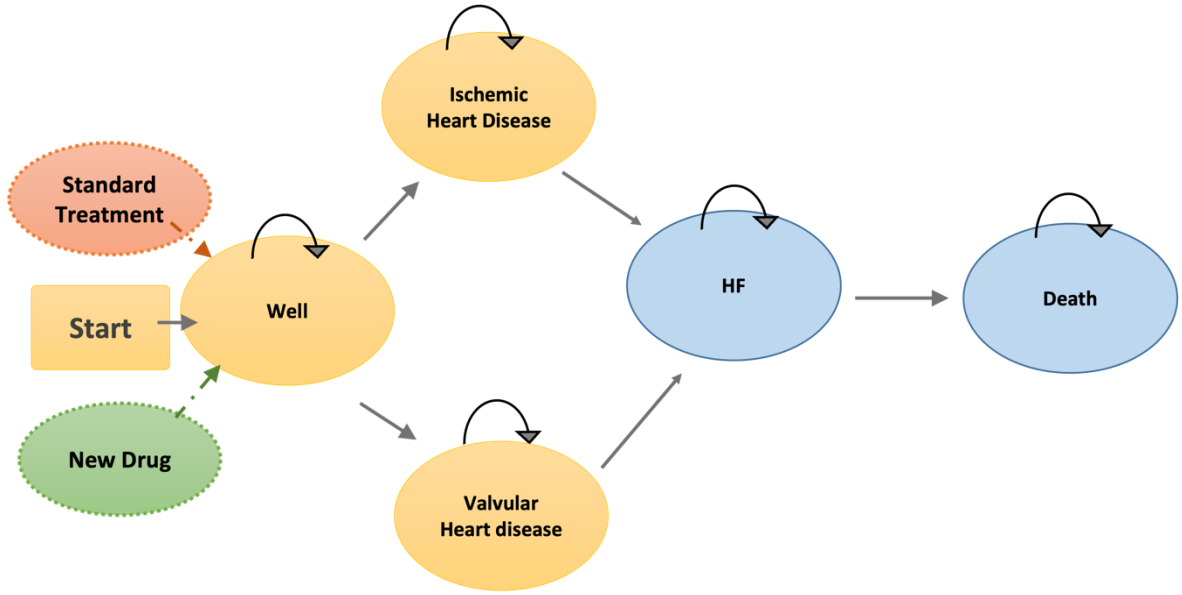


Figure 6: Heart Failure Markov Model diagram.

Transition States: "well", "ischemic heart disease", "valvular heart disease" and "heart failure". "Death" is an absorbing state.

Acronyms: HF, heart failure.

Markov models have no "memory" i.e., once an individual arrives to a certain state, his "background" disappears (23). In practice, for example, this means that once patients arrive to the "heart failure" state, costs, utilities and future probabilities are the same for all patients occupying that state, regardless of the state they previously occupied (i.e., the underlying disease that led them to developing HF). In this example, the previous states leading to HF development were ischemic heart disease or a valvular heart disease. Consequently, the risk of another ischemic event or valve replacement will be similar for all patients in the "heart failure" state, independent of what the original cause of heart failure was. In order to overcome this limitation and "add memory" to the model, it is possible to add "extra" states; in this case, this would translate into two separate HF states: one for individuals with an ischemic heart disease background and another for valvular heart disease. These are called semi-Markov Models **(Figure 7).**

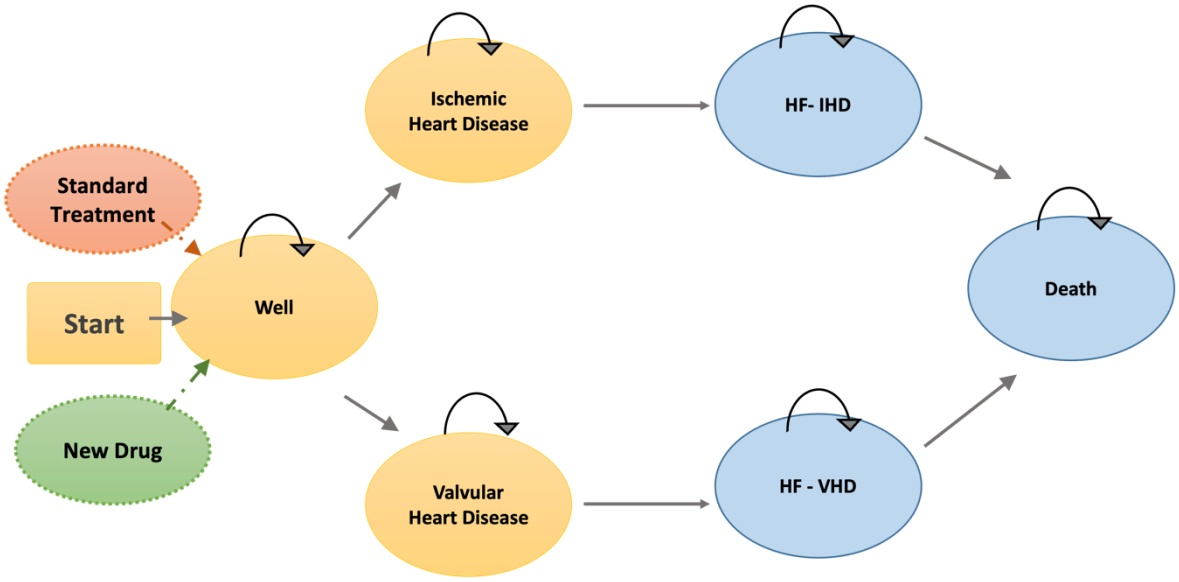


Figure 7: Heart Failure Markov Model with two added "memory states", HF-IHD and HF-VHD.

Acronyms: HF, heart failure; IHD, ischemic heart disease; VHD, valvular heart disease.

An important characteristic of the Markov Models is their ability to model long-term results. Markov models can incorporate two measures of time: time elapsed since the start of the model (called model time) and time spent in a given state (called state time) (42). Clinical trials and observational studies report outcomes for a relatively restricted follow-up period and the term "long-term follow-up" is often used in trials to define a timeframe of a few months, up 10-20 years, depending on the study subject. A Markov model is able to evaluate a drug or procedure benefits and costs beyond that, for example across the patients' lifetime. If long-term data is not available in the literature, the general practice is to extrapolate this information from studies of shorter duration, using parametric survival distributions fitted to the data available to predict the time data points for which no information is available. This process is well-established and guidelines for best practices can be found in the "NICE DSU Technical Support Document - Survival Analysis For Economic Evaluations Alongside Clinical Trials - Extrapolation With Patient-Level Data" document (43).

1.2.7 Markov Models in Cost-effectiveness Studies

The Markov models can be developed using grouped (cohort) or individual-level data (42). A cohort discrete-time state transition model (cDTSTMs) is a statistical approach used to simulate the progression of individuals through various states over time. Individuals are grouped into cohorts based on specific characteristics such as age and sex (42). This model then simulates

the disease progression of a hypothetical cohort within discrete time intervals. Transition probabilities between different states, estimated from longitudinal studies, clinical trials, life tables, and other sources, form the basis of constructing the model. Some transition probabilities may remain constant over time (time-homogeneous models), while others may vary (time-inhomogeneous models).

Alternatively, when individual patient data is available, an individual-level continuous time state transition model (iCTSTM) can be employed. In these models, instead of modelling the cohort progression as a whole, each individual is tracked over time, and the transitions between states are derived from survival analysis of individual data. For instance, in a disease with four possible states ("Well," "Mild Disease," "Severe Disease," "Dead"), patients can exist in different stages of the disease, and the time spent in each state is utilized for survival analysis (42). In this scenario, all potential transitions for a specific state at any given time (e.g., "remaining in the Well state," "transitioning from the Well state to Mild Disease," "transitioning from the Well state to Severe Disease," and "transitioning from the Well state to Death") are considered as competitive states and are treated as such in Survival Analysis **(see Figure 8).** In this case, because time between transitions is known for each individual, there are two type of analysis that can be done, depending if "memory" will be incorporated in to the model (44):

1) "Clock Reset" Analysis (equivalent to "pure" Markov Models) – the transition probabilities for the next state only depend on the time spent on the current state. This means that time resets to 0 each time the patient enters a new health state (i.e., no memory).

2) "Clock Forward Analysis" (equivalent to Semi-Markov models) – the future transitions for each individual not only depend on the current state time but also on the time since the patient entered the model initially. This analysis incorporates "memory" and uses Start-Stop Survival analysis to calculate survival hazards.

Figure 8: Schematic presentation of an individual followed through the disease stages in an individual-level continuous time state transition model. From Jackson, July 2018 (45).

1.2.8 Important definitions in Epidemiology Modelling

Below, I explain the most important concepts in epidemiology that will be used throughout this thesis:

1) Prevalence – the proportion of individuals in a population who have the disease or attribute of interest at a specific time point (i.e., a "snapshot" of the disease at a specific date).

$$\text{Prevalence} = \frac{\text{Number of people with the disease}}{\text{Total number of individuals in the population}}$$

2) Cumulative Incidence or Risk - it measures the occurrence of disease in the population and is defined as the proportion of the population with a new event during a given time ("period"). It is calculated by dividing the number of *new cases* during the period of interest by the *number of disease-free individuals* at the *start of the time period.* As any proportion, it ranges between 0 and 1.

$$\text{Cumulative incidence} = \frac{\text{Number of new cases during the period of interest}}{\text{Number of disease-free individuals at the start of this time period}}$$

In a survival analysis, the cumulative incidence of an event ***(e)*** at a time point ***(t)*** is defined as one minus the cumulative survival probability at that point ***(Surv(t))*** **(Formula 4)** (46).

Formula 4:

$$\textbf{Cum Incidence(e) = 1 - Surv(t)}$$

In cost-effectiveness studies the "time-point transition" probability of the event (i.e., transitioning from one state to another) can be derived from cumulative ("event-free") survival curves using the following formula **(Formula 5)**(42):

Formula 5:

$$tp\left(t_u\right)=1-S\left(t\right)/S\left(t-u\right)$$

where:

t **=** time point

u **=** length of the Markov cycle

tp **(*t_u*)** **=** transition probability between time-points (*t* and *t – u*).

t_u **=** time, or *t,* now measured as integer multiples of the cycle length of the model, *u*.

3) Incidence Rate - is defined as the number of new cases per unit of person-time, and it considers that not all individuals of the population will be followed for the entire duration of the study. We calculate this by dividing the number of new cases recorded during the follow-up period by the total number of "time units" contributed by each disease-free individual during the same period. Person-time can be expressed in different units, for example person-years, person-days, person-hours, etc.

$$\text{Incidence rate} = \frac{\text{Number of new cases during the follow-up period}}{\text{Total person-time by disease-free individuals}}$$

1.3 Congenital Heart Disease and Infective Endocarditis

Infective endocarditis (IE) is one of the most feared complications of congenital heart disease due to its significant burden of morbidity and high mortality (15-30%) (47,48). It is defined as an infection of a native or prosthetic heart valve, the endocardial surface, or an indwelling cardiac device (49). It is a rare but devastating disease affecting 1,5 to 11,6 cases per 100.000 person-years worldwide (50). Its prevalence is greater in individuals with risk factors, such as intravenous drug use, immunosuppression, intravascular catheters (usually used in hospital settings) and predisposing cardiac conditions (PCC) (50). The cardiac conditions considered by the ESC as at highest risk of IE are displayed in **Table 1**, and are all frequent within the ACHD population (47).

Table 1: Cardiac conditions with high risk of IE according to the 2015 ESC IE Guidelines.

(1) **Any prosthetic valve**, including a transcatheter valve, or those in whom any prosthetic material was used for cardiac valve repair.
(2) Patients with a **previous episode of IE.**
(3) Patients with **CHD** and other risk factors: - Any type of cyanotic CHD. - Any type of CHD repaired with a prosthetic material, whether placed surgically or by percutaneous techniques, up to 6 months after the procedure or lifelong if residual shunt or valvular regurgitation remains.

Acronyms: CHD, congenital heart disease; IE, infective endocarditis.

For the above reasons, ACHD patients are considered at special risk of developing IE, with a crude incidence of 3,8-11,5 cases per 1.000 person-years reported by Morris et al. in 1998 and, more recently, 1 case of IE per 348 CHD patients-year (adults and children) (51,52). In the adult CHD population alone, Kuijpers et al. recently reported an incidence of IE of 1,33/1.000 persons-years in the Netherlands, 27-44 times greater than in the general population (53).

1.3.1 Predisposition Cardiac Conditions in the General Population

It is worth mentioning that PCC are also present in the general population and their prevalence strongly increases with age (54). Duval et al. projected that 3,3% of the overall French population had a PCC, which rose to 6% and 7,5% in individuals > 50 and >75 years,

respectively **(Figure 9)** (54). These numbers reflect the increasing prevalence of cardiac valve dysfunction and valve replacement procedures associated with the normal aging process. Thornhill et al. estimated the incidence of IE in England to be approximately 4.968 cases/million persons-year among individuals considered high risk (defined by any of the ESC criteria included **in Table 1**) (55). This study also reported that the patients admitted for IE were mainly older (>50y age group) **(Figure 10**). Finally, the incidence of IE in high-risk populations was described in a recent study by Cahill at al. as 4,82/1.000 person-years in patients with surgical valve replacement (SARV) and 3,75/1.000 persons-years for TAVI recipients (56).

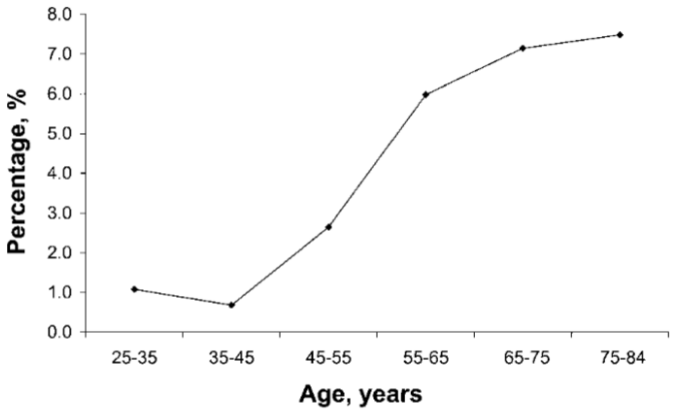


Figure 9: Age-specific prevalence of a predisposing cardiac conditions among French adults (54).

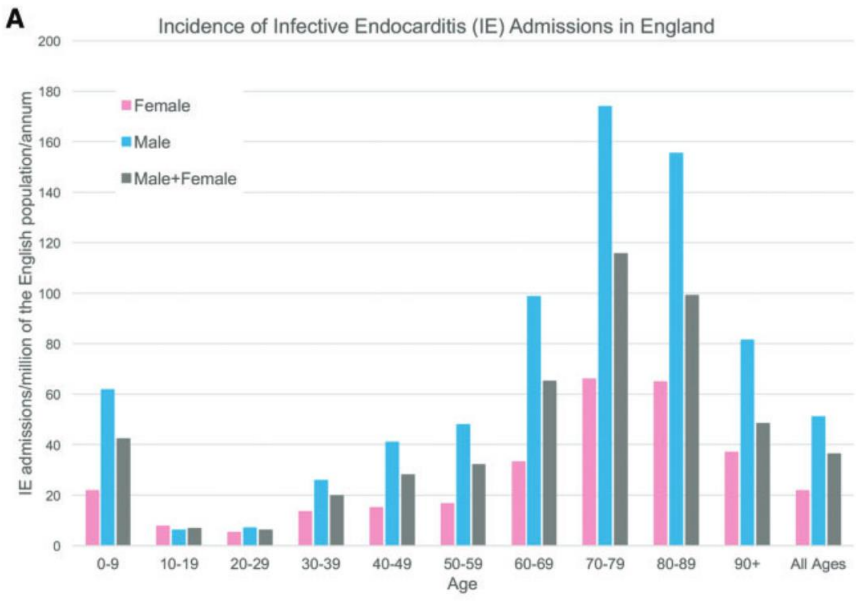


Figure 10: Incidence of infective endocarditis admissions in England in 2000-2015 (55).

1.3.2 Complications and Sources of IE

IE originates when a pathogen (usually from the oral cavity or skin) reaches the bloodstream, adheres to and colonizes the endocardium, valves or cardiac vessel tissue. The infection usually affects "damaged" valve tissue or prosthetic material and can produce septic emboli that affect downstream organs (the lungs in right-sided IE or the systemic circulation in left-sided IE). Once IE is suspected, it is paramount that blood cultures are taken swiftly before antibiotics are started. The full infection usually requires not only a prolonged hospitalization for intravenous antibiotics (typically 4-6 weeks in duration), but also often involves surgical removal of the infected prosthetic material in 40 to 80% of the cases, at times as urgent or emergency procedures (47,57,58).

IE is a life-threatening condition, not only for its impact on the heart that can result in heart failure or arrhythmia, but also through the potentially devastating effects of septic emboli (resulting in strokes and pulmonary embolisms) and multiorgan failure. The mortality is high and patients may survive with long-term sequalae and impaired quality of life (50,57). In post-IE surveys, patients who survived IE report physical weakness (78%), mental health issues (anxiety and depression in > 50%), concentration and memory loss problems (35%) and post-traumatic stress (11%) (59–61). Moreover, > 30% of previously employed patients are not able to return to work 1 year of the acute episode.

The pathogens most frequently associated with IE are Staphylococcus *sp* (species), Streptococcus *sp* and Enterococcus *sp*, responsible for 90% of all cases (62). The microorganisms associated with IE differ between non-CHD and CHD populations. The most common pathogen worldwide linked to IE is Staphylococcus aureus, but oral bacteria, such as the Streptococcus family, are responsible for up to 40% of IE cases (50,63). Indeed, patients with CHD are more likely to have Streptococcus viridians and Coxiella Burnetii isolated in their blood cultures than non-CHD individuals (58). Recently, Tutarel et al. described Streptococcus viridians as the most frequent pathogen isolated in an ACHD population treated in a tertiary center in the UK, responsible for 51% of the cases. Moreover, dental treatment was the most commonly identified predisposing event (in 30% of the cases), when one could be identified (57).

Bacteriaemia caused by dental procedures (for example root canal or dental extraction) has been identified as a possible cause of IE since the beginning of the 20th century. As such, in 1950, antibiotic prophylaxis was recommended before invasive dental procedures to minimize this risk. This recommendation has been subject to lively debate in the last 20 years, and indications for antibiotics have been restricted to selected high-risk patients in practice guidelines for invasive dental procedures (47). In the UK, the 2008 NICE guidelines took the most extreme stance of recommended against any antibiotic prophylaxis based on a CEA report (64). The NICE CEA model built to derive this recommendation used an estimation of a 50% reduction in IE by using antibiotic prophylaxis while overestimating the risk of allergic reactions to the drugs, by their own admission (65). More recent cost effectiveness studies had contrary results, and some authors reported a significant increase in IE since the NICE recommended against antibiotic prophylaxis in all patients (66,67).

Beyond the debate on antibiotic prophylaxis for dental procedures, it is clear that dental procedures are not the sole cause of IE, and the majority of cases of IE are caused by poor dental care (68–71). Poor dental health can result in chronic inflammation and sustained bacteraemia, with a significant risk of developing IE over time (72). Lockhart et al. reported that individuals with poor oral hygiene and gingival disease (defined by mean plaque and calculus scores of $\geq$2) presented a 4,5-fold increased risk of developing bacteraemia after tooth brushing, which could go up to an 8-fold increased risk if generalized bleeding was present during brushing (70). In a cohort awaiting dental extraction for tooth decay, tooth brushing alone was sufficient to cause bacteraemia in 23% (70). Moreover, Steckelberg and Wilson in 1993 estimated that daily transient bacteraemia was actually responsible for 60-75% of cases of IE in patients with no previous history of specific dental or non-dental interventional procedures (73). Various epidemiological studies have linked oral hygiene to 14-20% of all IE cases, with only 0,3 to 5% potentially avoidable with antibiotic prophylaxis (62,64). This was also confirmed in animal studies, where low-grade bacteraemia (used as proxy for everyday-life bacteraemia) induced IE in 70%-100% of the animals inoculated, depending on the pathogen and the inoculum size (74). In a study conducted in France in patients with IE and PCC, 30% presented periodontal infectious foci and 50% active caries (75). Likewise, a Danish study of native valve IE cases during a period of 10 years found that, in a population with high standards of dental hygiene, none had a clear dental origin (76). Therefore, promoting dental hygiene is potentially more effective for avoiding IE than antibiotic prophylaxis (62).

Based on these studies, daily dental hygiene is a pivotal recommendation for all congenital patients, along with frequent dental checkups (14). Moreover, good skin care, avoiding tattoos or piercings, is also recommended based on the same rationale. For patients considered at high-risk of developing IE and IE-related complications **(Table 1),** the ESC guidelines recommend twice a year dental follow-ups, and annual for the rest (47).

Programs evaluating and advocating oral health have proved to be effective in children and young adults, avoiding caries and improving plaque and gingival indices (77). Consequently, promoting dental hygiene and frequent dental checkups is a central part of ACHD care, and the benefits of dental care and the risks associated with poor dental hygiene should be clearly explained to young patients during their transition to ACHD services. Indeed, while in the general population IE is more likely after 50-60 years of age, in the ACHD population the mean age of IE is 30-40 years (57,58).

Self-reported dental care in the ACHD population varies widely worldwide, from 28% (in India) to 87% (Netherlands) of the patients reporting attending dental check-ups (78) **(Figure 11).** In Germany, patients with CHD had better dental health (fewer teeth decay score and apical periodontitis) compared with the non-CHD population (79).

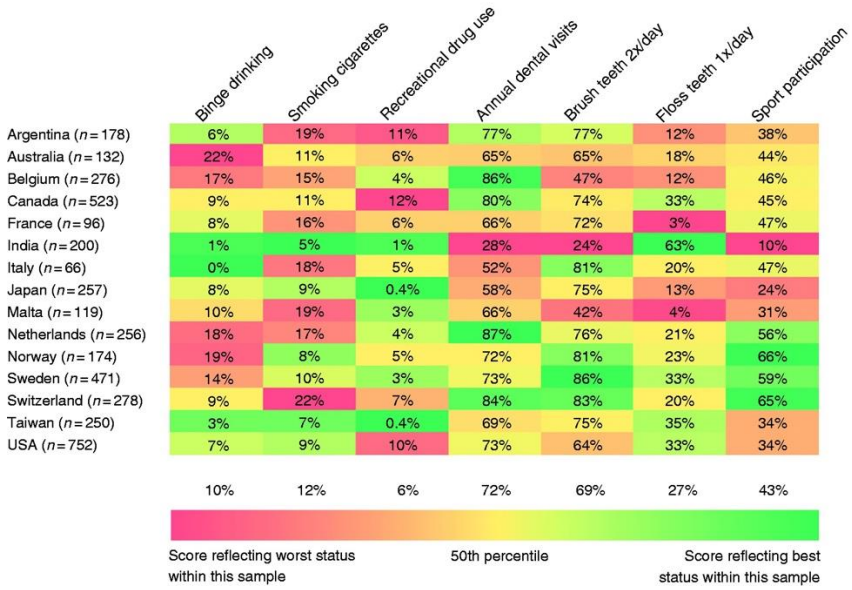


Figure 11: Health behaviors reported by adults with CHD across 15 countries, from Holbein et al (78).

1.3.3 Access to Dental Care in the UK

In 1952, dental care was deemed too expensive to be fully subsidized by the NHS and, as a result, dental care now operates as a separate entity, where dental care practices are independent from the national healthcare service (80). Patients can access dental care as private customers or via the NHS as co-payers. While some dental practices have opted to accept exclusively one type of patient, most offer a hybrid model – accepting both private and NHS patients (81).

The NHS commissions and reimburses dental practices using the "Unit of Dental Activity" (UDA), where the most basic procedure is a checkup equivalent to 1 UDA. The NHS commissioned more than 87 million UDAs in 2019 and this number has been static in the last 10 years **(Figure 12)** (82). Additionally, the dental care services have been severely impacted during the Coronavirus disease (COVID-19) pandemic **(Figure 13)** (83). Post-pandemic, between March 2021 and March 2022, only approximately 57 million units of NHS UDA were delivered, mostly for paying adults (52,5%), but also exempt adults (25,4%) and children (22,1%)(84).

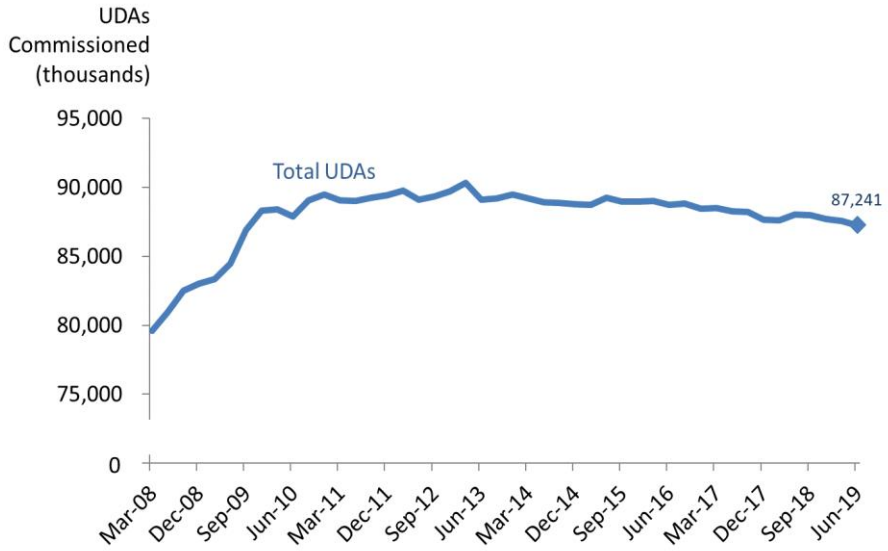


Figure 12: Time Series of UDAs Commissioned by Quarterly Change in England, 2008-2019 (82).

Acronyms: UDA, units of dental activity.

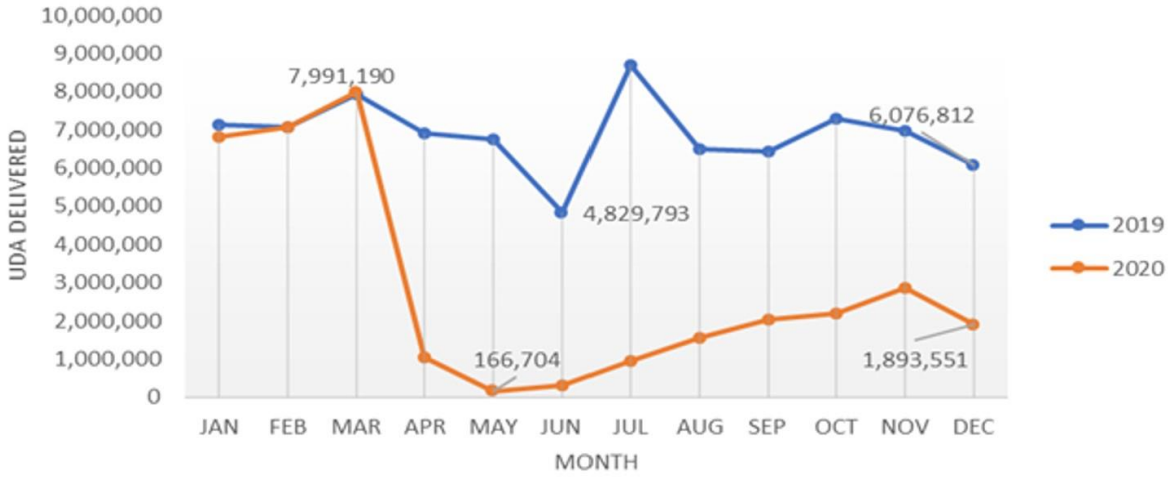


Figure 13: Total units of NHS dental activity delivered in 2019 and 2020 in England (84).

Acronyms: UDA, units of dental activity.

Since 2020, access to dental care in the UK has become increasingly difficult. The British Broadcasting Corporation (BBC), in an investigative news article published in August 2022, reported that dental practices across the UK were restricting access to NHS patients or not accepting new NHS patients at all (85). This led to patients being forced to seek private dental care or even abandon their dental care completely **(Figure 14).**

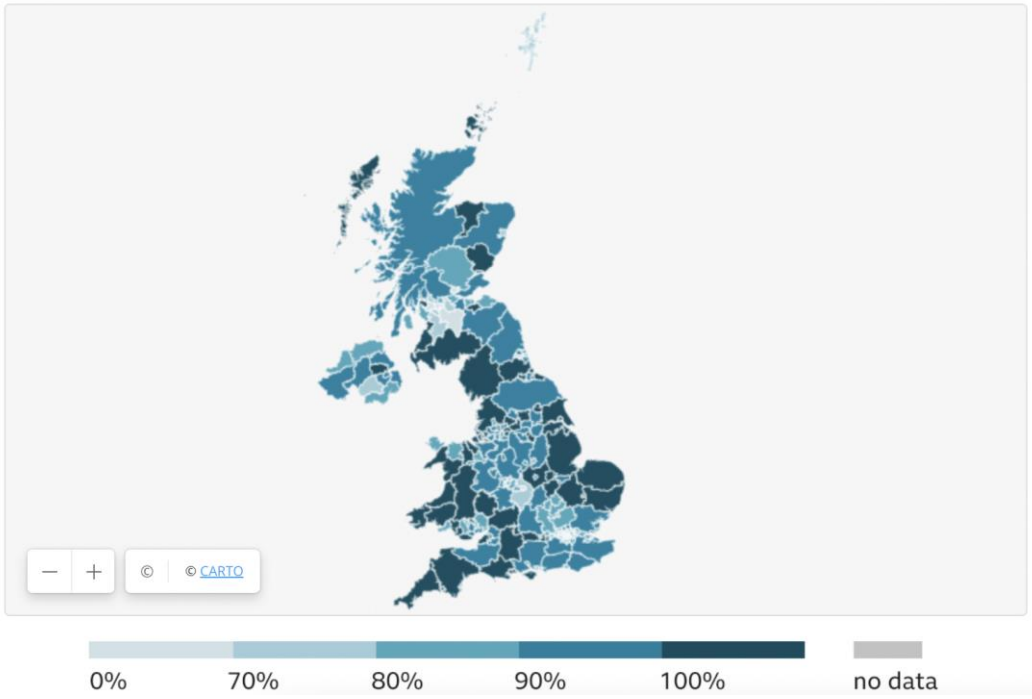


Figure 14: The percentage of dental practices not accepting new NHS patients, from (85).

1.3.4 The co-payment model

When procuring NHS dental care at adult age, except for a few exceptions **(Table 2),** patients are required to enter a co-payment model according to a price table with 3 levels, or Bands, where the patients' costs are fixed and only adjusted by procedure complexity (86) **(Table 3).** The prices can range from £23,80 (e.g. routine checkup) to £282,80 (e.g. dentures, bridges, and crowns) per consultation (87). It is important to highlight that the co-payment prices have been increasing, almost 4% annually **(Figure 15)**(84).

Table 2: Exemptions from co-payment model in the NHS, from (88,89)

Exempt from dental care charges	**No exemption for**
- Pregnant women or women who had a child in the last 12 months - Under 18y or under 19y if under full-time education - Being treated in an NHS hospital and your treatment is carried out by the hospital dentist (but one may have to pay for any dentures or bridges) - Under 20y and a dependent of someone receiving low-income benefits - Receiving low-income benefits such: • Income Support • Income-related Employment and Support Allowance • Income-based Jobseeker's Allowance • Pension Credit Guarantee Credit • Universal Credit (in certain circumstances)	- Contribution-based Job Seeker's Allowance. - Contribution-based Employment and Support Allowance

The detailed use of dental care by exemption groups is displayed in **Appendix, Figure S1** (90).

Table 3: Full out-of-pocket prices, sustained by users, from NHS Dental Care Guide (86):

Bands of dental care	Cost for patient	UDAs	Services covered (examples):
Band 1	£ 23,80	1	- clinical examination, assessment and report - marginal correction of fillings - a scale and polish (if clinically necessary) - photographs and X-ray
Band 2	£ 65,20	3	- fillings - free gingival grafts - treatment for severe gum disease - removing teeth (extraction) - root canal treatment
Band 3	£ 282,80	12	- bridges, crowns and dentures

Treatment Band	2017-2018	2018-2019	2019-2020	2020-2022
Band 1	£20.60	£21.60	£22.70	£23.80
Band 2	£56.30	£59.10	£62.10	£65.20
Band 3	£244.30	£256.50	£269.30	£282.80
Urgent	£20.60	£21.60	£22.70	£23.80

Figure 15: Change in the co-payment costs, from 2017 to 2022 (84).

On the contrary, the NHS Business Services Authority reimburses the dental practices at a variable UDA rate, which is established by individual annual contracts (91). These contracts are published in the "NHS Payments to dentists in England" report yearly. In this report, the totality of UDAs contracted and the baseline monetary value for those services are detailed for each individual practice (91). The price for UDA reimbursement varies widely across the UK, but the average cost for the NHS was £27,04 per UDA in England for the year 2018-2019 (92) **(Figure 16).** The most recent report in 2021-2022 shows an increase in the average price to £28,90 (91).

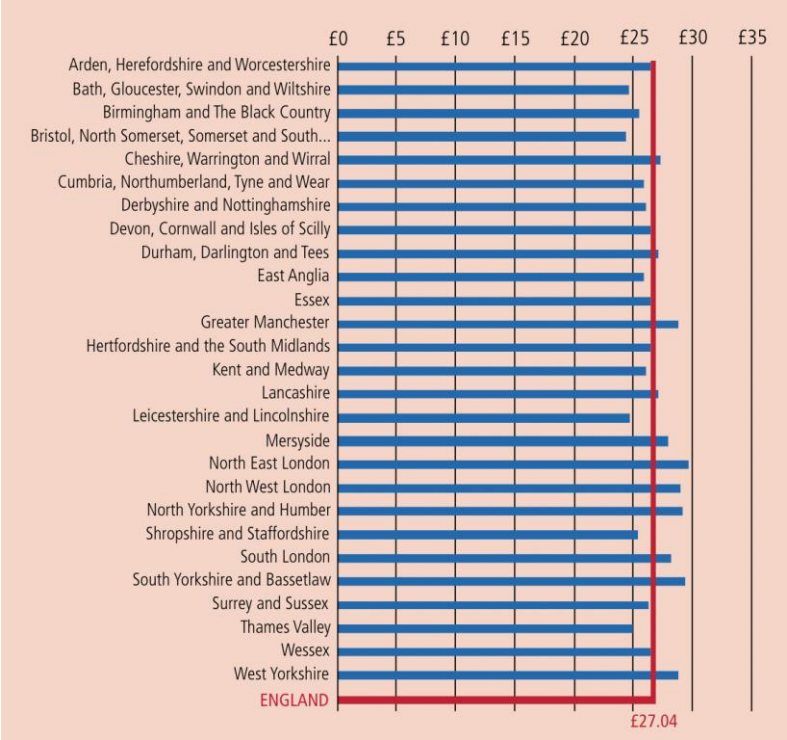


Figure 16: Geographical variation of UDAs reimbursement prices by the NHS, from (92).

For patients, one of the main constraints when trying to secure dental health services is the limited availability of NHS Dental services depending on geography and the cost of such services (81). Different UK surveys showed that approximately 30% of the population do not attend the recommended dental check-ups (71). According to the Eurostat, in 2019, 2% of the adult UK population reported an unmet need for dental examination due to being too expensive (93). Where availability of the NHS dentist practices are limited, prices in private clinics can also be a problem: the charges can increase to £120,00 for a first visit or dental check-up, and rise further to £320,00 for tooth extractions (94). Therefore, private care is not a valid option for a significant portion of the population. NHS charges are significantly smaller but still constitute a barrier for the service, particularly for the most vulnerable section of the population. This issue was recognized by the London School of Economics (LSE)-Lancet commission for the Future of The NHS, published in 2021, who recommended that co-payment should be abolished in the UK to avoid health inequalities and reduce the future burden of diseases related to poor dental hygiene arriving to the NHS in the upcoming years (95,96). While obstacles to high-quality dental care access have the potential to impact on the entire UK population's health and will probably have significant public health consequences in the near future, these effects are even more devastating in CHD groups and other patients with a PCC, due to the heightened risk of IE.

1.3.5 Objectives of the first CEA Analysis (Part A - Cost-Effectiveness Analysis of Providing Free Dental Care for Patients at High Risk of IE)

The first part of thesis aims to evaluate the cost-effectiveness of delivering free dental care for patients considered at high risk of IE within the UK NHS context, using an analytic decision Markov-model. Our main hypothesis is that offering free dental checkups annually leads to an improvement in personal dental hygiene and oral care, reducing chronic "low-grade" bacteremia and, consequently, the risk of IE.

1.4 Congenital Heart Disease and Pulmonary Hypertension

1.4.1 Definition of Pulmonary Hypertension

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary pressure (mPAP) above 20mmHg, measured invasively with a right heart catheter (RHC) (2022 97,98). The normal mPAP at rest is 14±3,3 mmHg and can increase slightly with age (99,100). Increases in pulmonary artery pressures can be as "primary", i.e., caused by remodeling of the pulmonary arteries leading to raised pulmonary vascular resistance (PVR) or secondary to other diseases (cardiac, lung, hepatic, thrombo-embolic and systemic diseases). Secondary mechanisms that can contribute to a raise in pulmonary artery pressures include elevated left heart filling pressures, elevated pulmonary blood flow due to cardiac or extra-cardiac shunts or increased thoracic pressures.

The definition of pre- or post-capillary PH is hemodynamical and rely on the assessment of the mPAP and the PVR. The PVR dependents not only on the mPAP, but also the pulmonary capillary wedge pressure (PCWP), as a surrogate for systemic (usually left side) venous / filling pressures. The PVR also dependents on the cardiac output, as an increased pulmonary flow (Qp) due to a systemic-pulmonary shunt (for example due to an atrial septal cardiac defect) can elevate the mPAP without causing an increase on pulmonary vascular resistance **(Formula 6).**

Formula 6

$$\mathbf{PVR = (mPAP - PCWP) / CO}$$

where:

PVR = pulmonary vascular resistance (in Wood Units)

mPAP = mean pulmonary artery pressure (mmHg)

PCWP = pulmonary capillary wedge pressure (mmHg)

CO = cardiac output (litres/min)

The 2022 ESC Guidelines define pre-capillary PH as mPAP > 20mmHg associated with raised pulmonary vascular resistance (PVR) above > 2 Wood Units [WU]) and low left-side pressures (PCWP below ≤15mmHg) (97). A post-capillary PH is defined as mPAP > 20mmHg with raised PCWP > 15mmHg with normal PVR ≤ 2), but a combination of pre- and post PH is also possible **(Figure 17).**

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

Figure 17: Hemodynamic definitions of pulmonary hypertension by the 2022 ESC PH Guidelines

Acronyms: CO, cardiac output; CpcPH, combined post- and pre-capillary pulmonary hypertension; IpcPH, isolated post-capillary pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WU, Wood units.

The clinical definition of PH distinguishes between 5 different clinical subgroups **(Table 4)** (97)**.** It discriminates between pre-capillary pulmonary arterial hypertension (PAH or Group 1), where both mPAP and PVR are raised in the absence of other causes of pre-capillary PH such as lung disease (Group 3), chronic thrombo-embolic conditions (Group 4) or other systemic rare conditions (Group 5)(101). Patients with combined pre and post or only post-capillary PH are included in Group 2.

In all forms of PH, the raised PVR translates into increased right ventricle (RV) afterload, which can ultimately lead to its failure.

Table 4: Clinical Classification of PH, from 2022 ESC PH Guidelines (97)

Group	Subgroup
GROUP 1 - Pulmonary arterial hypertension (PAH)	1.1 Idiopathic 1.2 Heritable 1.3 Associated with drugs and toxins 1.4 Associated with: - 1.4.1 Connective tissue disease - 1.4.2 HIV infection - 1.4.3 Portal hypertension - 1.4.4 Congenital heart disease - 1.4.5 Schistosomiasis 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement 1.6 Persistent PH of the newborn
GROUP 2 - PH associated with left heart disease	2.1 Heart failure: 2.1.1 with preserved ejection fraction 2.1.2 with reduced or mildly reduced ejection fraction 2.2 Valvular heart disease 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
GROUP 3 - PH associated with lung diseases and/or hypoxia	3.1 Obstructive lung disease or emphysema 3.2 Restrictive lung disease 3.3 Lung disease with mixed restrictive/obstructive pattern 3.4 Hypoventilation syndromes 3.5 Hypoxia without lung disease (e.g., high altitude) 3.6 Developmental lung disorders
GROUP 4 - PH associated with pulmonary artery obstructions	4.1 Chronic thrombo-embolic PH 4.2 Other pulmonary artery obstructions
GROUP 5 - PH with unclear and/or multifactorial mechanisms	5.1 Hematological disorders 5.2 Systemic disorders 5.3 Metabolic disorders 5.4 Chronic renal failure with or without hemodialysis 5.5 Pulmonary tumor thrombotic microangiopathy 5.6 Fibrosing mediastinitis

1.4.2 Pulmonary Arterial Hypertension in ACHD

Pulmonary hypertension (PH) is a frequent complication of CHD, affecting up to 10% of all patients with CHD and up to 30% of patients born with a septal defect (102,103). PH in CHD can be pre- or post-capillary (PH groups 1 and 2, respectively). CHD can also be associated with developmental lung disease or hypoventilation that can cause PH (Group 3) or peripheral pulmonary stenoses (Group 4). All the above can occur alone or in combination (102).

In this thesis, we focus on Group 1 PAH, or pulmonary arterial hypertension associated with congenital disease (PAH-CHD). The histological features of pulmonary vascular disease (PVD) accompanying PAH disease affect mostly distal pulmonary arteries, with typical lesions such as medial hypertrophy, intimal and adventitial fibrosis, *in situ* thrombosis and plexiform lesions (104). PAH-CHD shares similar histological characteristics with other forms of PAH, such as idiopathic or heritable PAH (IPAH and HPAH, respectively), but its management and outcomes differ (102).

In the REHAP National registry in Spain, PAH-CHD was the second cause of PAH after idiopathic PAH (105). In the UK, the 2022 National Audit reports that PAH-CHD accounts for almost 30% of all PAH etiologies in the UK, with a similar prevalence as IPAH and PAH associated with connective tissue disease (PAH-CTD) (106).

While survival in PAH-CHD is generally considered to be better when compared with other forms of PAH **(Figure 18)**, PAH is a devastating complication of CHD, significantly impacting both their quality of life and survival (107,108).

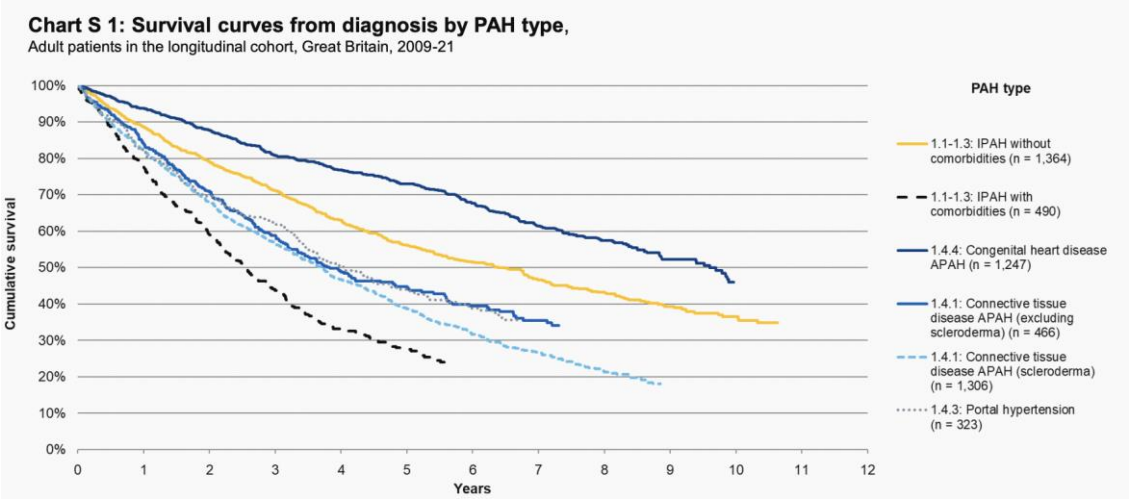


Figure 18: Survival curves for PAH subgroups from the 2022 UK PH Audit Report

The management and survival in PAH-CHD depend on the sub-type of PAH-CHD. The main 4 subgroups are described in **Table 5.** PAH-CHD associated with small or corrected defects is generally considered as aggressive as idiopathic PAH, while adult patients with Eisenmenger Syndrome (ES) have a comparatively better overall survival **(Figure 19**) (109). Yet, ES patients rarely reach the 5th or 6th decade of life and complications are common (109,110).

Table 5: The PAH-CHD can be further categorized as the following subgroups (based on Table 21 of the 2022 ESC PH Guidelines).

1) Eisenmenger syndrome	Includes all large intra- and extracardiac defects that begin as systemic-to-pulmonary shunts and progress to severely elevated PVR and to reverse (pulmonary-to-systemic) or bidirectional shunting.
2) PAH associated with prevalent systemic-to-pulmonary shunts • Correctable • Non-correctable	Includes moderate-to-large defects. PVR is mildly to moderately increased and systemic-to-pulmonary shunting is still prevalent, whereas cyanosis at rest is not a feature.
3) PAH with small/coincidental defects	Markedly elevated PVR in the presence of cardiac defects considered hemodynamically non-significant (usually ventricular septal defects <1 cm and atrial septal defects <2 cm of effective diameter assessed by echocardiography), which themselves do not account for the development of elevated PVR.
4) PAH after CHD defect correction	Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after correction in the absence of significant, post-operative, hemodynamic lesions.

Acronyms: PAH: Pulmonary arterial hypertension; PVR, pulmonary vascular resistance.

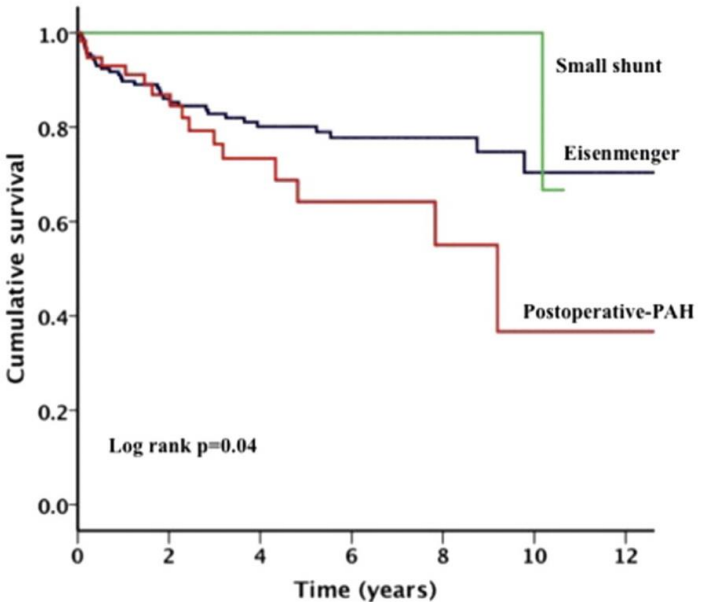


Figure 19: Kaplan Meier curve comparing patients with different types of PAD-CHD; from Alonso et al. 2015, (109).

1.4.3 PAH Treatment

The use of PAH therapies targeting the prostacyclin, nitric oxide, and endothelin pathways (either in monotherapy or in combination) is nowadays well-established and endorsed emphatically by international guidelines for IPAH, HPAH and PAH-CTD **(Table 6)** (97). However, the evidence on the use PAH drugs in PAH-CHD patients is modest at best and mostly driven by small RCTs, retrospective studies or data from large PAH trials in which a small percentage of PAH-CHD patients have been included (111–114). The available data suggests these therapies can result in an improvement in functional status and hemodynamics for congenital patients, with some retrospective studies suggesting a survival benefit (115,116).

Table 6: Pulmonary arterial hypertension medication in adults

Endothelin receptor antagonists (oral administration)	Ambrisentan Bosentan Macitentan
Phosphodiesterase 5 inhibitors (oral administration)	Sildenafil Tadalafil
Prostacyclin analogues (Prostanoids)	Iloprost (inh) Treprostinil (iv, inh, sc, oral) Epoprostenol (iv)

	Beraprost (oral, not approved in European Union)
Prostacyclin receptor agonist (oral administration)	Selexipag
Soluble guanylate cyclase stimulator (oral administration)	Riociguat

Acronyms: inh, inhaled; iv, intravenous; sc, subcutaneous.

In the last decade, the management of PAH naïve-treatment has evolved from PAH drug monotherapy to upfront combination in high risk groups (117). More recently, this recommendation has been changed and updated based on new studies reporting an improvement in long-term outcomes with upfront combination therapy (118,119). As such the 2022 ESC guidelines recommend dual combination therapy for all naïve-patients with idiopathic, heritable or drug/toxin induced PAH, even in the low-risk groups (i.e., <5% year-mortality risk), with sequential escalation to prostanoids analogues if needed **(Figure 20)** (97). Patients with PAH associated with *repaired* congenital heart defects, albeit in small numbers, were included in pivotal studies such as AMBITION (upfront therapy with Ambrisentan + Tadalafil vs monotherapy with Ambrisentan or Tadalafil) and OPTIMA (Macitentan + Tadalafil), hence they share the same treatment algorithm as idiopathic PAH (120,121). Triple therapy with intravenous/subcutaneous prostanoids is reserved for those considered at high risk of mortality (97).

The algorithm for treating naïve PAH patients is displayed in **Figure 20** from the 2022 ESC PH Guidelines (97).

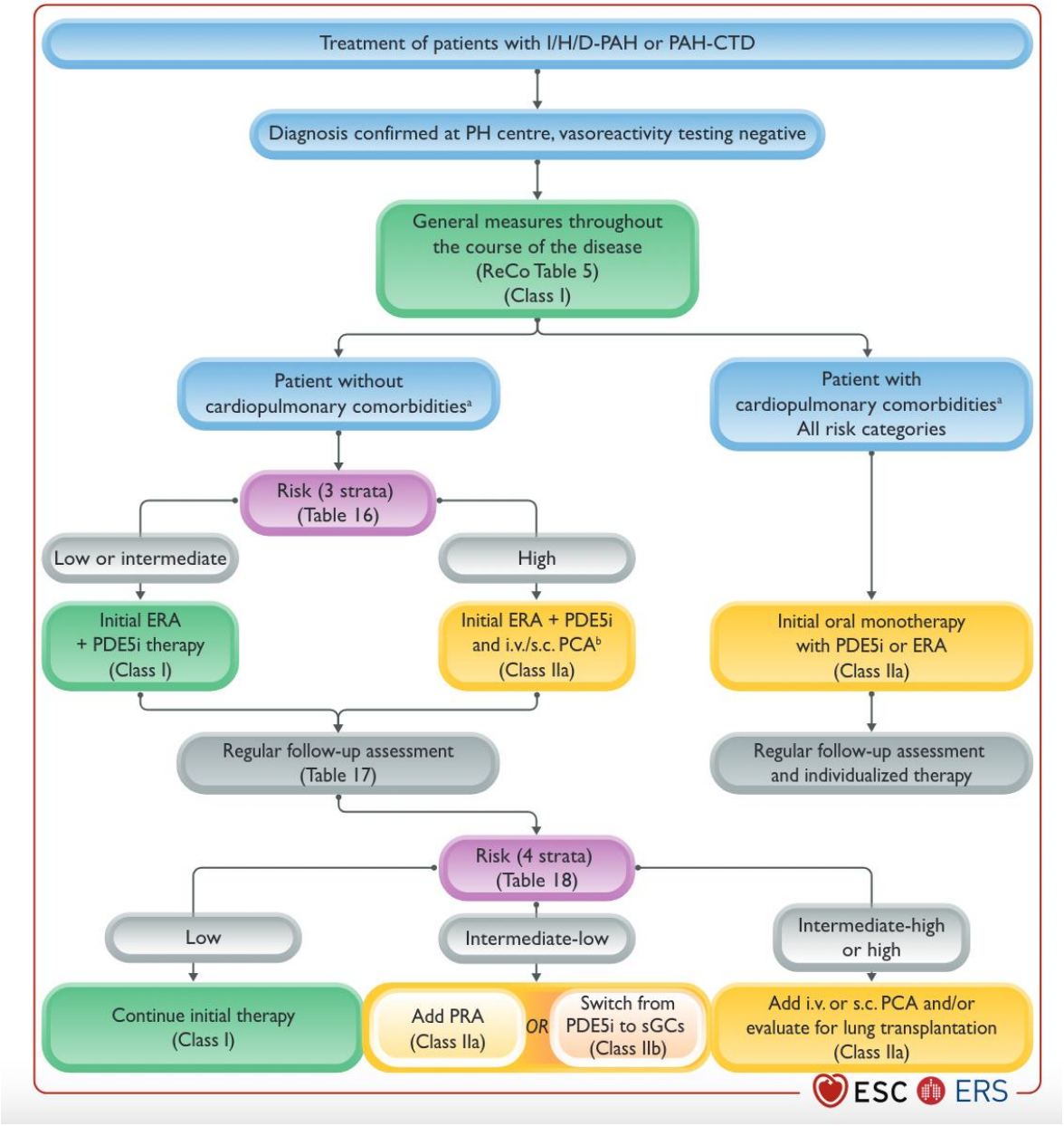


Figure 20: Management of naïve-PAH patients according to the 2022 ESC/ERS PH Guidelines.

Acronyms: ERA, endothelin receptor antagonist; I/ H/D-PAH, idiopathic, heritable, or drug-associated pulmonary arterial hypertension; i.v., intravenous; PAH-CTD, PAH associated with connective tissue disease; PCA, prostacyclin analogue; PDE5i, phosphodiesterase 5 inhibitor; PH, pulmonary hypertension; PRA, prostacyclin receptor agonist; ReCo, recommendation; s.c., subcutaneous; sGCs, soluble guanylate cyclase stimulator.

In the setting of PAH-CHD, combination therapy is less well-established and is only recommended for PAH-CHD after defect correction (120–123). Moreover, because

uncorrected PAH-CHD subjects were excluded from the combination therapy RCTs, guidelines recommend upfront monotherapy and a sequential combination strategy if the treatment goals are not met **(Figure 21)** (124). Nevertheless, there is some evidence to suggest an improvement in clinical (6 minute-walking test [6MWT], Borg Scale status and WHO FC) and hemodynamic parameters after combining Sildenafil to Bosentan-treated ES patients (122).

Recommendations	Class[a]	Level[b]
In patients with PAH after corrected adult CHD, initial oral combination therapy with drugs approved for PAH should be considered for patients at low and intermediate risk, while initial combination therapy including i.v./s.c. prostacyclin analogues should be considered for patients at high risk	IIa	C[c]
In patients with adult CHD, including Eisenmenger syndrome, sequential combination therapy should be considered if patients do not meet treatment goals	IIa	C

Figure 21: ESC/ERS 2022 recommendations for the initial therapy in PAH-CHD, according to defect status.

Acronyms: CHD: congenital heart disease; i.v., intravenous; PAH, pulmonary arterial hypertension; s.c., subcutaneous.

Extrapolating the benefits of PAH drugs obtained from the RCTs that included very few or no PAH-CHD patients to the CHD cohort is not without problems. PAH-CHD patients differ from other PAH subtypes in three main points: 1) CHD patients have distinct anatomy and physiology which, in some cases are considered beneficial for survival in the setting of PAH (e.g., the presence of a septal defect or patent ductus arteriosus acting as a "relief valve" for the RV (102).

2) CHD patients are usually much younger at the moment of diagnosis and treatment initiation. Recent data from the COMPERA European Registry show that mean age at the diagnosis of IPAH is 66 ±15,5 years, while PAH-CHD patients are younger (45 ±16,8y) (125).

3) Their survival is superior (especially for adult patients with ES)(106).

On the other hand, enrolling these patients in RCTs can be difficult, especially in view of the variety of anatomies and physiologies existent in CHD; therefore, retrospective studies will likely remain the main source of data for these patients.

1.4.3 Funding of PAH drugs in the UK

NHS England publishes specific guidelines for PAH therapies titled the "NHS England Clinical Commissioning Policies" (126,127). The NHS commissioning guidelines are heavily based on economic and cost-effectiveness analysis, hence do not strictly follow the European or American recommendations in terms of PAH treatment algorithms. For example, it is standard policy that treatment-naïve PAH patients should be started on a PDE5 monotherapy based on "economic grounds", according to the latest 12th Annual National Audit of Pulmonary Hypertension in Great Britain, 2020-2021 (106). National PH Centers are obliged to comply with the NHS recommendations and standards and report their compliance to the NHS England **(Table S1, Appendix).** This information is compiled and published in the National Pulmonary Hypertension annual audit reports, which are monitored for quality of care and funding purposes (106).

Therefore, in practice, upfront oral combination therapy is reserved for high-risk PAH patients; monotherapy remains the first line of therapy for the majority, followed by rapid escalation as a sequential strategy, if needed. This is especially true for unrepaired / uncorrected PAH-CHD patients, where the lack of RCT-associated-cost-effectiveness studies leads to more restrictive treatment options in the UK, whereas other European countries have been more liberal (128,129). One example is Selexipag, an oral prostacyclin receptor agonist, which is only commissioned for congenital PAH-CHD associated with corrected simple CHD, whereas its use in Europe is extended to other PAH-CHD types (128,130).

1.4.4 Objectives of the second CEA Analysis (Part B - Cost-Effectiveness Analyses of PAH Combination Therapy in PAH-CHD)

With that this in mind, my goal for the second part of this thesis is to design an analytic decision model to investigate the potential long-term cost-effectiveness of combination therapy in PAH-CHD, in patients with unrepaired and repaired defects, using retrospective data from our patient cohort combined with information available in the literature. The main hypothesis is that combination therapy is cost-effective as a treatment strategy for patients with PAH-CHD, driving an improvement in quality of life and slowing the natural progression of the disease.

1.5 Overall rationale and objectives of the thesis

In this thesis, my aim was to evaluate two health policies affecting ACHD patients, in a cost-evaluation/cost-effectiveness framework. This work is divided into 2 parts:

Part A) Cost-Effectiveness Analysis of Providing Free Dental Care for Patients at High Risk of IE

The first model aims to evaluate the cost-effectiveness of providing free dental care for patients with ACHD at high risk of IE. This health policy was first analyzed in 2020, as part of an LSE MSc Thesis entitled "Free dental care for patients at high risk of developing infective endocarditis – a cost-effectiveness study" and the results showed that the policy was not cost-effective. This work developed an analytic model, combining a decision tree (for the short-term analysis) with a Markov model (for a long-term analysis), focusing on the decision of offering free dental care vs co-payment (new strategy vs and current policy, respectively). It modelled a hypothetical cohort of 1.000 ACHD patients (starting at age 18y) who could be offered one or the other strategy. For both cases, in the short-term model, the individuals could remain well or develop the disease (IE) and suffer the associated risk of death. If they remained well or survived the IE episode, patients would enter the long-term model - a Markov Model - with a life-time horizon, where they could remain well or progress to other states, such as Valve Replacement, Heart Failure or Death, in an annual basis **(Figure 22)**. According to the cost-effectiveness model built in 2020, providing this service to patients at high risk of infective endocarditis would result in an ICER of £66.000,00 per QALY gained (if the free dental care was started at 18 years of age) or £96.000,00 per QALY (if started at 50 years of age). Nevertheless, this model had a few important limitations:

1) Patients were only allowed to have IE in the short-term model (once). However, because Markov models have "no memory", patients who arrived at the long-term model had similar probabilities to transition to future states independently of their IE background. Therefore, the benefit of the new policy was counted once (and translated into different numbers of patients in each strategy arm achieving the long-term model), but the costs of the policy were included in every "alive state" a posteriori. The 2020 model followed the design of previous cost-effectiveness studies on providing antibiotic prophylaxis to patients at high risk of IE) (64,66). Nevertheless, in clinical practice, individuals with PCC (e.g., prosthetic valve, cyanosis, etc.) are at risk of IE during their entire lifetime. Therefore, the assumption of being at risk of IE only once while dental care had annual life-horizon costs negatively influenced the results of the

model. Moreover, it is well-described that patients with previous IE have a higher risk of developing a new episode, therefore the one-time-risk led to a significant underestimation of the disease in this population (55).

2) The global health scenario greatly changed in the last few years, when the NHS was deeply impacted by the COVID-19 pandemic. The pandemic also impacted the UK population in different degrees, with the young, disabled, ethnic minorities and care home residents being amongst the most affected (131). As the pandemic exacerbated health inequalities, it also brought to the attention of the public and government systemic issues. Recognizing these challenges is an important first step to create new and fairer models of care. In this context, the "LSE–Lancet Commission on the future of the NHS: re-laying the foundations for an equitable and efficient health and care service after COVID-19" (published in Lancet in 2021) performed a comprehensive analysis of systemic problems within the NHS. Among other issues, the inequalities in dental care access were recognized and it was recommended to abolish the co-payment model currently in place. According to this report, co-payment acts as a barrier for dental care access particularly for the most vulnerable, hence exacerbating health inequalities. The same report estimated that abolishing this policy would cost 1 billion/year (96).

Therefore, taking the above in consideration, I deemed it relevant to re-examine the prior assumptions and redesign the model to ensure it better captures all the potential clinical scenarios associated with an episode of IE, while incorporating the post-COVID-19 NHS setting.

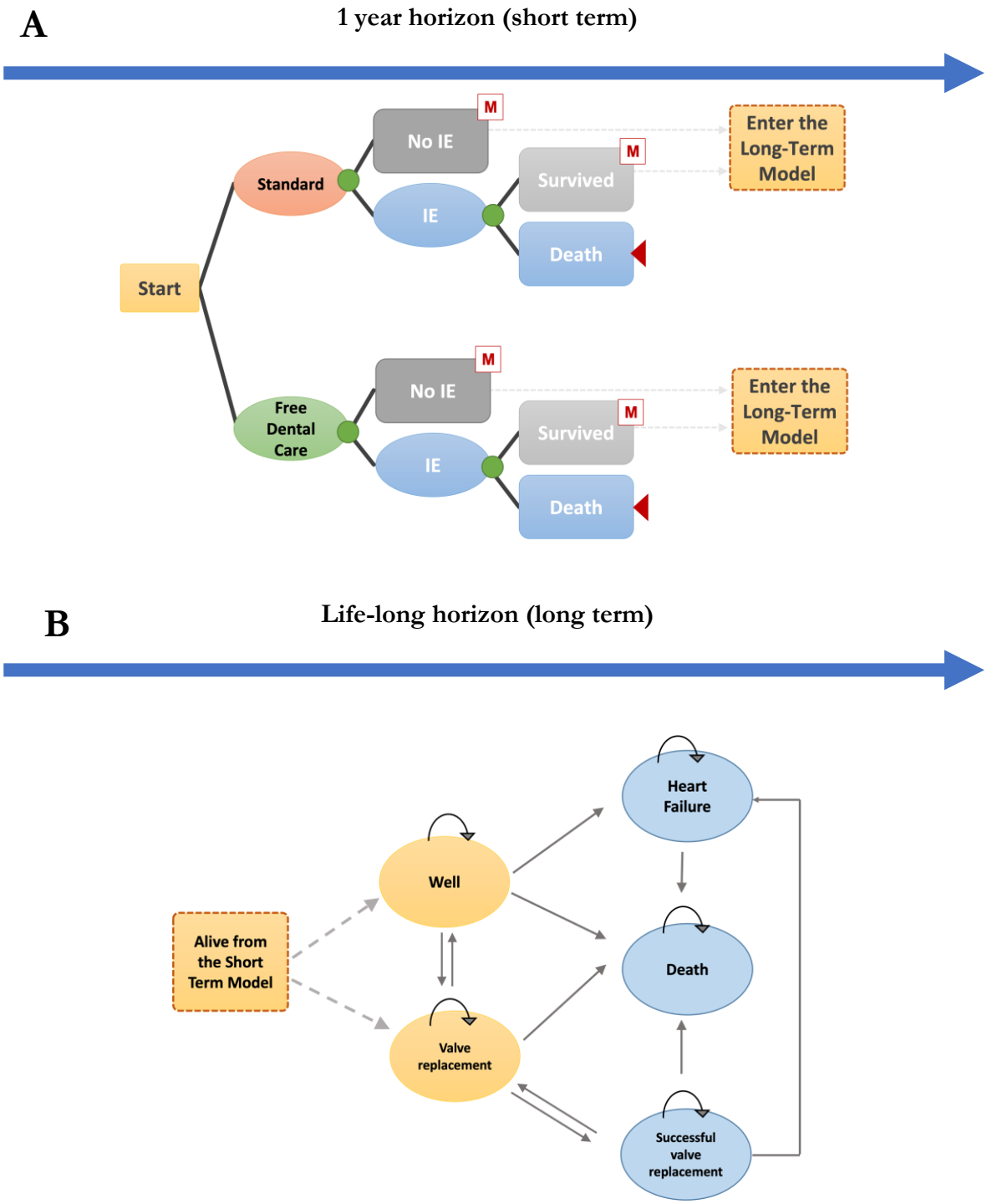


Figure 22: Free Dental Care Mode 2020. A) Short-term model using a decision tree; B) Long-term Markov Model.

Acronyms: IE, Infective Endocarditis.

Part B) Cost-effectiveness analysis of combination PAH therapy vs monotherapy in PAH-CHD

The second model evaluates the cost-effectiveness of treating patients with PH-ACHD with combination PAH therapy. The benefits of the proposed therapy, when compared with the standard treatment (monotherapy) are based on observational studies with short follow-up; therefore, the goal is to model the potential long-term costs and benefits of both strategies, using a Markov Model for economic decision analysis.

2. Hypothesis

2. Hypotheses

1) Providing free dental care for adult patients that are considered at risk of developing an IE throughout their lifetime is cost-effective from the perspective of the healthcare provider (NHS), compared with the current co-payment model. The hypothesis assumes that providing free dental services can detect and early treat dental infections and also improve the quality of individual dental care, consequently reducing IE risk and IE-related complications (such as need for valve replacement, development of congestive heart failure or death). The decrease in IE cases would then be reflected a) in the quality of life and years of life gained and 2) in a reduction of NHS costs relating to IE and IE-complications.

2) Using dual combination PAH therapy in adult patients with PAH-CHD is cost-effective from the perspective of the healthcare provider (NHS) when compared with PAH monotherapy. The model operates on the assumption that combining therapies enables the deceleration of disease progression, leading to enhanced quality of life, extended time-to-deterioration, and ultimately, increased survival rates.

Both models used the current NICE willingness-to-pay threshold (£20.000,00-£30.000,00/QALY) to evaluate cost-effectiveness.

3. Objectives

3. Objectives

Main Objective:

Evaluate two health policies affecting ACHD patients, in a cost-evaluation/cost-effectiveness framework.

Secondary Objectives:

1) Evaluate the cost-effectiveness of delivering free dental care for patients considered at high risk of IE within the UK NHS context.

2) Investigate the potential long-term cost-effectiveness of combination therapy in patients with PAH associated with repaired and unrepaired congenital heart defects.

4. Methodology

4. Methodology

Part A) Cost-Effectiveness Analysis of Providing Free Dental Care for Patients at High Risk of IE

4.1. Overall Methodology

In order to assess the cost-effectiveness of free dental care vs standard policy (co-payment), a Markov model was constructed in R software using the packages *heemod* and *BCEA* (132–134). The model was designed to comply with the NICE technology appraisal guidance and its subsequent actualizations (34,135,136). The code developed for this work is accessible upon request, on the Git Hub repository: (https://github.com/abarradaspires).

4.1.1 The Model

To assess the cost-effectiveness of free dental care vs standard policy, a cohort discrete-time state transition Markov model was constructed. This model is displayed in **Figure 23.** It follows of a hypothetical *cohort* of 1.000 ACHD patients at high risk of IE, starting from when they transition to Adult Care Services and lose their free NHS dental care (i.e., age 18 y), spanning their entire life-time horizon (60 cycles of 1 year duration each). This time-horizon was chosen with the aim to, as much as possible, capture the entire natural progression of the disease.

The model is structured as follows:

1. All patients enter the model in the "Well" state.
2. In the following cycle, patients occupying the "Well" state can either remain on that state or progress to "IE" (Infective Endocarditis), "Valve Replacement", "Heart Failure" or "Death" states.
3. Patients can only remain on "IE" for 1 cycle, therefore in the subsequent cycle they will either be on the "Recovered IE" or the "Death" states.
4. Survivors of IE in the "Recovered IE" state can remain in that state or advance to "Heart Failure", "Death" or suffer (another) episode of "IE". A similar pathway is available for the "Valve Replacement" state.
5. "Death" is an absorbing state, meaning it does not allow any further transitions.

6. A 3,5% annual rate discount for both costs and health effects was used, based on NICE recommendations, applied to all costs and utilities after the model's second year (cycle 2) (135).

7. A half-cycle correction was applied to the Markov model, which assumes that events occurred in the middle of the cycle. This strategy is used to avoid that all events occur on the start or the end of the cycles, which could under or overestimate costs and benefits (23).

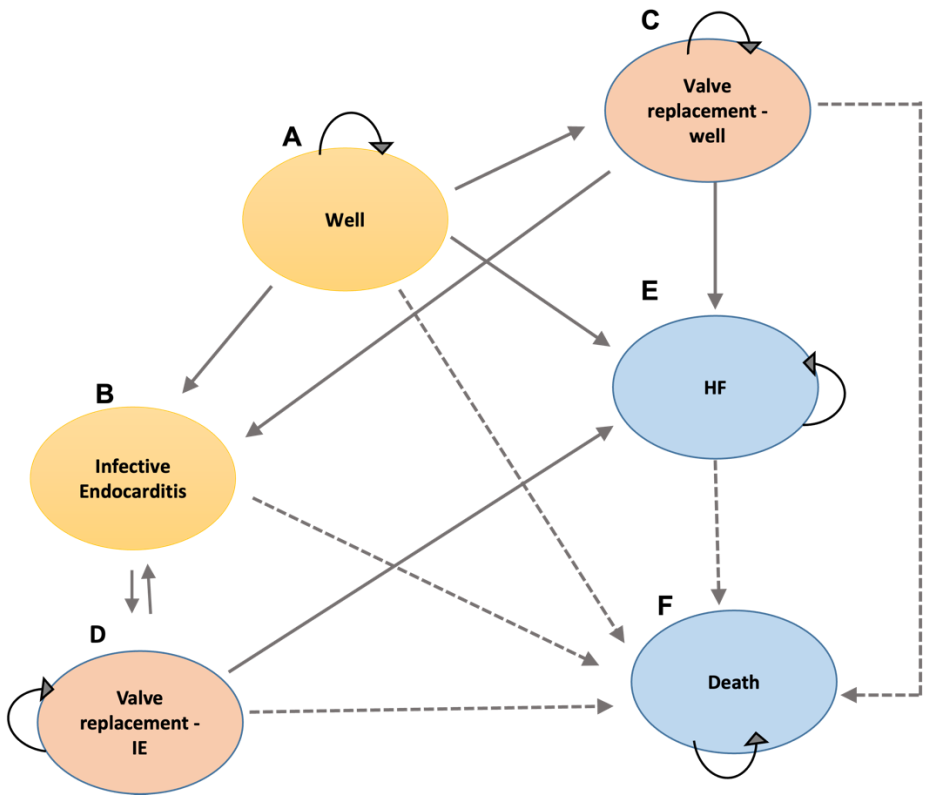


Figure 23: Markov Model diagram to analyze the CEA of free-dental care vs standard care. Acronyms: HF, heart failure; IE, infective endocarditis.

Patients entered the model in the "Well" state and can progressed to "Infective Endocarditis", "Valve Replacement", "Heart Failure" or "Death" stages every cycle. Patients can only remain in the "IE" for the duration of once cycle, and those who survive the IE progress to the "Recovered IE" state; from there, they can subsequently remain or transition to "HF", "Death" or suffer a new episode of "IE". "Death" is an absorbing state.

4.1.2 Model Assumptions

The model follows the following fundamental assumptions:

1) Given the option of free dental care, all ACHD patients at risk of IE will attend a dental check-up.

2) Regular dental check-ups will provide not only dental care, but also education on dental and oral hygiene best practices. Consequently, patients' individual dental hygiene and overall oral care status will improve.

3) The annual risk of developing IE will be reduced if patients attend regular dental follow-ups and follow good dental hygiene practices.

4) Only one dental check-up per year per patient was included in the base case model. Biannual check-ups were investigated in the sensitivity analysis.

5) For simplicity purposes, only the most basic type of dental treatment, the "dental check-ups" (i.e., Band 1 type of care including marginal correction of fillings, clinical-indicated scale and polish and photographs and X-ray) were evaluated in the base case model; hence, more complex dental procedures (including fillings, etc) were assumed to be not necessary. The cost-effectiveness of more complex dental care needs was studied in the sensitivity analysis.

6) For individuals needing valve replacement electively or during an episode of IE, a bioprosthetic valve or homograft implantation was assumed, hence the probability of needing a re-do surgery was incorporated in the model. This assumption was based on the fact that, in ACHD, right-sided IE is present in 15 to 50% of cases and bioprosthetic valves are the usually preferred on that setting (57,58). Additionally, in left-side IE affecting the aortic valve, data from Barradas-Pires et al. showed that only 7% of ACHD patients received a mechanical valve (137).

4.1.3 Features of the economic analysis

The basic characteristics of the base model are described in **Table 7:**

Table 7: Features of the economic analysis for free-dental-care vs standard care

Parameters	Input	Source	Deterministic / Probabilistic Analysis
Comparators	1. Standard Dental NHS care for adults (co-payment) 2. Free annual dental care (checkups) for adults at high IE risk		NA
Population	Adults (≥18 years old at high risk of IE)		NA
Time-horizon	Lifetime (60 cycles)		30 years (or cycles) if started at age 50 years
Perspective	UK NHS	NICE reference case (135,136)	NA
Measuring and valuing health effects	Quality-adjusted life years (QALYs)		NA
Discount rate	Costs: 3,5% Outcomes: 3,5% (discounts applied after the first cycle)		NA
Cohort size	1.000		NA
Start age	18 years		Start at age 50y (with a time horizon of 30 years)
Proportion of patients male and female	50%	Assumed	NA

Acronyms: NA, not applicable; UK, United Kingdom; NHS, national health system.

4.1.4 Baseline Probabilities

4.1.4.1 Infective Endocarditis

The probabilities of developing IE in high-risk patients was collected from the work from Thornhill et al., published in 2018, reporting the incidence of IE in the English population between 2000 and 2013 (55). In high-risk patients, the incidence was found to be 4,96 per 1.000 person-years, which was similar to the one reported by Cahill et al. (4,82 per 1.000 persons-years for surgical valve replacement and 3,75 per 1.000 persons-years for percutaneous valve recipients) (56). The probabilities of developing a second episode of IE (i.e., transition from "Recovered IE" to "IE") or an IE occurring in the "Valve replacement" were also collected from Thornhill et al., 2018.

Regarding the effectiveness of the intervention (i.e., offering free dental care), there are no RCTs or observational studies comparing a possible risk change between these strategies. Mang-de-la Rosa et al. report that poor dental hygiene could account for 15 - 20% of all IE, therefore the reduction in the overall risk of IE with free dental care was assumed to be approximately 15% (relative risk [RR] = 0,85), (62).

4.1.4.2 Valve Replacement

The probability of requiring a valve replacement in the "Well" state was based on the work by Tutarel et al., which reported an incidence of 2 surgeries per 100 patient-years in the ACHD population (138).

The probability of needing a surgical procedure during IE was conservatively estimated at 40%, although other series describe a surgical treatment for up to 82% of IE-CHD cases and 73% in non-CHD cases (57,58,139). Therefore, those scenarios were further explored further in the sensitivity analysis.

In patients with a previous valve replacement, i.e., the ones occupying the "Valve Replacement" state or the "Recovered IE" (adjusted by the proportion who needed a surgical treatment in the previous IE state), a time-dependent probability of a new surgical VR was applied according to the time occupying those stages (state-time). These probabilities derived from the work from Barradas-Pires et al. who followed a cohort of ACHD patients after an aortic valve replacement surgery for aortic regurgitation for 10 years (137); beyond this follow-up time, the survival probabilities of needing a new valve replacement were extrapolated from this data using a fitted Weibull function (43).

4.1.4.3 Heart Failure

The incidence of developing HF for individuals occupying the "Well" state was assumed to be 1,2 per 1.000 ACHD patients-year in the base case model from Rush et al. (140). After a recovered IE, this incidence increased to 2,62 cases per 100 person-year using data for Netzer et al., who followed a cohort of IE up to 20 years after the index episode (141). The HF transition probabilities after valve replacement were adapted from a previous NICE CEA analysis in IE treatment (65).

4.1.4.4 Mortality Probabilities

The mortality rate for the "Well state" was collected from the national life-stables for the UK population during 2017-2019, made publicly available by the Office of National Statistics (ONS) (142). More recent data (years 2018-2020) was discarded to minimize the potential impact of the COVID19 pandemic on the population's life-expectancy. The mortality rate between age x and (x +1) is defined by the ONS as "the probability that a person aged x (exact) will die before reaching age (x +1)". The mortality rates were collected for ages 18 to 100 years (both included), in a yearly sequence. Since mortality rates differ for males and females and the model population was assumed to be composed by 50% each, an average mortality for each age was calculated.

The probability of death during an episode of IE used in the base case was 15% (58,141).

The mortality probabilities for the HF state were computed using the work from Diller et al., published in 2015 (9). This work described the causes of deaths in an ACHD population followed in a UK tertiary centre and the cumulative mortality due to HF were reported by age **(Figure S2 Appendix).** Due to the lack of individual patient data, the mortality probability at every age year (from 18 - 80 years) was retrieved using the methodology proposed by Diaby et al. (143).

The mortality for the population in the "Valve Replacement" was assumed to be 0,0177 in the first year (to incorporate the post-surgical risk), collected from Beurtheret et al., 2017 (144). After the first year, mortality probabilities were computed using the work by Sotade et al., which followed a large cohort of patients up to 10 years after valve replacement surgery, and reported their cumulative mortality stratified by age (18 - 64y and ≥ 65y) (**Figure S3, Appendix)** (145). This study was specifically chosen due to its long follow-up and data from both young and old cohorts. The mortality for each year of follow-up was again retrieved using the Diaby methodology. Different parametric distributions were fitted to extrapolate the mortality beyond the reported follow-up time of the study, as advised by NICE guidelines, and chosen using the

AIC and BIC goodness-of-fit criteria (43). The process was conducted for the 18 - 64y and the ≥65y cohorts survival curves separately; goodness-of-fit and fitted curves can be consulted in the **Appendix, Figures S4-S5 and Tables S2-S4.**

4.1.4.5 Outcome probabilities

The probabilities used for transitions were described in **Table 8** and the subsequent matrix probabilities for the model in **Table 9.**

Table 8: Probabilities used in the transitions between health states and its sources.

Developing IE			
IE in High-Risk Groups	**Incidence**	**Probability / Risk**	**Source**
Overall high-risk population	4.968 per 1 million person-years	0,004968	Thornhill 2018 Cahill 2022 Netzer 2002 (55,56,141)
Risk in previous IE	14.359 per 1 million person-years	0,014359	
Risk after valve replacement (elective)	4.652 per 1 million person-years	0,004652	
Proportion Cases attributed to Poor Dental Care			
	Rationale	**Value**	**Source**
Proportion of cases attributable to Poor Dental Care	4 - 20% IE cases attributed to poor dental care. Only 0,3 to 5% attributed to lack of antibiotics prior to dental procedures	15%	Mang-de la Rosa 2014 (62)
Effectiveness	Assumed 15% reduction in risk of IE with intervention (free dental care)	RR = 0,85	Mang-de la Rosa 2014 (62)
Valve Replacement State			
	Incidence	**Probability / Risk**	**Source**
Probability of valve replacement (from "Well State")	20–40y: 2,15 per 100 patients-year	0,002	Tutarel 2014 (138)

	40–60y: 2,25 per 100 patients-year > 60y – 1,23 per100 patients-year		
Probability of valve replacement (during IE)		0,4	Tutarel 2018 Van Melle 2022 (57,58)
Probability of re-do surgery after valve replacement in the "Valve Replacement State" and "Recovered IE state) *		Based on freedom from reintervention survival: • 1st year: 98,0% • 5th year: 96,5% • 10th year: 85,4% • After 10 years: Weibull function with: Shape = 1,37 Scale = 182	Barradas-Pires, 2022 (137)
Heart Failure State			
	Incidence	**Risk/ Probability**	**Source**
From "Well State" (General ACHD)	General ACHD: 1,2 cases per 1.000 patients-year Complex lesions: 3,0 cases per 1.000 patients-year	0,0012	Rush 2021(140)
From "Recovered IE"	2,62 cases/ 100 patients / year	0,0262	Netzer 2002 DSA range from Franklin 2016 (66) 09/09/2023 10:32:00
From "Valve Replacement"		0,006	Nice 2008 (64) Based on the work from

			Frary et al., 1994.
Mortality			
	Incidence	**Risk/ Probability**	**Source**
From "Well state"		2017-2019 National UK life tables	UK ONS (142)
From "IE state"		0,15	Netzer 2002 Van Melle 2022
From "Valve Replacement state" • Early (1st year) • Afterwards:		1,77% Based on Sotade 2020 survival curves. Beyond the 10 years of follow-up, the following distributions were fitted: • 18 - 64y: Lognormal function with a Meanlog = 3,51 and Sdlog = 1,41 • ≥65y: Weibull function with: shape = 1,93 and scale = 0,147	Beurtheret 2017 (144) Sotade 2020 (145)
From "HF state"		Adapted from the cumulative incidence of mortality for ACHD patients with HF	Diller 2015 (9)

Acronyms: ACHD, adult congenital heart disease. HF, heart failure; IE, infective endocarditis; ONS, Office of National Statistics; VR, valve replacement.

4.1.5 Transition Probability Matrix

Table 9: Probabilities used in the transitions between health states and its sources.

Standard Strategy	Well	IE	Valve Replacement	Recovered IE	HF	Death
Well	**C**	0,004968	0,002000	0	0,001250	UK ONS Life Tables
Infective Endocarditis	0	**0**	0	**C**	0	0,200000
Valve Replacement	0	0,004652	**C**	0	0,006000	1st year: 0,017700 After: mortality curves after valve replacement surgery
Recovered IE	0	0,014359	0	0	0,082000	Mortality curves after IE
Heart Failure	0	0	0	0	**C**	Mortality curves for ACHD with HF
Death	0	0	0	0	0	**C**

Free Dental Care Strategy	Similar probabilities except: Prob of transition between Well and IE * RR Prob of transition between Valve Replacement and IE * RR Prob of transition between Recovered IE and IE * RR

Acronyms: ACHD, adult congenital heart disease. HF, heart failure; IE, infective endocarditis; RR, relative risk.

4.1.6 Health-related Quality of life (Utilities)

The utilities used for the "Well state" were recollected from the most recent published utilities for the UK population, by age, based on the work of Alava et al. (146) **(Table 10).** This work computes the utilities based on the EQ-5D-3L questionnaires collected from the 2014 Health Survey for England (147). Although some studies report that ACHD patients might have a reduced utility when compared with same sex and age general population, there are no clear consensus in the literature, therefore this was not included this model (148). For the "Heart Failure" state, utilities were collected from the work from Di Tanna et al., assuming patients were in New York Heart Association (NYHA) functional class (FC) II and III, and that those utilities were not affected by age (149).

To account for the decline in quality of life during an IE episode, the utility in this state was discount by 50% from the values for the same-age general population. This reduction was based on the work of Verhagen at all (2010) and Berg et al. (2010), where patients with IE reported up to 60% of deterioration on their health perception (60,61). The "Valve Replacement" state utilities were collected from a recent NICE cost-effectiveness analysis on moderate-risk adults who went for surgical aortic valve replacements, and then adjusted by the age of the population in the model cycle; additionally, the first year in the state (i.e., immediately after surgery) a small utility penalization was applied, when compared with the subsequential years, to incorporate the quality of life lost during the post-surgical recovery time (26). The utility for "IE Recovered" state was collected from the "high-risk" group in the same NICE CEA work (26).

Table 10: Utilities used for each model health state and its sources.

State	Utility	Used in the model	Source
Well - UK utility by age	**Female / Male**		Alava 2022 (146)
30-49y	0,913 / 0,934	0,924	
50-69y	0,846 / 0,879	0,863	
70-89y	0,760 / 0,810	0,785	
90y or older	0,692 / 0,753	0,721	
Heart Failure – Overall	0,64–0,72	0,70 (FC II)	Di Tianna 2021(149)
Heart Failure – by NYHA			Di Tianna 2021 (149)
NYHA I	0,79–0,86		
NYHA II	0,75–0,81		

NYHA III NYHA IV	0,61–0,69 0,51–0,66		
Infective endocarditis	50% reduction during the year of IE	0,5 * age utility general population	Estimation based on the work of Verhaegen, 2009 and Berg 2010 (60,61)
Valve Replacement 1st year > 1 year	 0,78 0,80	 0,78 0,80 (adjusted by age in the model)	NICE 2021 (26) (based on the work from Baron 2018 and Gleason 2018)
IE Recovered	0,72	0,72 (adjusted by age in the model)	NICE 2021 (26) (based on the work from Baron 2018 and Gleason 2018)
Death	0	0	

4.1.7 Costs

4.1.7.1 Dental Costs

The NHS reimbursement prices for UDAs depends on individual dental practice contracts, collected annually in the "NHS Payments to Dentists in England" Report. This report details the totality of UDAs contracted and the baseline monetary value for those services for each dental practice (91). The unitary price for the UDA is calculated by dividing the baseline contract (in £) by the number of contracted UDAs for each practice annually. To assess the average prices throughout the country, we followed the British Dental Association (BDA) methodology, which only included practices with at least 1 UDA contracted and excludes those ones with mixed contracts (dental and orthodontic activity) (150). Moreover, outliers unitary UDA prices were also removed (with a minimum cost >£4,00 and maximum <£100,00). Due to the skewness of the UDA cost price across England regions **(Appendix, Figure S6),** the median was used in this work £29,25 (with 25% and 75% quantiles £26,42 and £32,08, respectively).

In the model, the cost of the dental reimbursement for the NHS depended on the strategy evaluated: in the "Standard" strategy (co-payment), the NHS would only pay the UDAs contracted to the Dental Practices (1 UDA for 1 individual checkup per year), whereas on the "Free Dental Care" strategy, it would cover the cost of UDA plus the cost of the co-payment for Band 1 treatments shouldered by patients (£23,80).

In the sensitivity analysis, other scenarios were explored, the cost for 2 dental checkups a year or 1 dental checkup and one Band 2 Treatment (which is 3 UDAs plus copayment of £65,20) were further explored.

4.1.7.2 Hospitalization, Outpatient and Drugs Costs

The costs of outpatient-care and hospitalization admission were collected from the National Schedule of NHS Costs 2020/21, which is the official source of costing data for NHS activity and it is publicly available online (151). The 2020/2021 report is the most recent, and therefore was chosen for this work.

For all alive states, the cost for one outpatient clinic visit with an electrocardiogram (ECG) and an echocardiogram were included; the only exception was the HF state, where 2 clinic reviews a year were added.

The inpatient care cost depends on whether the admission was elective or non-elective (the latter can also be short and long, with different costs assigned). Moreover, in some cases, the hospitalization costs also consider patient complexity, measured as the level of comorbidities (according to the Charleston Index [CC]) or, in case of AICU, the number of organs supported. In this work, non-elective long stay prices were chosen for admission costs, considering that IE in CHD admissions are rarely elective in the real-world practice. Additionally, when the admission costs depended on the complexity indexes mentioned above, the final price used was calculated by using a weighted average, and the weights were obtained using the number of episodes (or "activity") registered for each index range that year.

The hospitalization costs for IE, valve replacement surgery and heart failure are displayed in **Table 11.**

For IE admissions, correctly calculating the total length stay is pivotal to capture the entire cost of the admission. Since 2019, the Schedule of NHS Costs does not include average admission length for each diagnosis; hence, following the methodology used by previous NICE reports, the average length of admission was collected from the 2016-2017 and 2017-2018 NHS Schedule Costs reports and assumed to be similar in 2020-2021 (26,152). According to these previous reports, the average length of an IE admission was 12 days, which does not match the typical treatment duration of minimum 4 to 6 weeks of intravenous (IV) antibiotics (42 days) recommended by clinical guidelines (13,47). Previous cost-effectiveness studies have address

this issue by adding the cost of extra days of bed usage to the baseline cost of an IE ward hospitalization, along with the price for antibiotics for those extra days (66). In this work, a similar methodology was used to calculate the cost for the extra 30 days of bed occupancy, but the extra cost of the antibiotics was not added, as it was assumed to be already incorporated in the hospitalization bundle price. During the IE ward admission, extra cost of an in-patient dental review was added for every patient and it was assumed that 30% of these would need a dental extraction, based on the work by Bouchard et al. (153). For every ward hospitalization for valve replacement in the model, the cost for critical care on AICU was also included (26).

Table 11: Hospitalizations and Outpatients Care Costs for the free dental care model

Service Code	Activity	Average length of stay	Unit Cost	Weighted Unit Cost	Source
Hospitalization Costs					
EI Ward hospitalization		12 days		£7.389,00	National Schedule of NHS Costs 2020/21 (151)
EB02A CC Score 10+	4135		£7.990,24	(£615,75 /day)	
EB02B CC score 5-9	1.477		£6.156,00		
EB02C CC Score 0-4	319		£5.314,00		
Extra Days of Ward Admission (calculation)		30 extra days * £615,75		£18.472,50	
HF ward admission		9 days		£4.093,00	
EB03A CC Score 14+	33.095		£5.187,00		
EB03B CC Score 11-13	29.242		£4.054,00		
EB03C CC Score 8-10	21.492		£3.285,00		
EB03D CC Score 4-7	12.916		£2.915,00		
EB03E CC Score 0-3	1.580		£2.518,00		
Complex, Single Heart Valve Replacement or Repair Ward Hospitalization	209	13 days	£24.676,00	£21.937,00	
ED24A CC Score 11+	117		£19.437,00		
ED24B CC Score 6-10	66		£17.697,00		
ED24C CC Score 0-5					
Critical Care for Cardiac Surgical Adult patients,				£2.468,00	

(Cardiac Surgical AICU - according to the number of organs supported) XC01Z 6 or + XC02Z 5 XC03Z 4 XC04Z 3 XC05Z 2 XC06Z 1 XC07Z 0	1.872 6.133 15.941 35.454 43.717 28.728 5.703		£4.811,86 £3.354,23 £2.922,72 £2.734,50 £2.501,84 £1.604,38 £1.914,03		
CD03A Minor Dental Procedures, 19 years and over			£245,08		
CD07A Minor Extraction of Tooth, 19 years and over			£2.016,43		
Outpatient Care					
331 CHD appointment (OPC – Consultant-led)			£166,12		National Schedule of NHS Costs 2020/21 (151)
EC21Z Complex Echocardiogram for CHD (OPC)			£405,91		
EC22Z - Electrocardiogram Monitoring or Stress Testing, CHD (OPC)			£315,30		

Acronyms: * Multiplied; AICU, adult intensive care unit; CHD, congenital heart disease; OPC, outpatient care; HF: heart failure; IE: infective endocarditis.

Cost for Heart Failure Treatment

It was assumed that 50% of the population assigned to the HF state would need to have a hospitalization every year, in conformity with previous CEA IE models (65). Moreover, the HF state was the only one that included outpatient drug costs (HF treatment), assuming a combination of 3 possible treatment strategies **(Table 12).**

Table 12: A) Drug and devices costs for HF state (during hospitalizations and outpatients care); **B)** Medication costs per heart failure strategy

Therapy	Average cost per year (365 days)	Source
Bisoprolol 10mg od	£10,95	British National Formulary (BNF) 2023 (154)
Furosemide 40mg od	£8,60	
Enalapril 10mg bd	£31,03	
Spironolactone 50mg od	£29,33	
Sacubitril / Valsartan 97/103 mg bd	£1.193,55	
Dapagliflozin / Empagliflozin 10mg od	£476,98	
Ivabradine 5mg bd	£74,83	
ICD CRT-P CRT-D	£9.692,00 £3.411,00 £12.293,00	NICE - Technology Appraisal Review - Implantable cardioverter defibrillators and cardiac resynchronisation therapy (155)

Acronyms: bd, twice a day; CRT, Cardiac Resynchronization Therapy (P – pacing, D, defibrillator); ICD, Implantable Cardioverter Defibrillator; od, once a day.

Strategies for HF scheme therapy	Cost (annually)	Source
Strategy 1: Drug cost using Entresto and SGLT-2i	£1.719,41	BNF 2023 (154)
Strategy 2: Drug cost without Entresto (Enalapril used instead) but on SGLT-2i	£556,89	
Strategy 3: Drug cost without Entresto (Enalapril used instead) nor SGLT-2i	£79,91	
Used in the model:	20% on Strategy 1; 40% Strategy 2; 40% in Strategy 3; Plus: 10% in Ivabradine 5% with CRT-D	Assumed

Acronyms: CRT-D, Cardiac Resynchronization Therapy with defibrillator; HF: heart failure; SGLT-2i, SGLT-2 inhibitors.

4.2 Sensitivity analysis

The sensitivity analysis was conducted using 3 methods:

1) Different Scenarios. The baseline model was re-run changing the following parameters:

- Life-time horizon (10 years);

- Starting the model from 50y of age, followed for a 30-year horizon. This scenario aimed to explore the cost-effectiveness of the free-dental-care strategy in the age group in whom PCC prevalence increases to 3% in the general population; hence extrapolating the model beyond the young ACHD population (54,55);

- Need for 2 yearly check-ups (the recommended practice in the ESC guidelines for high-risk patients)(47);
- Need for a more complex type of procedure (Band 2 types).

2) Determinist Sensitivity Analysis or DSA **(Table 13).** The DSA aimed to explore uncertainty around the model parameters, by applying of possible range of values in chosen variables. The work used a one-way DSA, where the impact of the parameter variation on the results was assessed for one factor at a time.

3) Probabilistic Sensitivity Analysis or PSA **(Table 13).** For PSA, a probability distribution was defined for selected model input parameter. When the model was run, a value for each input was randomly selected simultaneously from its respective probability distribution. The model was run repeatedly – 1.000 times for the base case – using a Monte-Carlo simulation.

The PSA results were reported using the average QALY and cost difference across simulations. The PSA in this model follows a Bayesian approach, hence Bayesian 95% confidence intervals (also knowns as "credible intervals") were calculated instead of the frequentist (and more common used) 95% confidence intervals (156). The credible intervals were estimated by using the highest density interval (HDI) Bayesian method across simulations (package bayestR) (157).

Table 13: Parameters used for DSA and PSA Sensitivity Analysis

	Deterministic	Probabilistic	Source
Probability of IE	0,001 - 0,050	Beta	Cahill 2022 Netzer 2022 Thornhill 2018
Probability of death during IE	0,09 - 0,22	-	Netzer 2022, Van Melle 2022
Probability of needing a valve replacement in IE	0,40 - 0,80	-	Tutarel 2018 Van Melle 2022
Number of dental check-ups a year	1 - 2	-	2015 ESC Recommendations
Effectiveness of Free Dental	0,80 - 0,96	Lognormal	Assumption

Cost UDA	£11,00 - £50,00	Gamma	NHS Dental Payment to Dentists (91)
Cost IE ward admission	£5.314,00 - £7.990,00	Gamma	NHS Scheduler for NHS Costs (151)
Cost IE admission – Extra Days	£0 - £20.000,00	Gamma	
Cost dental extraction during IE admission	£0 - £3.968,33	Gamma	
Cost critical care after VR surgery	£1.604,38 - £4.811,86	Gamma	
Cost ward admission after VR surgery	£17.697,00 - £24.676,00	Gamma	
Cost HF ward admission	£2.518,00 - £5.187,00	Gamma	
Cost HF drugs (assumed no CRT or Ivabradine)	£79,91 - £1.719,41	Gamma	

Acronyms: CRT, Cardiac Resynchronization Therapy; HF: heart failure; IE: infective endocarditis; VR: valve replacement; UDA: unit of dental activity;

The following variables did not vary in the probabilistic analysis:

- The cost-effectiveness threshold (20-30.000,00/QALY)
- Health state costs
- Utility scores (based on the paper from Alava 2022)
- Mortality probabilities for the general population (based on UK national life-tables).
- Mortality probabilities associated with HF in ACHD
- Mortality probabilities after valve replacement
- Reintervention probabilities after valve replacement (with or without previous IE).

Due to high number of interactions, the sensitivity analysis was done using a High-Performance Computing System.

Part B) Cost-Effectiveness Analyses of PAH Combination Therapy in PAH-CHD

4.3 Overall Methodology

In constructing the second model, a different approach was employed, specifically in terms of the clinical data utilized to populate the model. The patient characteristics utilized in this model were sourced from a highly specialized Tertiary Centre for ACHD and PH, located in London, UK. The demographic, clinical and follow-up information for all patients referred and treated at this unit is systematically recorded and stored in an Infoflex software, which is founded on a structured SQL-language database. Boasting a massive database of over 10.000 patients and 100.000 variables, the project required a Data Science approach commonly used in Big Data projects **(Figure 24)**. For this project, the patients' data was extracted from this database, and attention was given to ensure proper anonymization and code reproducibility during the process of collecting, cleaning, and analysing the data. This approach guarantees that the data and code produced will not only be useful in this project, but also in future research endeavours.

R software (version 4.2.1, 2022-06-23, RStudio, PBC) was used for all data manipulation. statistical analyses and model development. This model was constructed using the cost-effectiveness R package *hesim*, which allows modelling Markov and Semi-Markov simulations using individual data (158). The code developed for this model is accessible upon request, on the Git Hub repository: (https://github.com/abarradaspires).

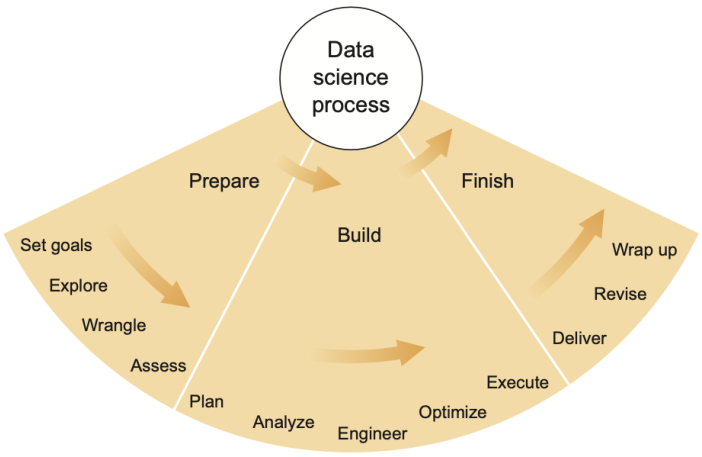


Figure 24: The lifecycle of a data science project, from (159).

4.3.1 Population

All patients with CHD referred to the Royal Brompton Hospital (RBHT) Pulmonary Hypertension Unit from June 1990 to the present day were reviewed. Clinical events and follow-up data were collected up to December 2022. All patients with PH and CHD were assessed, but only adults with PAH-CHD were included. The exclusion criteria included:

- Children (<16y).
- No pulmonary hypertension.
- PH associated with heart disease (PH group II), respiratory illnesses (PH group III), chronic thrombo-embolic disease (PH group IV) or systemic/multifactorial (PH group IV).
- Patients with Fontan circulation.
- Patients with no follow-up (only referral data in the system).

For the model development stage, only CHD patients on PAH treatments were included.

For simplicity purposes, the work divided PAH-CHD clinical subgroups in 2 major subgroups:

A) Unrepaired / Uncorrected PAH-CHD:

- Patients with complex cardiac anatomies: unrepaired atrioventricular septal defect (AVSD), pulmonary atresia with aorta-pulmonary malformations (segmental PAH), among others.

2) Patients with Eisenmenger Syndrome (ES) due to:

- Pre-tricuspid defects.
- Post-tricuspid defects (ventricular septal defect, patent ductus arteriosus and aorta-pulmonary windows).

3) Predominant systemic-pulmonary (Left to Right) shunts.

4) CHD with (coincidental) small defects.

B) PAH associated with repaired CHD defects.

4.3.2 The Model

For this second project, a Markov individual-level model was constructed using a continuous times state transition model (CTSTM) with inhomogeneous time (i.e., the times between state transitions could differ). The Base Case Markov model is displayed in **Figure 25**. It follows of a hypothetical cohort of adult patients with PAH-CHD, at the first moment they started being follow-up in the RBHT adult PH centre (i.e., 16 y). To translate the progression of the disease, the WHO functional class scale (from I to IV) was used as "health states" in the model as a proxy to the natural disease progression. The WHO FC states I and II were combined as they

share similar good prognosis, as per the 2022 ESC PH guidelines (97). The strategy of using WHO FC as health states is common in PAH cost-effectiveness analysis - while changes in survival are difficult to prove in most PAH subsets (as the duration of most RCTs are 12 to 16 weeks), it is well documented that the survival and quality of life are closely linked with WHO FC, including in PAH-CHD (115,116).

The model aimed to simulate these patients' individual trajectory for a life-time horizon, which in this case was considered maximum 60 cycles or up to 100 years of age (whatever arrived first). For that purpose, the model used serial follow-up clinical data from outpatient consultations, subsequently admissions etc, or any health-care interaction where at least the WHO FC and the treatment was recorded by the clinical team. Two therapeutical strategies were compared: monotherapy with PAH drugs vs PAH combined therapy (using 2 oral PAH drugs). In this model, patients with no PAH treatment during the entire follow-up or on triple therapy were excluded.

The model was structured as follows:

1) Patients with PAH-CHD could enter the model at any disease stage (i.e., WHO FC I-II, III or IV). Subsequently, patients could progress to clinical improvement (i.e., lower FC adjacent to their initial one), clinical deterioration (higher FC adjacent), clinical stability (unchanged FC) or death.

2) Treatment for PAH could be started at any point during the alive states.

3) The Nation Health Service (NHS) perspective was used for the costs.

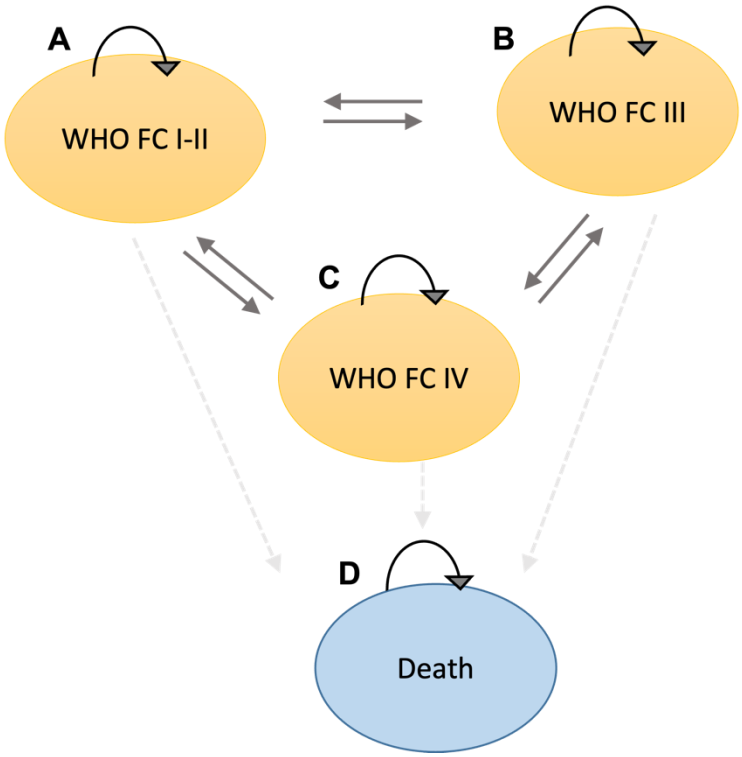


Figure 25: Markov Model diagram of the CEA analysis for PAH combination therapy vs monotherapy in PAH-CHD.

Acronyms: FC, functional class; WHO, World health Organization.

Patients can enter the model at any WHO FC and are subsequently transitioned according to the probabilities assigned to the transition between states. Death was considered an absorbing state.

Moreover, due to the heterogeneity of the PAH-CHD population and potential dissimilar responses to PAH therapy, this model was run 3 times, using groups:

Model 1: Included all adult patients with PAH-CHD.

Model 2: Only included adult patients with PAH associated with unrepaired CHD defects.

Model 3: Only included adult patients with PAH associated with closed CHD defects.

4.3.3 Model Assumptions

1) Based on the work of Sitbon et al, we assumed that all combinations of iPDE5 (Sildenafil/Tadalafil) + ERA (Bosentan/Macitentan/Ambrisentan) could result in the similar clinical benefits. The less expensive combination was used for the analysis (i.e., Sildenafil with

Bosentan) (160). Only ERA and iPDE5 drugs were considered in this model, and all other possible monotherapy or combination regimes were excluded (Prostanoids, Riociguat, etc.).

2) For simplicity purposes, the cost for monotherapy was considered the yearly iPDE5 cost (even though some patients had monotherapy with ERAs).

3) Patients in state "WHO FC IV" might be candidates to Prostanoids depending on the underlying type of PAH. In this model, only intravenous Prostanoids were considered for simplicity purposes. The proportion of patients assigned to intravenous PAH therapy followed the subsequent clinical assumptions:

A) For model 1 and 2, were complex and uncorrected post-tricuspid shunts individuals were included, only 10% of patients achieving WHO FC IV state would be candidate to prostanoids. This was a clinical assumption made to the fact that most patients with uncorrected post-tricuspid shunt, unrepaired AVSD or pulmonary atresia with segmental hypertension would not be offered intravenous therapy due to the risk of systemic embolism.

B) For model 3, which included only PAH individuals with repaired CHD, it was assumed that 100% would be candidate to intravenous therapy.

4) Heart and lung transplant state were not contemplated in this model due to its low occurrence rate among the PAH-CHD population, particularly unrepaired (161).

5) Patients were considered to be on "no PAH treatment" if had no PAH medication during the entre follow-up or if the duration of the PAH therapy was < 1 year. Those patients were excluded from the model.

6) Patients were considered to be on "monotherapy" if they were on single medication for at least 1 year or if it was started in the year of 2022 (hence, were right-censored). In the same way, patients on combination therapy for < 1 year who were then left on monotherapy were considered to have monotherapy alone in the model.

7) Patients were considered to be on "combination therapy" if the treatment regime was active for at least 1 year of it was started in the year 2022 (i.e., right-censored).

4.3.4 Features of the economic analysis

The basic characteristics of the base model are described in **Table 14**:

Table 14: Features of the economic analysis for monotherapy vs combination PAH therapy:

Input	Data	Source	Probabilistic distribution
Comparators	1. Standard Care - PAH monotherapy 2. Combination PAH therapy		
Population	Adults (≥16 years old) with: Model 1: All PAH-CHD. Model 2: PAH associated with unrepaired CHD. Model 3: PAH associated with closed CHD defects.		NA
Time-horizon	Lifetime (60 cycles)		NA
Perspective	UK NHS	Based on NICE reference case (135,136)	NA
Measuring and valuing health effects	Quality-adjusted life years (QALYs)		NA
Discount rate	Costs: 3,5% Outcomes: 3,5% (discounts not applied on the first cycle)		NA
Cohort size	1.000 simulations		NA
Start age	16y		NA
Percentage of patients male and female	50%	Assumed	NA

Acronyms: NA, not applicable; PAH, pulmonary arterial hypertension.

4.3.5 Data Collection and Outcome definition

During the initial visit and referral to the RBHT PH center, baseline data including sex, age, date of birth, diagnosis, initial WHO FC, and previous treatments were collected. Additionally, if available, baseline echocardiogram data and right heart catheterization (RHC) results prior to any new treatment initiation (both monotherapy and combination) were also obtained. For each patient, serial follow-up data were collected at every interaction with the clinical team, including

hospitalizations, outpatient appointments, daycases, video appointments, and telephone appointments. During these follow-up encounters, the system recorded the patients' WHO FC and treatment strategy.

There were 2 outcomes considered in this work:

1) Death - The death registry is centralized within the NHS, enabling instantaneous updates of clinical records regarding mortality outcomes. For this study, the outcome of mortality encompasses all causes of death, not exclusively those associated with PAH deterioration.

2) Transition between states (present/absent).

4.3.6 Statistical Analysis

All values are presented as mean with standard deviation (SD) or median with interquartile range (IQR), as appropriate. Comparisons between groups were made using parametric (T-test, ANOVA or Chi-square) or non-parametric (Wilcoxon test and Fisher test) tests, depending on the variable's distribution (for continuous variables) or counts (for categorical).

For the CEA model, only patients on "PAH monotherapy" or "PAH combination" were included. Again, patients which were in monotherapy and were subsequential started on PAH combination were considered as separate cases in the model (right censored and left truncated), with time in the model re-started to zero when the second treatment strategy was commenced. The duration of treatment was calculated for all patients, representing the interval between the start and end of their treatment. For individuals who were actively undergoing treatment at the time the data collection ended (end of 2022), the end date was right-censored. Throughout the entire follow-up period, all outcomes, including death, were recorded. However, for the CEA model, the transition outcomes, including death, were right-censored and limited to the time on treatment. Hence, for the CEA analysis, the outcomes that occur after the end of the treatment were right-censored. A survival analysis with baseline data for all individuals was also conducted using the non-censored outcomes.

Survival analysis and freedom from reintervention events were analysed using Kaplan-Meier survival curves, and log-rank test was used for comparisons between the groups. Univariable and multivariable Cox proportional hazard models were used to calculate the hazard ratio for transitions. The treatment strategy and age were considered time-dependent covariates in the survival analysis, and the Start-Stop approach was used to that effect. The covariates sex and presence/absence of Down syndrome were also added as covariates to the model, as they are

known to impact the PAH-CHD natural progression (115). When the transition occupancy was reduced (i.e., transitions between states were scarce and the outcome had reduced number), the model was adjusted to exclude covariates to improve fitting. For all analyses, a value of $p \leq 0.05$ was considered significant.

4.3.7 Baseline Probabilities

Transitions among all three alive states (WHO FC I-II, WHO FC III, and WHO FC IV) were permitted, as well as progression to the "Death" state, which was regarded as an absorbing state **(Figure 25).** The transition probabilities were calculated by fitting a parametric survival regression model for each possible transition (12 possibilities). For each state transition, the 3 other potential routes available from that state were considered competitive pathways. This is exemplified in **Figure 26.** The Weibull parametric survival distribution was used to fit all potential transitions and was chosen based on the AIC criteria.

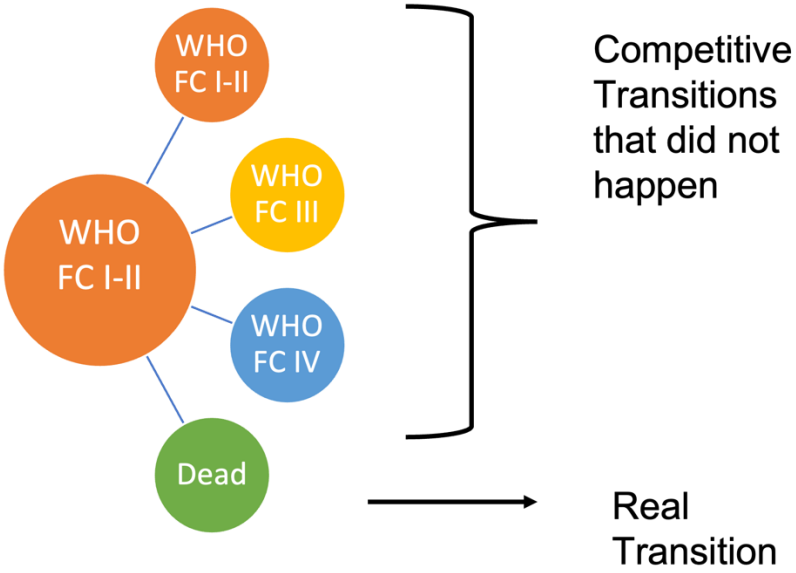


Figure 26: Potential routes of transition after occupying state WHO FC I-II.

From the state WHO FC I-II, individuals can transition to states WHO FC III, IV, Death or remain in the original. If a patient transitions to "death state" in a certain period of time, the other 3 alternative routes for the initial state are considered competitive states.

The transition matrix for the probabilities of transition between states are displayed in **Table 15.**

Table 15: Transition Probabilities Matrix for PAH model

	WHO FC I-II	WHO FC III	WHO FC IV	Death
WHO FC I-II	Each individual transition probability (12 options) was modelled separately fitting a parametric survival distribution (in this case, Weibull).			
WHO FC III				
WHO FC IV				
Death	**0**	**0**	**0**	**C**

4.3.8 Health-related Quality of life (Utilities)

There are no WHO FC utilities in the literature specifically developed in patients with PAH-CHD, hence we opted to use utilities from the work developed by Keogh and colleagues in patients with IPAH and PAH-CTD **(Table 16)** (162)**.** These utilities were used in previous cost-effectiveness models in PAH, which facilitated comparability (163,164).

Table 16: Utilities used for the PAH model and its source.

State	Utility - Mean	Utility - SD	Source
WHO FC I	0,73	0,09	Keogh (162)
WHO FC II	0,67	0,10	
WHO FC I-II	0.70	0,10	
WHO FC III	0,60	0,10	
WHO FC IV	0,52	0,09	
Dead	0,00	0,00	

Acronyms: SD, standard deviation; WHO FC, Functional class based on the World Health Organization scale.

4.3.9 Costs

The costs of outpatient-care and hospitalization admission were collected from the National Schedule of NHS Costs 2020/21 (151). The hospitalization and AICU costs are associated with complexity indexes mentioned in the previous model, hence the final price was calculated by using a weighted average, and the weights were obtained using the number of episodes ("activity") registered for each index range that year (**Table 17).**

Table 17: Hospitalizations and outpatient care Costs for the PH model

Service Code	Activity	Unit Cost	Weighted Unit Cost	Source
Hospitalization Costs				
PH Non- Elective Ward admission			£5.841,00	National Schedule of NHS Costs 2020/21(151)
EB15A - Primary PH with CC Score 9+	191	£6.486,87		
EB15B - Primary PH with CC Score 4-8	75	£4.412,31		
EB15C - Primary PH with CC Score 0-3	8	£3.800,95		
HF ward admission			£4.093,00	
EB03A CC Score 14+	33.095	£ 5.187,00		
EB03B CC Score 11-13	29.242	£ 4.054,00		
EB03C CC Score 8-10	21.492	£ 3.285,00		
EB03D CC Score 4-7	12.916	£ 2.915,00		
EB03E CC Score 0-3	1.580	£ 2.518,00		
Critical Care for Adult Care (AICU General)			£2.386,00	
XC01Z 6 or +	7.034	£2.625,34		
XC02Z 5	27.962	£2.769,13		
XC03Z 4	98.348	£2.781,83		
XC04Z 3	220.733	£2.612,99		
XC05Z 2	292.889	£2.491,23		
XC06Z 1	253.343	£1.888,73		
XC07Z 0	15.838	£1.977,41		
Daycase				
EB15A – PH with CC Score 9+	85	£1.135,88	£937,00	
EB15B – PH with CC Score 4-8	255	£921,03		
EB15C – PH with CC Score 0-3	198	£871,80		
Outpatient Care				
331 CHD appointment (OPC – Consultant-led)		£166,12		
EC21Z - Complex Echocardiogram for CHD (OPC)		£405,91		

EC22Z - Electrocardiogram Monitoring or Stress Testing, CHD (OPC)		£315,30		
DZ31Z - Cardiopulmonary Exercise Testing (OPC)		£208,60		
DZ32Z - Field Exercise Testing (OPC)		£181,78		
High-Cost Drugs				
PHCD00398 Ambrisentan	1.665	£1.374,01		
PHCD00402 Iloprost	3.440	£504,59		
PHCD00403 Macitentan	4.168	£1.329,98		
PHCD00405 Riociguat	848	£1.329,76		
PHCD00406 Selexipag	1.832	£1.340,33		
Bosentan – 125mg BD (yearly)		£1.320,77		BNF 2023 (154)
Sildenafil – 20mg TDS (yearly)		£5.434,07		
Epoprostenol (considering a dose of 32ng/kg/min for a 70kg patient)		£48.642,93		

Acronyms: AICU, Adult intensive care unit; BD, twice a day; CC, Charleston Index; CHD, congenital heart disease; HF, heart failure; OD, once a day; OPC, outpatient care; PH, pulmonary hypertension; TDS: three times a day.

The overall costs by Health State were calculated based on the number of clinical interactions registered by year and by WH FC in our real-life data **(Table S5, Appendix).** The total costs by WHO FC are displayed in **Table 18.** For patients in WHO FC I-II, the model included the yearly price of a day case (an appointment with the clinical team and basic exams such as echocardiogram, ECG and 6MWT) and a clinical appointment with the PH consultant in the outpatient department. It was also considered that 50% might require an admission for any cause (arrythmias, starting oral PAH treatment, infections, PAH complications such as HF, hemoptysis, etc.). In the WHO FC IV, the cost of PAH up-titration with intravenous Epoprostenol was also added (for 10% of all PAH-CHD model; 10% of unrepaired PAH-CHD model and 100% of patients with PAH associated with corrected defects model). An AICU cost was also included yearly in this state: in the first year for intravenous PAH therapies initiation and for other complications in the subsequential years (including line infection, heart failure needing inotropes, etc.).

Table 18: Overall Costs by Health State

State	Medical Care	Cost per Unit (£)	Units per year	Final Cost (£)
WHO FC I -II	Hospitalization	5.841,00	0.5	2.920,50
	Daycase	937,00	1	937,00
	OPC clinic	166,12	1	166,12
	Echocardiogram	405,91	1	405,91
	ECG	315,30	1	315,30
	6MWT	181,78	1	181,78
				Total cost per state per year: £4.926,61
WHO FC III	Hospitalization	5.841,00	1	5.841,00
	Daycase	937,00	1	937,00
	OPC clinic	166,12	2	332,24
	Echocardiogram	405,91	1	405,91
	ECG	315,30	1	315,30
	6MWT	181,78	1	181,78
				Total cost per state per year: £8.013,23
WHO FC IV	Hospitalization	5.841,00	1	5.841,00
	Daycase	937,00	1	937,00
	OPC clinic	166,12	2	332,24
	Echocardiogram	405,91	1	405,91
	ECG	315,30	1	315,30
	6MWT	181,78	1	181,78
	AICU admission*	2.386,00	0.1	238,60
	Epoprostenol*	48.642,93	0.1	4.864,29
	AICU admission#	2.386,00	1	2.386,00
	Epoprostenol#	48.642,93	1	48.642,93
				*Total cost per state per year (Model 1 and Model 2): £13.116,12 #Total cost per state per year (Model 3): £59.042,16
Dead				Total cost per state per year: £0,00

Acronyms: 6MWT: 6-minute walking test; AICU, Adult intensive care unit; ECG, electrocardiogram; OPC, outpatient care; PH, pulmonary hypertension; WHO FC, Functional class based on the World Health Organization Functional scale.

* Model 1: All PAH-CHD population and Model 2: Unrepaired PAH-CHD subgroup.

Model 3: PAH associated with repaired CHD defects subgroup.

4.4 Sensitivity analysis

The sensitivity analysis was conducted using the probabilistic sensitive analysis (PSA) method. The distributions used to sample the parameters imputed in the model, from sample of 1.000 simulated individuals, are displayed in **Table 19:**

Table 19: Parameters distribution used for Sensitivity Analysis

Parameters	Distribution used for PSA
Utilities	Beta
Drug Costs	Fixed (BNF)
Hospital Costs	Gamma

Again, due to high number of interactions, the sensitivity analysis of this model was performed on a High-Performance Computing System.

5. Results

5. Results

Part A) Cost-Effectiveness Analysis of Providing Free Dental Care for Patients at High Risk of IE

5.1 Base case model

Free dental care was associated with a lower healthcare expenditure of £275,59 per person, while also improving outcomes, reflected in a net gain of 0,47 QALYs and 0,48 life-years per patient compared with the standard co-payment model **(Tables 20 and 21**) over the 60y timeline horizon. Based on these results, if an annual checkup was offered to 1.000 high-risk of IE patients during their lifetime, the NHS could save up to £275.580,00. These savings were mostly driven by a lower number of IE episodes, translating into reduced spending on hospitalizations, surgeries, and HF drugs **(Table 20 and Table 21).** Additionally, 39 cases of IE and 12 premature deaths per 1.000 patients could be avoided (**Table 22** and **Figure 27**).

Table 20: Base case results (per person) for the dental care model

	Total Cost (£)	Total QALYs	Total LYs	Cost Difference (£)	Incremental QALY	ICER (£/QALY)
Standard	71.639,94	45,31	51,86	NA	NA	NA
Free Dental Care	71.364,35	45,79	52,34	- 275,58	0,47	-582,61

Acronyms: ICER, incremental cost effectiveness ratio; LYs, life-years; NA, not applicable; QALY, quality-adjusted life years.

Table 21: Detailed costs (per person) according to treatment strategy

Detailed Costs	Cost Dental Care (£)	Cost Outpatient Care (£)	Cost IE Hospitalization (£)	Cost of VR surgery and Critical Care (£)	Cost of HF Drugs (£)
Standard	1.503,94	46.512,65	14.089,59	5.890,83	3.642,93
Free Dental Care	2.763,41	46.912,30	12.633,50	5.588,11	3.467,04

Acronyms: HF, heart failure; IE, infective endocarditis; VR, valve replacement.

Table 22: Total Counts by Health State for 1.000 patients entering the model.

Strategy	Nº IE	Nº Deaths	Nº in "Well" state in the last cycle
Base	261	432	420
Free Dental Care	222	419	439

Acronyms: IE, infective endocarditis.

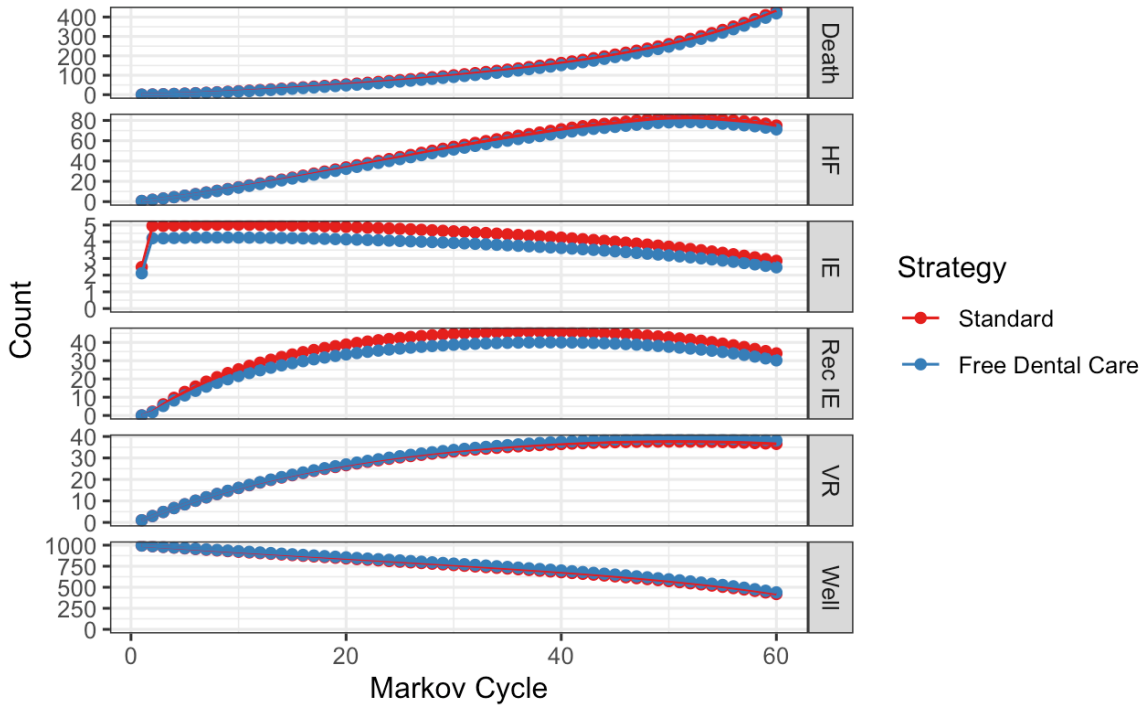


Figure 26: Number of patients (n = 1.000) occupying each state by cycle time and strategy.

Acronyms: HF, heart failure; IE, infective endocarditis; Rec IE, recovered infective endocarditis; VR, valve replacement.

5.2 Sensitivity Analysis

5.2.1 Scenario Analysis

Table 23 displays the CEA sensitivity results for the pre-specified scenarios. Offering free dental care was cost-effective even when the life-time horizon was reduced, with a higher ICER if the free dental care strategy was started after 50y of age. When assessing the model for extra dental care procedures, both in terms of number of annual visits and complexity of dental work,

the free dental care strategy would still be cost-effective, under the WTP NICE thresholds (less than 20.000,00 - 30.000,00/QALY), but not cost-saving.

Table 23: Sensitivity Analysis Results for the Case-Analysis

Scenario	Cost Difference (£)	Incremental QALY	ICER versus baseline (£/QALY)
10-year horizon	-28,87	0,013	-2.266,73
Start age at 50y (30-year horizon)	-140,05	0,095	-1.466,47
2 Dental Check Ups / Year	983,88	0,474	2.080,00
1 Dental Checkup PLUS 1 Complex dental procedure every year*	3.178,34	0,473	6.719,22

Acronyms: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life years.

*Standard care: 4 UDA = 1 UDA for checkup + 3 UDA for Band 2 Procedure (NHS payment);
Free Dental Care: 4 UDA + co-payment cost: £23,80 for Band 1 + £65,20 (Band 2).

5.2.2 One-way Deterministic Sensitivity Analysis (DSA)

The DSA results are presented in **Figure 28**. In the one-way sensitivity analysis, the variables with most weight in the model were the probability of IE in high-risk individuals, followed by the efficacy of the free dental care strategy. The free dental care strategy would still be cost-effective if the incidence of IE in high-risk patients considered in the model was 1 per 1.000 person-years (ICER of £7.942,18/QALY), whereas an incidence of 1 case for 10.000 person-years (which reflects the incidence of IE in the general population) would cross the NICE WTP threshold (ICER £66.046,63/QALY).

The efficacy of the dree dental care strategy also carried significant weight in the model and, even if this stratgey would prevent only 5% of the cases (i.e., RR =0,95), it would still be cost-effective with an ICER at £4.677,84/QALY; while with 1% efficacy (i.e., RR =0,99) the ICER would be higher, at £36.228,06/QALY.

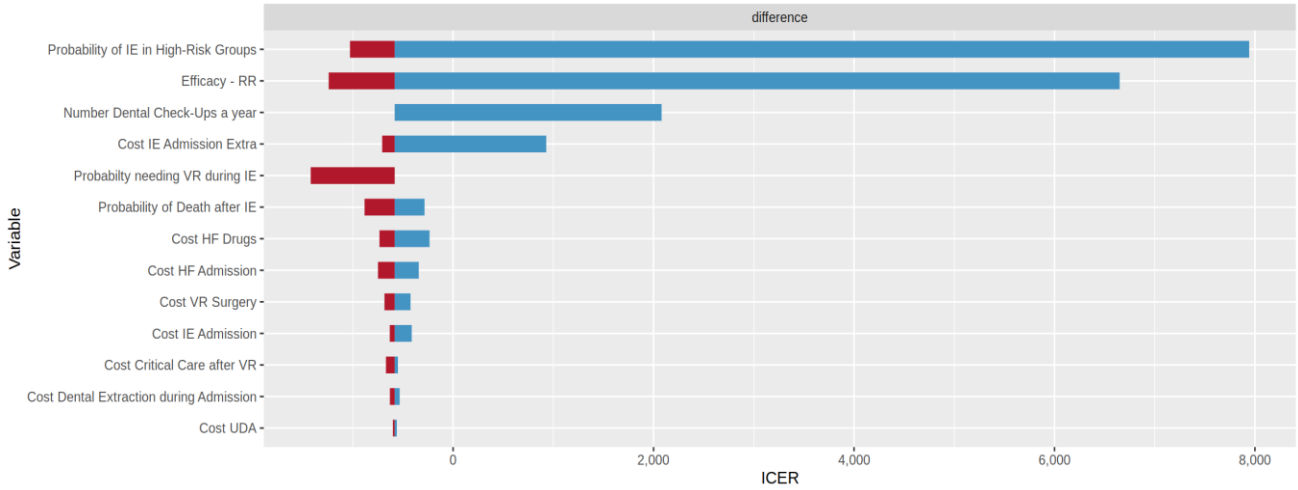


Figure 27: Tornado graph displaying the variations on ICE using range parameters.

ICER is expressed in £/QALY.

Acronyms: IE, infective endocarditis; RR, relative risk; VR, valve replacement; UDA, unit of dental activity.

5.2.3 Probabilistic Sensitivity Analysis

The results of the probabilistic sensitivity analysis for the CEA and the NMB are displayed in **Tables 24 and 25**, respectively. The table shows the average costs, average QALY gains and ICER per individual. In the simulation model, the mean ICER was £-2.454,91 per QALY gained, thus cost-effective and cost-saving under the current NICE WTP thresholds. Moreover, using the low end of the NICE WTP (£20.000,00/QALY), the free dental care strategy would still provide a net monetary benefit (NMB) of £34.270,73.

Figure 29 A displays the CEA graph over the 1.000 simulations and shows that standard care led to an increase in costs and reduction in QALYs in 85% of the simulated cases. Consequently, providing free dental care was cost-effective in most of the simulations, even when the highest WTP are considered **(Figure 29 B).** The graph displaying the Expected Value of Perfect Information (EVPI) for free dental care strategy is displayed in **Figure S7 of the Appendix.**

Table 24: CEA results of the probabilistic sensitivity analysis.

	Mean Total Cost (£)	**Mean Total QALY**	**Mean Cost Difference in £ (95% credible intervals)**	**Mean Effect Difference in QALY (95% credible intervals)**	**ICER (£/QALY)**	**NMB (WTP £20.000/ QALY)**
Standard	106.059,89	35,13	NA	NA	NA	596.541,00
Free Dental Care	102.313,20	36,65	-3.746,69 (-9.622,17 to 2.796,18)	1,53 (-0,57 to 3,40)	-2.454,91	630.686,80

Acronyms: ICER, incremental cost effectiveness ratio; NMB, Net Monetary Benefit; QALY, quality-adjusted life years.

Table 25: NMB results of the probabilistic sensitivity analysis.

NMB (in £)							
WTP £/QALY	**1.000,00**	**5.000,00**	**6.000,00**	**10.000,00**	**20.000,00**	**30.000,00**	**50.000,00**
Standard	0	0	0	0	0	0	0
Free Dental Care	5.272,89	11.377,70	12.903,90	19.008,71	34.270,73	49.532,75	80.056,80

Acronyms: ICER: incremental cost effectiveness ratio; NMB, Net Monetary Benefit; QALY: quality-adjusted life years; WTP, willingness-to-pay.

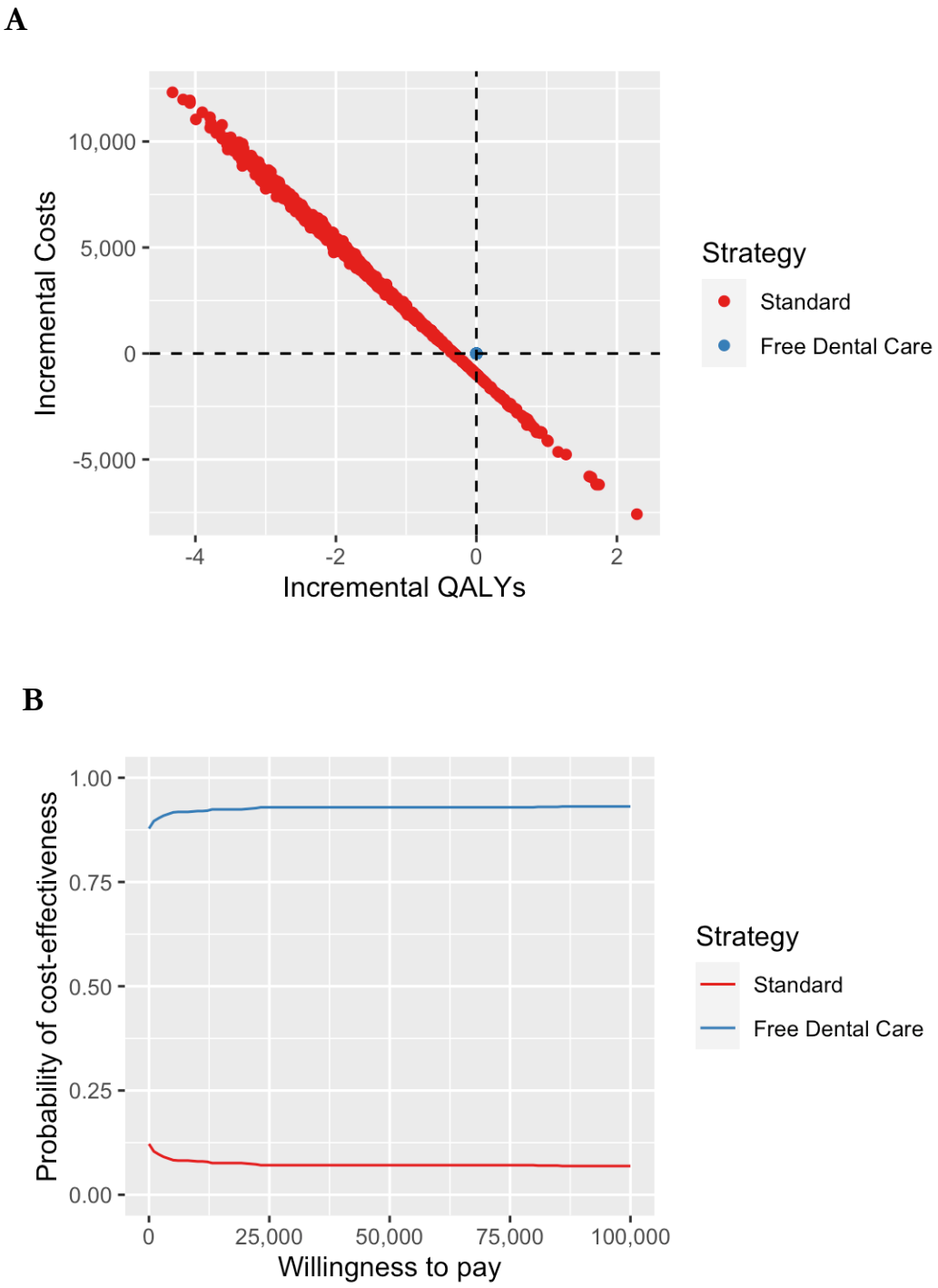


Figure 28: A) CEA graph over the 1.000 simulations; **B)** Probability of cost-effectiveness (x axis) of both strategies when different WTP thresholds are considered (y axis).

Costs are expressed in £. WTP is expressed in £/QALY.

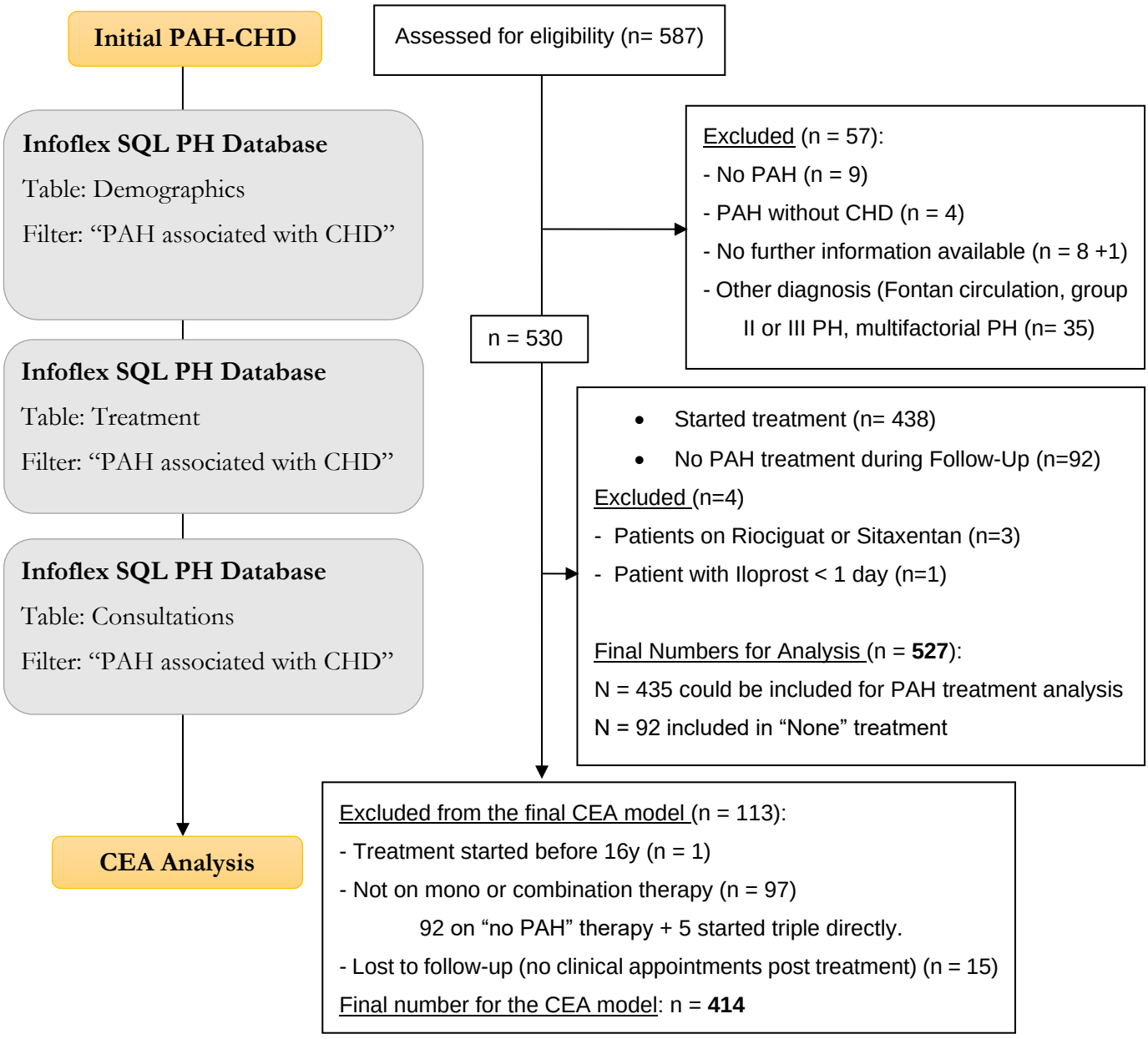
Acronyms: QALYs, Quality-Adjusted Life years; WTP, willingness-to-pay.

Part B) Cost-Effectiveness Analysis of Combination PAH Therapy in PAH-CHD patients

5.3 Population

Between April 1999 and December 2022, 587 patients with PAH-CHD were included in the RBHT PH SQL database. Of those, 530 were confirmed as PAH-CHD and further analyzed. Only 414 were included in the Markov model. The flow diagram for this study is shown below:

Population Flow Diagram



Of the 414 patients with PAH-CHD on treatment, 234 were only treated with PAH monotherapy during the follow-up, 33 with only combination, and 147 were first treated with monotherapy and subsequently escalated to combination therapy. **(Figure 30).** As the patients with two strategies were counted as separate cases in the model, a total of 381 (234 + 147) patients were considered receiving PAH monotherapy and a total of 180 (33 + 147) PAH combination therapy, hence a final population count of **561.**

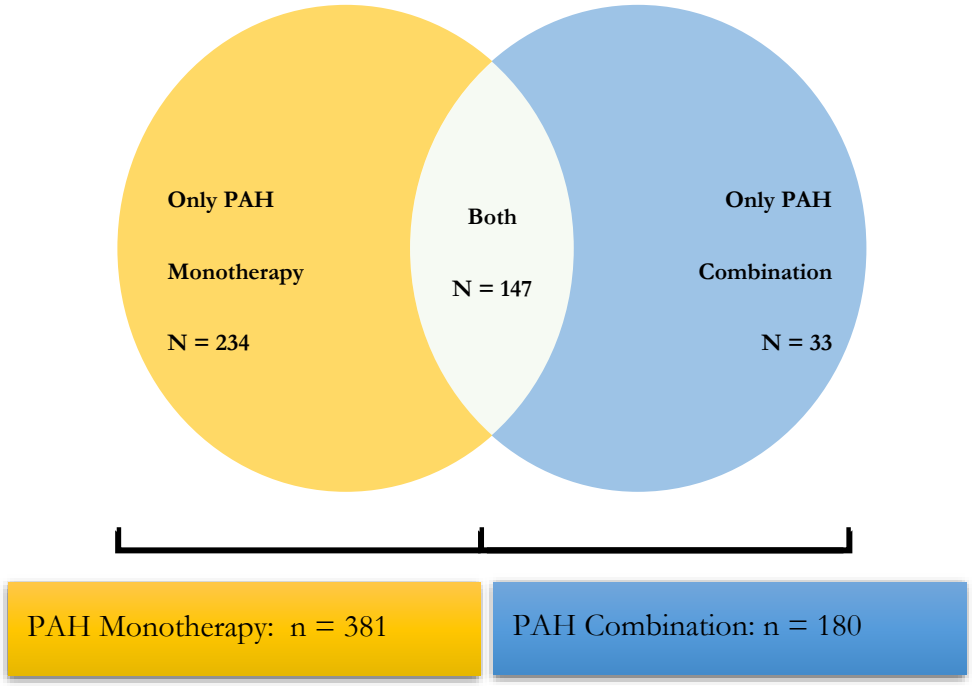


Figure 29: Venn Diagram of the population according to PAH treatment strategy.

5.4 Baseline Characteristics

In the baseline analysis, a total of 527 patients with PAH-CHD were included, of whom 60.9% were female, with a median age of 36 years at the start of treatment (IQR: 27-45y). The majority of patients had complex CHD anatomy (37,6%) or ES with post-tricuspid shunts (31,7%) and were at WHO functional class III (71,7%).

Among the 414 patients included in the CEA analysis (i.e., treated), a significant proportion (85,7%) had no prior exposure to PAH therapies at the time of inclusion or had been treated for less than one year (6,0%). The remaining patients had received treatment for 1-5 years (4,8%) or more than 5 years (3,4%). In the majority of cases (71,0%), the initial drug prescribed was an iPDE5, while the remaining patients (29,0%) were initiated on an ERA.

A comprehensive depiction of the population demographics, categorized by treatment strategy, is presented in **Table 26.** No significant differences were found between the two treatment regimens in terms of PAH-CHD anatomy or sex, but patients on combination therapy were older at the start of therapy and had a higher WHO FC **(Figures 31 and 32).**

Table 26: Baseline Characteristics by PAH Treatment Strategy

	Monotherapy (N=381)	Combination (N=180)	Total (N=561)	p-value
Sex (n, %)				0,567
Female	248 (65,1%)	122 (67,8%)	370 (66,0%)	
Male	133 (34,9%)	58 (32,2%)	191 (34,0%)	
CHD Anatomy (n, %)				0,262
Complex Anatomy	143 (37,5%)	68 (37,8%)	211 (37,6%)	
ES with post-tricuspid shunt	131 (34,4%)	55 (30,6%)	186 (33,2%)	
After corrective cardiac surgery	71 (18,6%)	28 (15,6%)	99 (17,6%)	
ES with pre-tricuspid shunt	14 (3,7%)	12 (6,7%)	26 (4,6%)	
Systemic-to-pulmonary shunts	12 (3,1%)	11 (6,1%)	23 (4,1%)	
Small defects	10 (2,6%)	6 (3,3%)	16 (2,9%)	
Age at treatment initiation (years)				0,017
Median (Q1, Q3)	37,00 (28,00-45,00)	40,00 (31,00-48,00)	38,00 (29,00-46,00)	
WHO FC at treatment initiation (n, %)				0,047
I	11 (2,9%)	2 (1,1%)	13 (2,3%)	
II	61 (16,0%)	32 (17,8%)	93 (16,6%)	
III	309 (81,1%)	143 (79,4%)	452 (80,6%)	
IV	0 (0,0%)	3 (1,7%)	3 (0,5%)	
Last WHO FC (n, %)				0,551
I	27 (7,1%)	11 (6,1%)	38 (6,8%)	
II	128 (33,6%)	60 (33,3%)	188 (33,5%)	
III	216 (56,7%)	100 (55,6%)	316 (56,3%)	
IV	10 (2,6%)	9 (5,0%)	19 (3,4%)	
Genetic Syndromes (n, %)				0,390
None	251 (65,9%)	130 (72,2%)	381 (67,9%)	
Trisomy 21	117 (30,7%)	43 (23,9%)	160 (28,5%)	
DiGeorge	5 (1,3%)	1 (0,6%)	6 (1,1%)	
Noonan	1 (0,3%)	2 (1,1%)	3 (0,5%)	
Turner	2 (0,5%)	1 (0,6%)	3 (0,5%)	
Bonneville-Ulrich	1 (0,3%)	1 (0,6%)	2 (0,4%)	
Klippel-Feil	1 (0,3%)	1 (0,6%)	2 (0,4%)	
Ehlers-Danlos	1 (0,3%)	0 (0,0%)	1 (0,2%)	
Williams	0 (0,0%)	1 (0,6%)	1 (0,2%)	
Russell Silver	1 (0,3%)	0 (0,0%)	1 (0,2%)	
19p13.3 Microduplication	1 (0,3%)	0 (0,0%)	1 (0,2%)	

Acronyms: ES, Eisenmenger syndrome; WHO FC: Functional class based on the World Health Organization

scale; Q1, first quartile; Q3, third quartile.

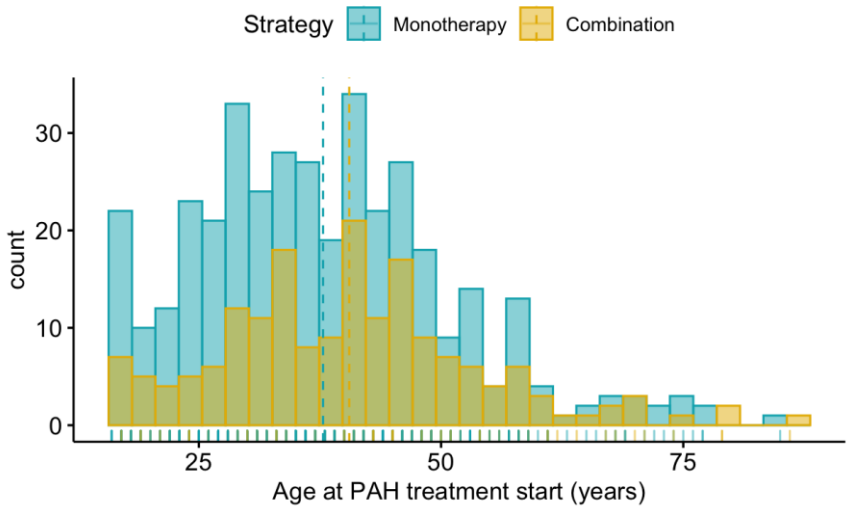
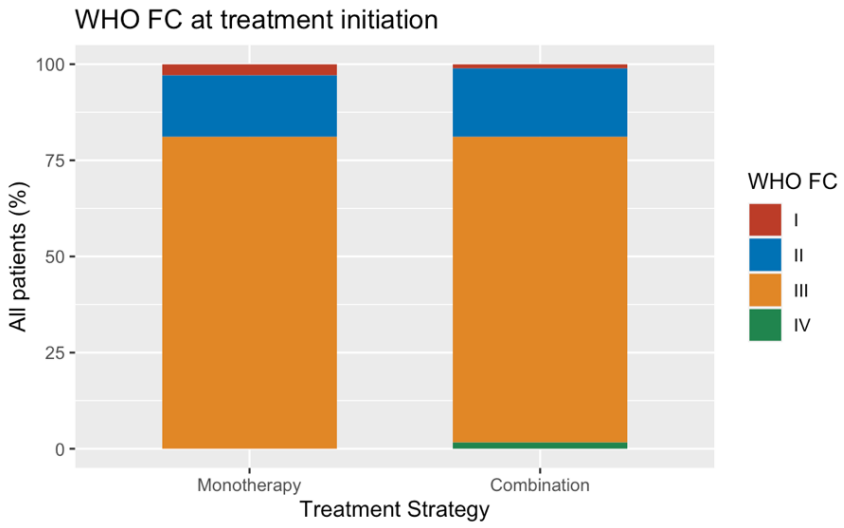


Figure 30: Age Histogram at treatment initiation, by treatment strategy

A



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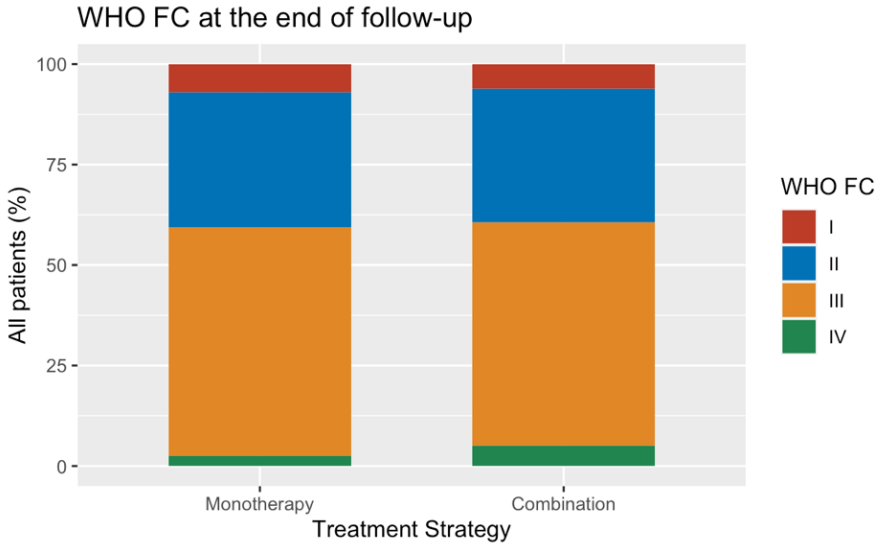


Figure 31: Distribution of WHO FC at treatment initiation **(A)** and at the end of follow-up **(B)**

Right heart catheter (RHC) data before starting treatment was only available for 76 patients and is shown in **Table 27.** In **Table 28,** the available information on left ventricular function and functional status using the 6-minute walking test (6MWT) distance before treatment initiation are shown.

Table 27: Hemodynamic data by treatment strategy

	Monotherapy (N=381)	Combination (N=180)	Total (N=561)	p-value
CHD Anatomy (n, %)				0,320
N	57	19	76	
After corrective cardiac surgery	23 (40,4%)	5 (26,3%)	28 (36,8%)	
Small defects	9 (15,8%)	2 (10,5%)	11 (14,5%)	
Complex Anatomy	7 (12,3%)	4 (21,1%)	11 (14,5%)	
System-to-pulmonary shunts	5 (8,8%)	5 (26,3%)	10 (13,2%)	
ES with post-tricuspid shunt	8 (14,0%)	1 (5,3%)	9 (11,8%)	
ES with pre-tricuspid shunt	5 (8,8%)	2 (10,5%)	7 (9,2%)	
Interval between RHC and treatment (days)				0,565
Median (Q1, Q3)	104,00 (34,00- 383,00)	59,00 (24,50-340,00)	102,00 (31,00-368,75)	
RA pressure (mmHg)				0,414

Median (Q1, Q3)	7,00 (5,00-11,00)	6,50 (4,25-8,25)	7,00 (5,00- 0,25)	
Mean PAP pressure (mmHg)				0,120
Median (Q1, Q3)	45,00 (38,00-57,00)	53,00 (44,00-67,00)	47,50 (38,25-60,00)	
PCWP pressure (mmHg)				0,957
Median (Q1, Q3)	10,00 (7,00-13,00)	10,00 (7,75-11,50)	10,00 (7,00-13,00)	
Cardiac Output (litres/min)				0,396
Median (Q1, Q3)	4,25 (3,18-5,80)	5,20 (4,10-5,60)	4,60 (3,50-5,60)	
PVR (Wood Units)				0,449
Median (Q1, Q3)	6,74 (5,86-10,69)	10,35 (7,63-13,84)	8,26 (5,86-12,93)	

Acronyms: CHD, congenital heart disease; ES, Eisenmenger Syndrome; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; RHC, right heart catheter; Q1, first quartile; Q3, third quartile.

Table 28: Left ventricular function and 6MWT distance at treatment initiation

	PAH Monotherapy (N=381)	Combination Therapy (N=180)	Total (N=561)	p value
Baseline LVEF (%)				0.724
N	194	102	296	
Median (Q1, Q3)	63,00 (57,00-70,00)	63,00 (56,00- 70,75)	63,00 (57,00- 70,00)	
Interval between 6MWT and treatment (days)				< 0.001
N	85	89	174	
Median (Q1, Q3)	83,00 (11,00-666,00)	453,00 (141,00-1291,00)	260,50 (39,00-993,50)	
6MWT Distance				0.027
N	84	88	172	
Median (Q1, Q3)	289,00 (221,25-360,00)	325,00 (260,00-380,00)	307,50 (240,00-375,00)	
6MWT O2 Sat at rest				0.164
N	85	89	174	
Median (Q1, Q3)	86,00 (82,00-91,00)	87,00 (82,00- 93,00)	86,00 (82,00-92,00)	

6MWT O2 Sat at peak exercise				0.232
N	84	89	173	
Median (Q1, Q3)	70,50 (62,00-77,25)	73,00 (64,00-86,00)	72,00 (63,00-81,00)	
Borg Score at rest				0.455
N	43	66	109	
Median (Q1, Q3)	0,50 (0,00-0,50)	0,50 (0,00-1,00)	0,50 (0,00-1,00)	
Borg at peak exercise				0.419
N	45	65	110	
Median (Q1, Q3)	3,00 (2,00-5,00)	3,00 (2,00-5,00)	3,00 (2,00-5,00)	

Acronyms: 6MWT, 6-minute walking test; LVEF, left ventricle ejection fraction; O2 Sat, Oxygen saturation; Q1, first quartile; Q3, third quartile.

5.5 Outcomes

The overall median follow-up of this study was 7,07 years (IQR: 3,67-11,00 years). Of the 414 patients included, 152 died during the follow-up, giving a mortality rate of 8,42 deaths per person-year. Of the 561 patients included in the CEA model, 136 transitioned to death (censored to deaths that occurred during their time on PAH therapies). The median survival for patients on monotherapy was 15,63 years and for combination strategy 10,42 years.

5.5.1 Transitions

The number of transitions occurring in each group during the follow-up is displayed in **Table 29.** The goodness-of-fit AIC for each transition fitted to the Weibull distribution can be found in **Supplementary Table S6 (Appendix)** for the 3 models.

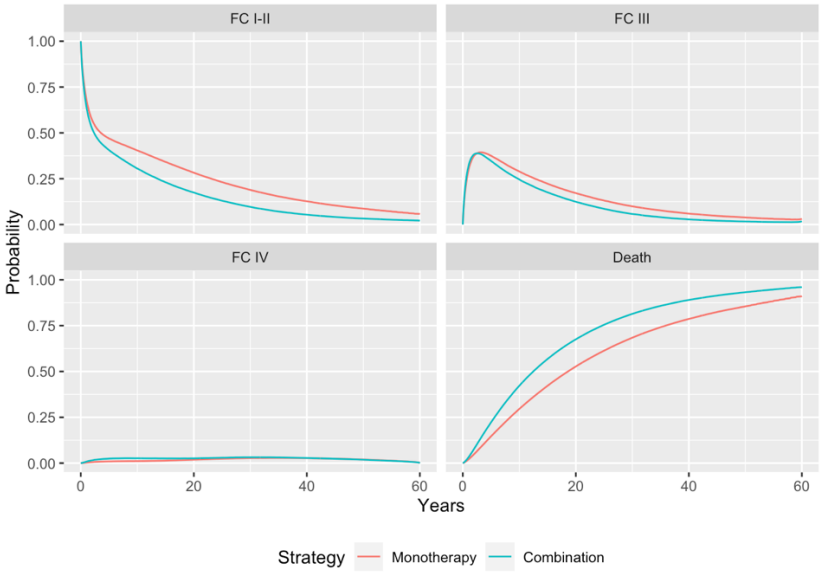
Table 29: number of outcomes (positive transitions) in the baseline data

Transition id	Transition Name	All PAH-CHD	Uncorrected PAH-CHD	PAH with closed CHD defect
1	FC I-II → FC I-II	439	348	91
2	FC I-II → FC III	407	336	71
3	FC I-II → FC IV	3	2	1
4	FC I-II → Death	34	30	4
5	FC III → FC I-II	530	441	89
6	FC III → FC III	660	582	98
7	FC III → FC IV	56	49	7
8	FC III → Death	92	78	14
9	FC IV → FC I-II	1	1	0
10	FC IV → FC III	42	38	4
11	FC IV → FC IV	30	26	4
12	FC IV → Death	10	8	2

Acronyms: CHD, congenital heart disease; FC, functional class; PAH, pulmonary arterial hypertension.

The probabilities of remaining in each health state, stratified by PAH-CHD subgroup and treatment strategy, are displayed in **Figure 33 (A-C).** The derived hazards for each transition are shown in **Supplementary Figures S8 (Appendix).**

A



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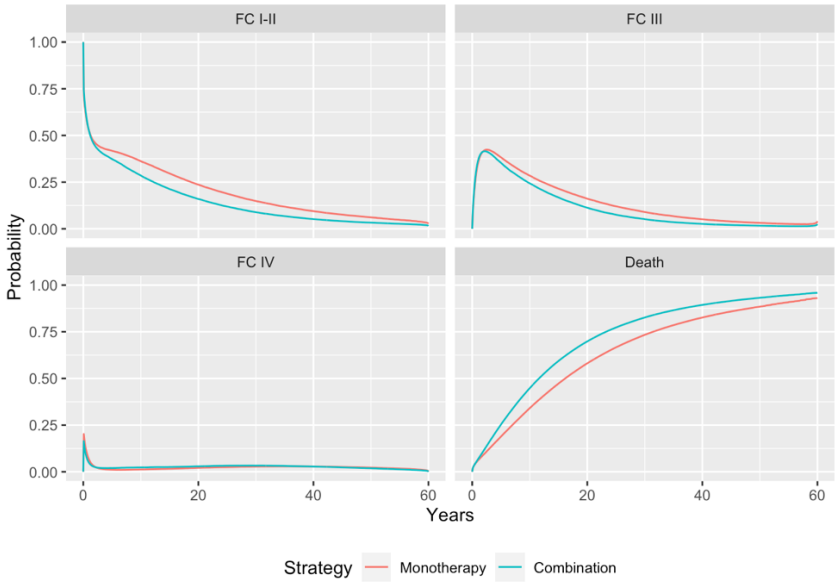

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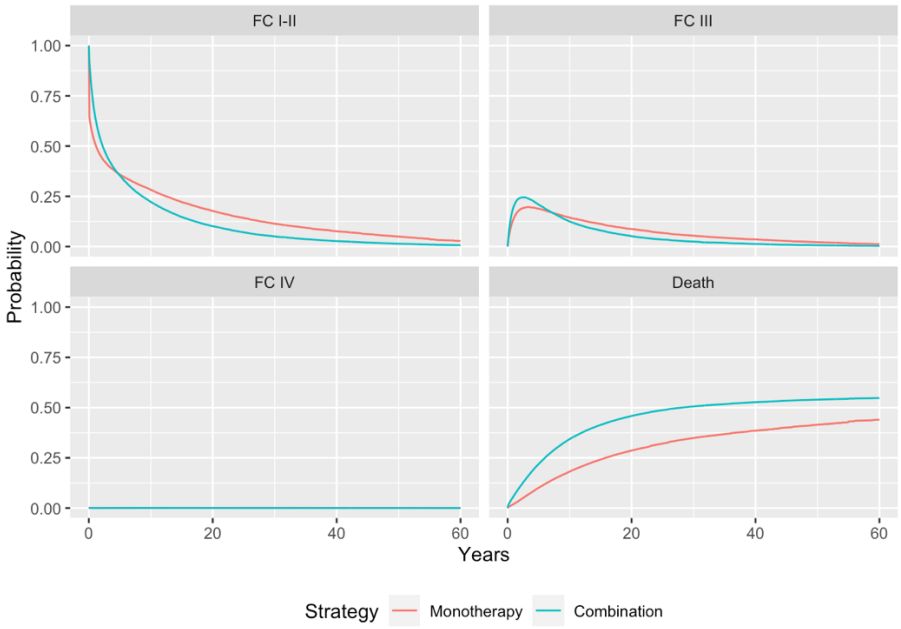


Figure 32: Graphs displaying the probabilities of occupying each health state according to treatment strategy**. A) Model 1:** All PAH-CHD population**. B) Model 2:** Unrepaired PAH-CHD subgroup. **C) Model 3:** PAH after CHD Defect Closure Group.

Acronyms: FC, functional class.

5.5.2 Survival analysis

The Survival curve in **Figure 34** shows the survival rate by PAH treatment strategy (n = 561), using the start and stop follow-up time and the p value from the Cox regression model**.**

The Kaplan Meier curves for unadjusted survival curves according to PAH-CHD anatomical subgroups and first/last WHO FC (using n=414, i.e., no duplicated treatment), are displayed in **Figures 35 to 37**, respectively.

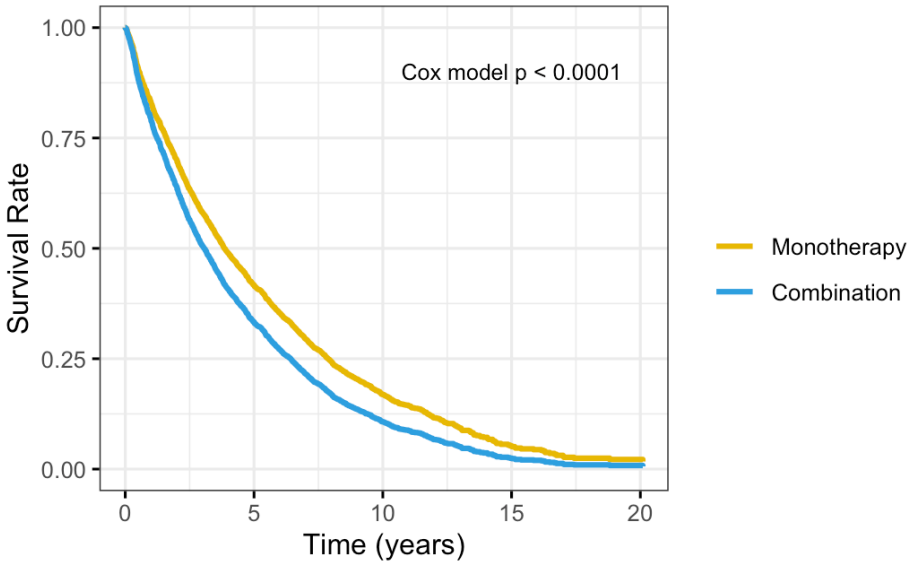


Figure 33: Overall survival according to PAH treatment strategy (n = 561)

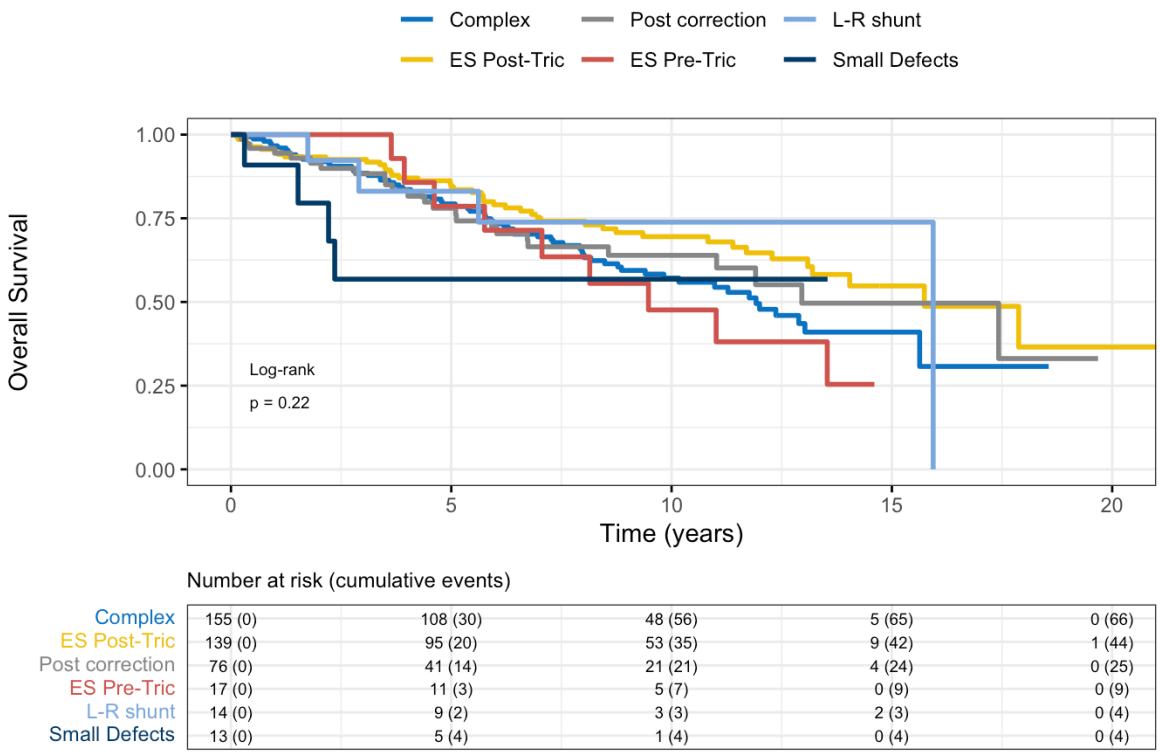


Figure 34: Overall survival according to PAH-CHD group (n= 414)

Acronyms: ES, Eisenmenger Syndrome; L-R, left-to-right; Post-tric, Post-tricuspid; Pre-tric, Pre-tricuspid.

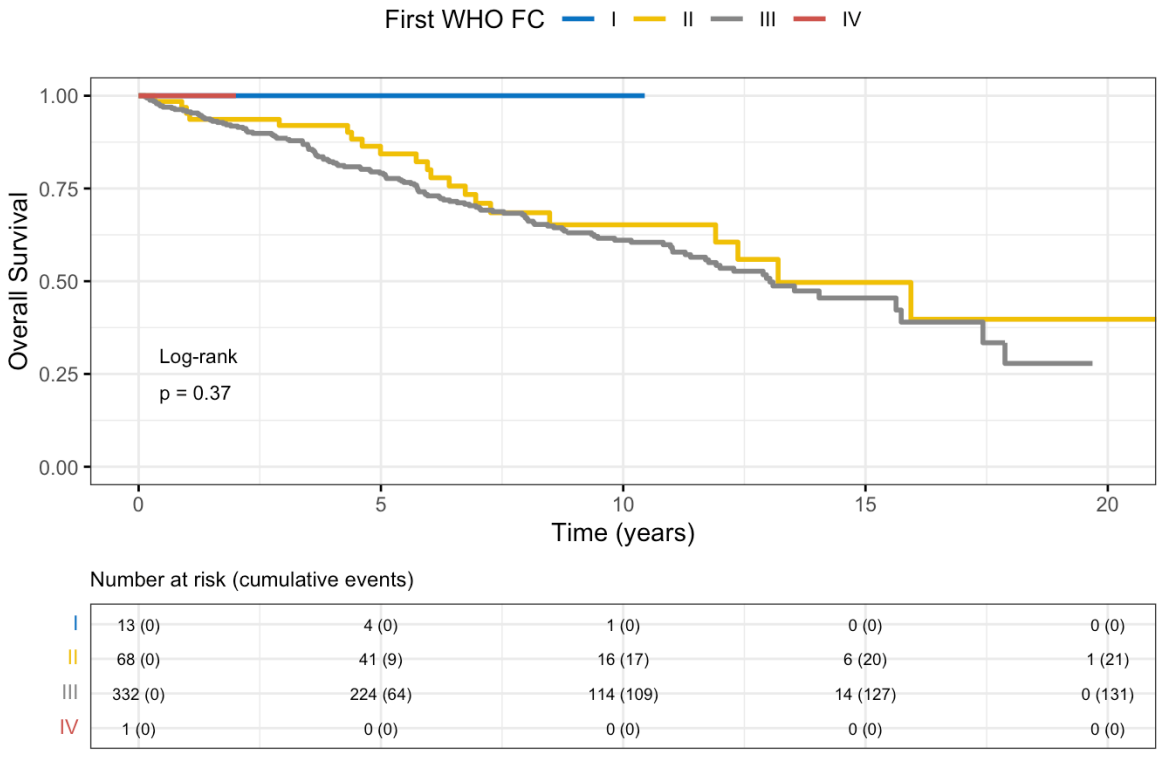


Figure 35: Overall survival according to initial WHO FC (n = 414)

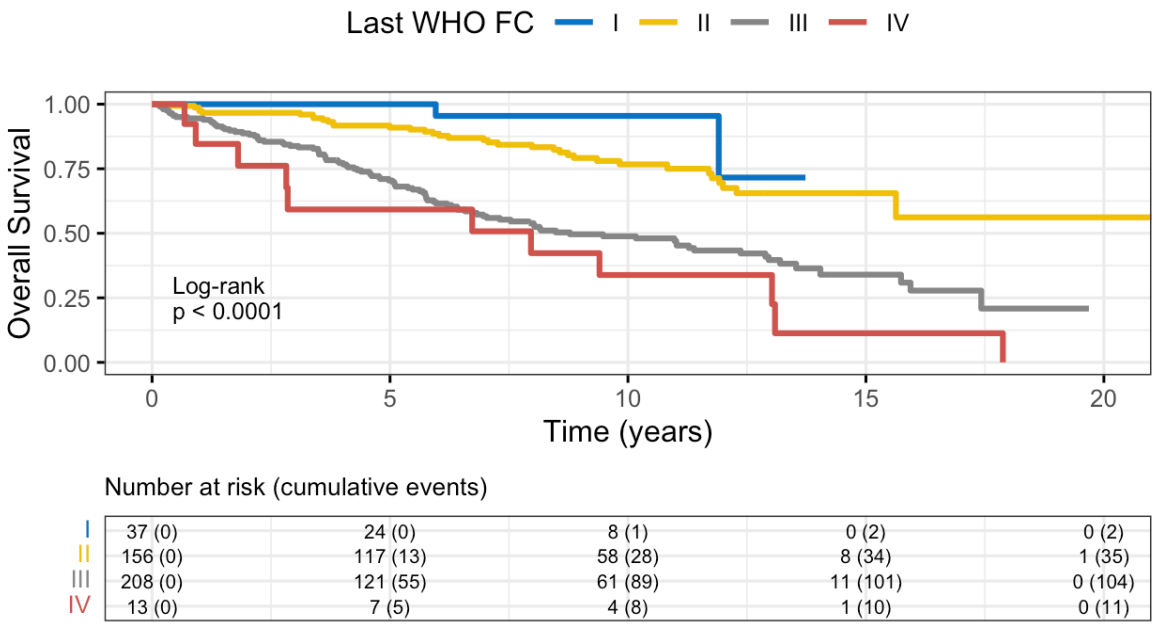


Figure 36: Overall Survival according to WHO FC at the end of the follow-up (n = 414)

5.6 Base case model

The following tables present the results of the CEA analysis, categorized by population subgroups utilized in the model **(Tables 30 to 35).** On the whole, PAH monotherapy demonstrated a marginal advantage in terms of QALYs (less than 2 QALYs) over the course of a lifetime across all 3 models. Nonetheless, across model 1 and 2, i.e., all PAH-CHD and uncorrected PAH-CHD groups, combination therapy resulted in reduced overall costs, particularly in terms of medical costs. The ICER for both models resulted in £7.446,00/QALY and £5.987,00/QALY, respectively, hence aligning the ICER with the cost-effectiveness threshold set by the NHS, which ranges from £20,000 to £30,000 per QALY. A detailed analysis of the transition probabilities showed that, for all PAH-CHD and unrepaired PAH-CHD models, while monotherapy increased years of life gained in WHO FC I-II (**Supplementary Table S7 in Appendix)**, the combination therapy did the same for more advanced FC classes, and almost doubled the life-years for patients in advanced FC IV **(Supplementary Table S8 in Appendix).** For corrected PAH-CHD, the base case analysis resulted in an ICER well above the NHS WTP threshold at £82.306,00/QALY for both strategies. Due to the low number of patients included in the model and similar transition probabilities between states, the model was driven by the differences in hazard rates between transitions "remaining in WHO FC IV" or "transition from WHO FC IV or to Death", which were higher in the Monotherapy group,

hence elevating the costs without significant gain in QALYs or life-years **(Supplementary Table S8 in Appendix).** Moreover, the costs for corrected PAH-CHD were markedly raised when compared with the previous two models, led by the elevated cost of Prostanoid therapy and relatively higher number of patients in advanced functional class states.

5.6.1 Model 1: All PAH-CHD Population

Table 30: Base case results (per person) for all the PAH-CHD population

All PAH-CHD Population					
Strategy	**Total Cost (£) with 95% CI**	**Total QALYs with 95% CI**	**Cost Difference (£) with 95% CI**	**Incremental QALY with 95% CI**	**ICER (£/QALY)**
Monotherapy	159.450,00 (84.526,00 to 285.526,00)	9,05 (7,55 to 10,35)	NA	NA	NA
Combination	146.036,00 (82.473,00 to 249.746,00)	7,25 (5,70 to 8,56)	-13.413,00 (-64.810,00 to 20.663,00)	-1,80 (-3,40 to 0,24)	7.446,00

Acronyms: CI, confidence intervals; ICER: incremental cost effectiveness ratio; NA: Not applicable; QALY: quality-adjusted life years.

Table 31: Detailed costs according to the treatment strategy for all PAH-CHD population

Strategy	**Cost of Drugs (£) with 95% CI**	**Cost of Medical Care (£) (hospitalizations, outpatients and exams) with 95% CI**
Monotherapy	74.780,00 (62.894,00 to 84.373,00)	84.670,00 (12.448,00 to 207.680,00)
Combination	75.176,00 (59.270,00 to 88.096,00)	70.861,00 (12.199,00 to 175.331,00)

Acronyms: CI, confidence intervals.

5.6.2 Model 2: Unrepaired PAH-CHD Group

Table 32: Base case results for the unrepaired PAH-CHD subgroup

Strategy	Total Cost (£) with 95% CI	Total QALYs with 95% CI	Cost Difference (£) with 95% CI	Incremental QALY with 95% CI	ICER (£/QALY)
Monotherapy	151.172,00 (78.356,00 to 286.391,00)	8,23 (5,84 to 10.00)	NA	NA	NA
Combination	143.023,00 (76.442,00 to 256.018,00)	6,86 (5,08 to 8,41)	-8.149,00 (-58.208,00 to 32.203,00)	-1,36 (-3,11, 0,62)	5.987,00

Acronyms: CI, confidence intervals; ICER: incremental cost effectiveness ratio; NA: Not applicable; QALY: quality-adjusted life years.

Table 33: Detailed costs according to the treatment strategy for the unrepaired PAH-CHD subgroup

Strategy	Cost of Drugs (£) with 95% CI	Cost of Medical Care (£) (hospitalizations, outpatients and exams) with 95% CI
Monotherapy	68.751,00 (49.921,00 to 82.338,00)	82.422,00 (12.609,00 to 215.743,00)
Combination	71.744,00 (53.744,00 to 87.617,00)	71.279,00 (10.893,00 to 179.369,00)

Acronyms: CI, confidence intervals;

5.6.3 Model 3: PAH after CHD Defect Correction Group

Table 34: Base case results for the repaired PAH-CHD subgroup.

Strategy	Total Cost (£) with 95% CI	Total QALYs with 95% CI	Cost Difference (£) with 95% CI	Incremental QALY with 95% CI	ICER (£/QALY)
Monotherapy	905.135,00 (104,560,00 to 4.591.942,00)	12,10 (5,90 to 15.80)	NA	NA	NA

Combination	729.833,00 (130.241,00 to 2.676.622,00)	9,97 (4,79 to 14,24)	-175.302,00 (-3.028.759,00 to 1.624.015,00)	-2,13 (-8,27 to 4,67)	82.306,00

Acronyms: CI, confidence intervals; ICER: incremental cost effectiveness ratio; NA: Not applicable; QALY: quality-adjusted life years.

Table 35: Detailed costs according to the treatment strategy for repaired PAH-CHD subgroup

Detailed Costs	Cost of Drugs (£) with 95% CI	Cost of Medical Care (£) (hospitalizations, outpatients and exams) with 95% CI
Monotherapy	113.251,00 (50.043,00 to 155.259,00)	791.884,00 (35.905,00 to 4.436.683,00)
Combination	115.473,00 (52.063,00 to 180.982,00)	614.359,00 (41.657,00 to 2.502.699,00)

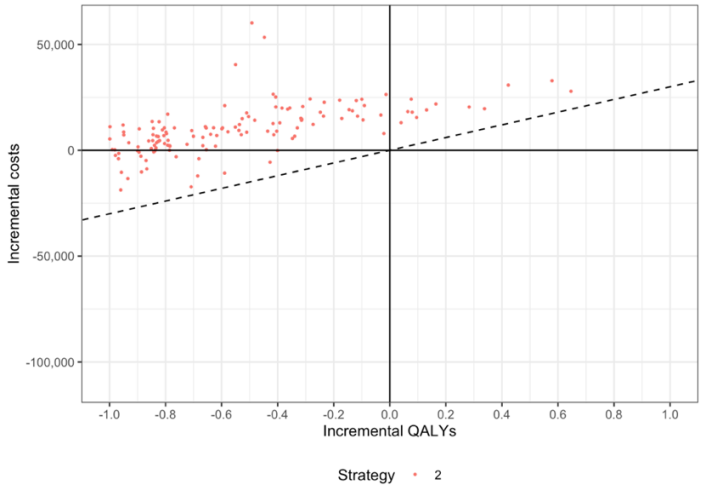
Acronyms: CI, confidence intervals.

5.7 Probabilistic Sensitivity Analysis

The probabilistic results for each PAH model are displayed in **Figures 38, 39 and 40.** Overall, the PSA analysis confirmed that, for model 1 and model 2 combination therapy was superior, based on small differences in QALYs and reduced overall costs. For the subgroup PAH with corrected CHD defects, there were no significant differences between the two strategies.

5.7.1 Model 1: All PAH-CHD Population

A



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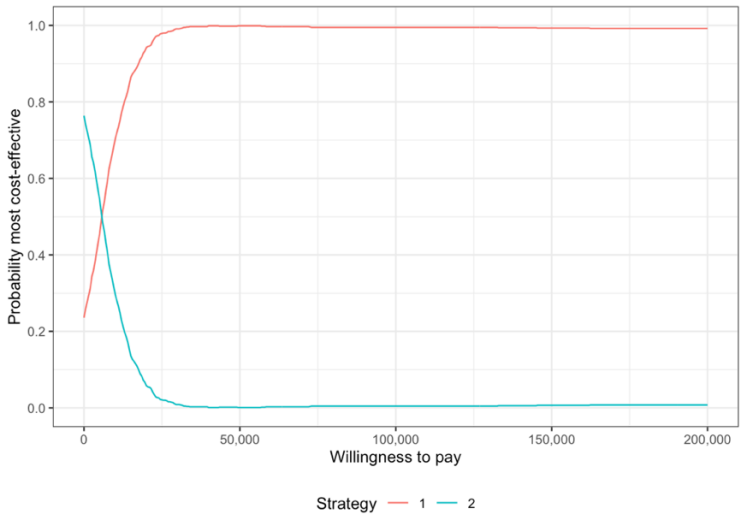
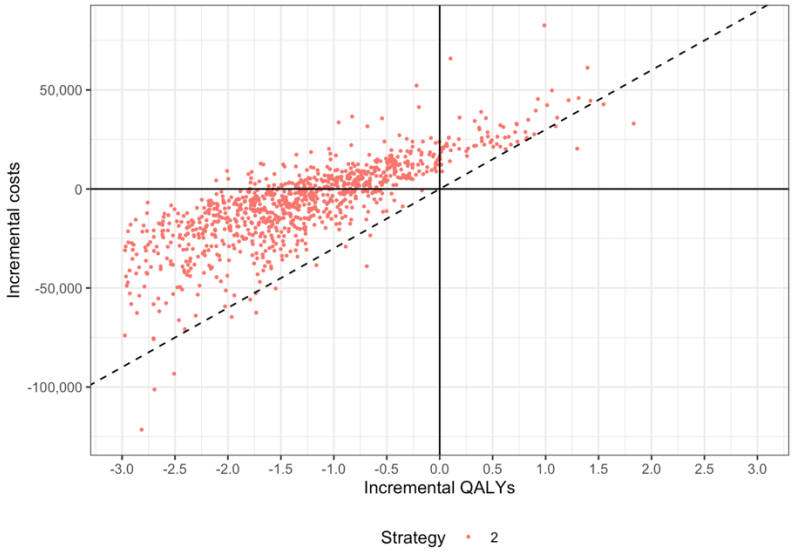


Figure 37: PSA results for the all PAH-CHD population. **A)** CEA graph over the 1.000 simulations; **B)** Probability of cost-effectiveness (x axis) of both strategies when different WTP thresholds are considered (y axis).

Costs are expressed in £. WTP is expressed in £/QALY. Acronyms: QALYs, Quality-Adjusted Life years. Strategy 1: PAH Monotherapy; Strategy 2: PAH Combination therapy

5.7.2 Model 2: Unrepaired PAH-CHD Group

A



B

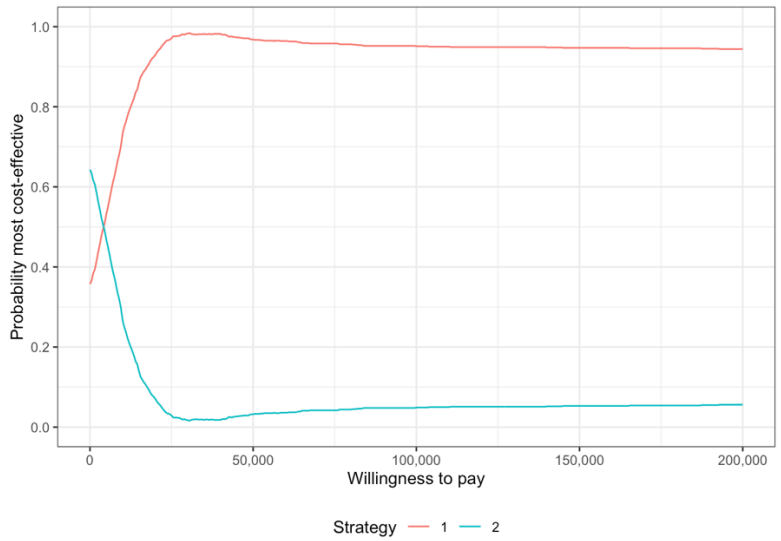
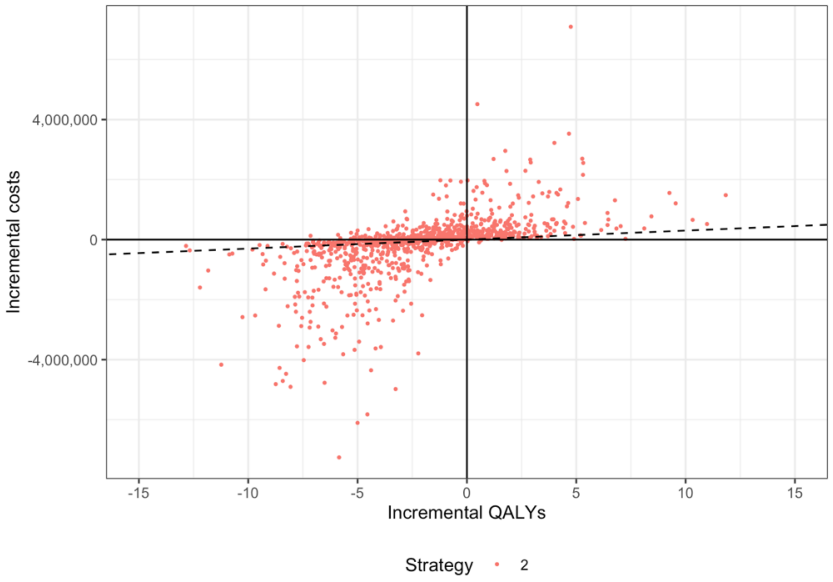


Figure 38: PSA results for unrepaired PAH-CHD subgroup. **A)** CEA graph over the 1.000 simulations; **B)** Probability of cost-effectiveness (x axis) of both strategies when different WTP thresholds are considered (y axis).

Costs are expressed in £. WTP is expressed in £/QALY. Acronyms: QALYs, Quality-Adjusted Life years. Strategy 1: PAH Monotherapy; Strategy 2: PAH Combination therapy

5.7.3 Model 3: PAH after CHD Defect Closure Group

A



B

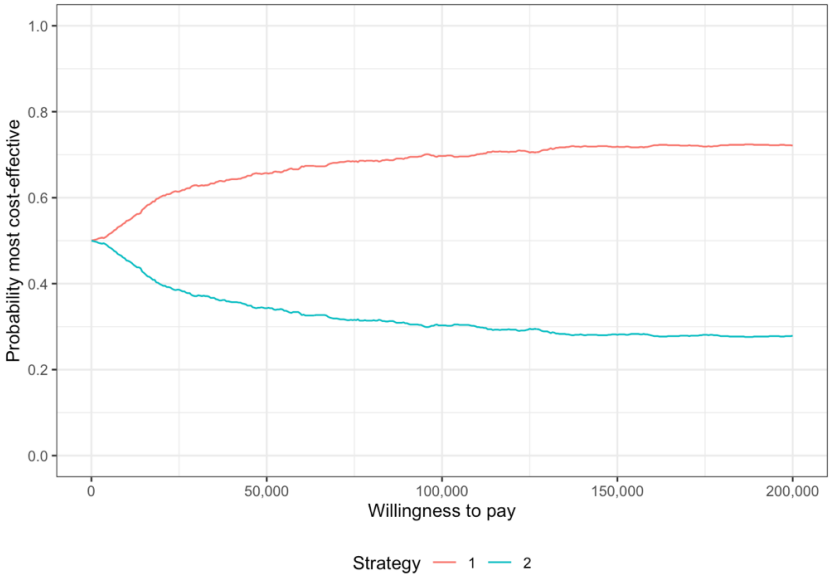


Figure 39: PSA results for PAH after CHD Defect Closure Group subgroup. **A)** CEA graph over the 1.000 simulations; **B)** Probability of cost-effectiveness (x axis) of both strategies when different WTP thresholds are considered (y axis).

Costs are expressed in £. WTP is expressed in £/QALY. Acronyms: QALYs, Quality-Adjusted Life years. Strategy 1: PAH Monotherapy; Strategy 2: PAH Combination therapy.

6. Discussion

6. Discussion

Part A) Cost-Effectiveness Analysis of Providing Free Dental Care for Patients at High Risk of IE

My work shows that providing free dental care for patients with increased IE-risk patients is likely to be both cost-effective and cost-saving for an NHS perspective. As far as we know, this is the first study exploring the cost-effectiveness of offering free dental care to adults at high risk of IE in the NHS setting. This work goes a step beyond the work by Franklin et al. in 2018, who demonstrated that offering antibiotic prophylaxis for risky dental procedures to individuals at high risk of IE (amoxicillin or clindamycin) was both cost-saving and cost-effective for the NHS, with an average cost saving closely to £40,00 per year per person and an incremental QALY gained of 0,0012 in the Penicillin vs no prophylaxis strategy.

Using the NHS estimates of the prevalence of ACHD (4 per 1.000 adults), 211.560 adults are currently living with CHD in the UK. Of these, 1,33 per 1.000 person-years might develop an IE according to Cahill et al., which would result in 281 cases of IE per year (52). However, during the year of 2020-2021, more than 14.000 hospitalizations for IE were recorded in England alone, 98% of which affecting adults. Therefore, not only would the ACHD population benefit from measures than can lower the risk of IE, but also all individuals with a PCC. Using the age-adjusted prevalence of PCCs in the UK adult population, well over 1 million UK adults (1.763.840) would be eligible for free dental care, with an estimated yearly cost of 51 million pounds in copayment (assuming only 1 dental check-up) versus 93 million pounds in the free care strategy.

Free full dental coverage for adults is only offered in a few countries worldwide (e.g. Austria, Mexico, Poland, Spain and Turkey) (80). Nevertheless, a deeper look into these countries' dental healthcare models shows that, although basic care is mostly covered (financed for example by social security or mandatory private insurance), it is usually limited to basic check-ups, voucher utilization and is severely limited by long waiting times (165). In the UK, the NHS establishes few exceptions to the co-payment model, for example children, pregnant women and young mothers, and some low-income beneficiaries. According to the results of our model, extending the number of beneficiaries to include patients at increased risk of IE is reasonable, both from a medical and a healthcare economics perspective.

This model has significant limitations:

1) Both the prevalence of IE and the effectiveness of the free dental care strategy carry an important degree of uncertainty in the model. The uncertainty around the risk of IE was extensively examined in literature, and it is consistently around 0,003 - 0,005 cases per 1.000 high-risk-patients per patient-year. The sensitivity analysis showed that offering free dental care would be cost-effective is most cases, except in the scenario where the model uses the general population IE incidence, because the risk is quite low. The uncertainty around the effectiveness of free dental care was more difficult to ascertain due to the lack of studies. We used the estimated burden of poor dental hygiene in IE cases to calculate the RR directly, as it led to more conservative values of effectiveness. Had we used the proportion of cases attributed to poor dental care as a risk reference to calculate the RR (this would be 0,7), it would lead to an increase effectiveness in the model.

2) The mortality rate applied in the model for the "well" state was taken from the general UK life-tables. However, congenital patients who are at high-risk for IE often have a prosthetic heart valve, history of IE or established cyanotic condition when they transition to ACHD care. Therefore, even if no major IE-associated event occurs during their lives, their survival is likely to be overestimated by using the general population mortality rate. A similar logic can be applied to QALYs, which may be overestimated in the model when considering the background medical history and comorbidities of this specific population.

3) The costs for an IE admission may be underestimated in this model for different reasons. Firstly, the costs used in the model for cardiac surgery admission were conservatively chosen to reflect single-valve IE, while some patients need multivalve surgery during an IE episode. Secondly, for simplicity purposes, no other complications of IE were modelled beyond the need for surgical interventions; nevertheless, other complications such as renal dysfunction, acute heart failure, embolic strokes and neurological problems are frequent in IE and have the potential for significant long-term sequelae (57,58).

Part B) Cost-Effectiveness Analysis of Combination PAH Therapy in PAH-CHD patients

This study presents compelling evidence supporting the cost-effectiveness of combination PAH therapy for patients with PAH associated with congenital heart defects (CHD), particularly for those who did not undergo previous repair. Notably, this study is pioneering in its exploration of combination PAH therapy in individuals with unrepaired CHD, offering a comprehensive assessment of its potential benefits beyond all-cause mortality, specifically focusing on improvements in quality of life, remaining in healthier states and avoiding disease progression.

One of the key strengths of this CEA model lies in its utilization of real-world data, which is primarily generated and employed for clinical and audit purposes. As a result, the model's outcomes hold direct applicability to our specific population. By incorporating a diverse range of ages, genders, genetic conditions, and CHD conditions, the model accurately reflects the patient demographics encountered in PAH - ACHD clinics. Furthermore, the inclusion of serial long-term individual patient data proves invaluable in developing a model that acknowledges 1) the heterogeneity in the timing of clinical status changes across individuals; 2) the variances in response to PAH treatment across time, which might depend not only on the drugs but also on other factors, such as age group, genetic conditions, to name a few.

Studies in the field of PAH-CHD are often limited by a reduced number of patients included and short follow-up time. One of the major strengths of my work is the long-term follow-up of over 400 patients, making it, as far as we are aware, one of the largest series analysed to date in a single centre. The guidelines' endorsement of combination therapy in unrepaired PAH-CHD is hindered by the scarcity of supporting literature. Evidence exists mainly for monotherapy, albeit still limited. Dimopoulos et al. followed 229 ES patients with and without PAH therapies and showed an increased survival over a four-year follow-up for those on treatment (115). In this study, the majority of ES patients were treated with monotherapy using Bosentan (73%) or Sildenafil (25%), with a minority later transitioning to combination therapy (6%) during follow-up. D'Alto et al. also reported improvements in WHO FC, oxygen saturations, and 6MWT distance travelled in ES patients on Bosentan (166). Despite this evidence, PAH therapy is still initiated relatively late in this population, and recent a Spanish study following 150 ES patients (both with pre- and post-tricuspid shunts), reported that PAH treatment was initiated when individuals were in a more advanced clinical status, including a higher WHO FC, lower oxygen saturations and reduced RV function assessed by tricuspid annular plane systolic excursion

(TAPSE) when compared with the non-treated group (129). Presence of pre-tricuspid shunts, monotherapy at baseline and WHO FC III-IV were identified as independent predictors of death. Few studies have focused on the efficacy of combination therapy in unrepaired PAH-CHD, and the ones that did showed some improvements in WHO FC, but varied results regarding the 6MWT distance or improvement in resting saturations (122,123). Gradually, clinical practice has shifted towards earlier combination therapy in ES over the last few years and, preliminary results from Escribano et al. published in 2022 described that the majority of ES patients (n=168) under their care were treated with combination PAH regimes using and early stepwise approach (167). This thesis adds to this data, showing that combination therapy tends to be started at older ages and advanced functional classes when compared with monotherapy, hence its true benefits need to be adjusted for those potential confounding variables.

This work has the following limitations:

1) The utilities employed in the model were not specifically developed for patients with PAH and CHD, which introduces the possibility of misestimation. However, there have been recent advancements in the development of other tools for assessing Health-Related Quality of Life (HRQoL) in PH patients, such as the emPHasis-10 score or the CAMPHOR scores (168,169). The emPHasis10 score, introduced in 2014, is a relatively new questionnaire-based tool designed to evaluate the quality of life in PH patients, including those with CHD, and has been demonstrated as a predictor of mortality in PAH-CHD patients (170,171). However, its association with WHO FC in this population and context remains unclear, and as a result, it was not incorporated into this model. Moreover, although our centre has been utilizing this tool since 2014, patients who were being monitored prior to that year lack previous data.

2) The impact of the COVID-19 pandemic was not included in this study. During the year of 2020 and part of 2021, hospital admissions and general exams were quite restricted in our center, and most patients contacts with the clinical team were either by video or telephone appointments, with the exception of emergency situations. The potential for functional class deterioration during these two years is probably minimized in our data, as patients with PAH-CHD were all advised to shield and avoid leaving their homes for many months.

3) This study did not incorporate the reasons for low-adherence or stopping PAH treatment, for example due to side effects or pregnancy. Therefore, the cost and utility-loss due to possible side-effects were not included in the model. Low adherence to treatment is estimated around

11.8%, and is reported to affect more PAH patients on monotherapy rather than combination regimes (172). Future models should account for such constraints.

4) In the real-world data used for this thesis, some transitions between states in the model had a lower number of patients. For this reason, the model was adapted and covariates removed to avoid over-fitting. This was especially true in transitions from the subgroup PAH-CHD repaired and advanced WHO FC states, which included few patients at the start and patients did not remain in the same state for long (due to the high mortality). The limited data on FC IV patients reflects what is observed in medical practice but did not allow the use of a more complex (and comprehensive) model adjusted by clinically relevant covariates. Therefore, the result of non-cost-effectiveness of combination therapy is probably underestimated due to the low number of cases and events recorded in this population.

5) Real-data usage of third line therapy (typically with Prostanoids) were not used in the model for simplicity and was instead estimated as a proportion of cases in FC IV. Exploring the role of a third treatment agent within these cost-effectiveness models, beyond monotherapy and dual combination, could not only increase the models' similarities with current clinical practices but also add significant information of its benefits, now that PAH treatment algorithms are shifting towards maximal therapy wherever possible. Triple therapy with iPDE5, ERA and medication acting on the Prostacyclin pathway, often intravenous or subcutaneous, have demonstrated a clear survival benefit in patients with advanced disease (WHO FC IV) and other high-risk features. However, their high monetary cost for the NHS and their impact on patients' quality of life and day-to-day activities, whether administered subcutaneously, intravenous or by inhalation, cannot be overlooked. The oral alternative, Selexipag (a prostacyclin receptor agonist), has been successfully used Group 1 (PAH) patients, but patients with unrepaired PAH-CHD were excluded from clinical trials and there is little information from observational studies. Small series of cases using Selexipag in ES patients have been reported, but it is necessary to gather more information to better assess its potential in this group (173,113). Due to the limited number of patients on Prostanoids or Selexipag in our database, we were unable to include them in the present model. To address this limitation, it is important to explore alternative approaches, such as machine learning models, which have the capability to work effectively with small sample sizes. These tools should be considered in future research in this area.

6) The utilization of real-world data from a single center limits the generalizability of the results on a global scale. Within a single tertiary healthcare center, practices are often standardized or at the very least consistent among team members, facilitated by regular multidisciplinary team discussions. The logical next step for the CEA would be to incorporate multicenter data from

well-designed registries to enhance the external validity and broaden the applicability of the findings across multiple healthcare settings.

7) In this model, the majority of patients were treatment-naïve, while a small minority had been receiving PAH treatment for over a year prior to commencing follow-up at our center. We included these data for a more diverse, real-life representation of this population. However, it is important to note that the initial benefits of PAH therapy, whether administered as single or combination treatment, may be underestimated in this model. As a result, the model may not fully reflect the role of initial combination strategy in treatment-naïve, unrepaired PAH-CHD patients. Collecting and utilizing multicenter data, including from hospitals where dual therapy is initiated earlier, might be key to answer this question.

7. Conclusions

7. Conclusions

1. Offering free dental care to patients at high-risk of IE appears to be cost-effective and cost-saving, based on current WTP NICE thresholds. Moreover, the different scenarios explored showed that both young and older ACHD patients with predisposing cardiac conditions can benefit from this strategy. While the incidence of IE is low and the number of cases prevented is also low, the high cost and long-term health impact of IE justify the implementation of a free dental care strategy for patients at increased risk.

2. From a national healthcare perspective point of view, the utilization of combination therapy for adult patients with PAH associated with CHD, particularly in unrepaired CHD, is a cost-effective approach. Although the difference in quality of life between monotherapy and combination treatment strategies may not be substantial, the significant increase in life-years gained, especially in advanced functional states, justifies the use of combination therapy, despite its higher treatment cost.

3. Further studies, preferably prospective in nature, are necessary to evaluate the effectiveness of combination therapy in unrepaired PAH-CHD patients with PAH. However, due to the rarity of this condition and the heterogeneity of anatomy and physiology, study design and analysis can be challenging. Consequently, multicentric retrospective or prospective studies are the most viable option for examining the long-term progression of these diseases and the impact of various treatment regimens. These studies should preferably employ models that allow for a low number of subjects with a high number of serial data points, ensuring reliable and replicable results.

4. In order to bridge the gap between patients and healthcare management, policy decisions regarding new drugs, procedures, and technologies should actively involve clinical practitioners, such as doctors and nurses. Their unique position and expertise allow them to provide valuable insights in the design and interpretation of studies. Equipping clinicians with fundamental skills in cost-effectiveness studies and data analysis is crucial for developing cost-effectiveness studies that accurately mirror the clinical impact of diseases, both for patients and the healthcare system. By doing so, clinicians can play a vital role in shaping the future of national health systems and

influencing budget allocation to ensure optimal medical care for their patients is always properly funded.

8. Future Lines of Research

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For future research, the data obtained from the pulmonary arterial hypertension (PAH) model will undergo analysis using machine learning techniques. These techniques are particularly suitable for datasets with a high number of variables compared to the number of individuals (known as "n<q" models). Approaches such as Lasso models or Neural Networks have the ability to effectively handle a large number of variables and work with highly correlated features. By incorporating these techniques, the model gains the advantage of improved discrimination capabilities and increased flexibility, resulting in a more generalized and applicable model for heterogeneous populations.

From a cost-effectiveness standpoint, cost-effectiveness analysis (CEA) models can be enhanced by integrating quality-of-life data collected through HRQoL scores specifically designed for patients with PAH-CHD. However, currently, such data are not readily available. To address this gap, our research group is actively engaged in the development of quality-of-life scores tailored to adult patients with PAH-CHD. Additionally, we are in the process of establishing a multicentre database for this specific population within the UK. In a later stage, we hope to also engage with other European centres in a collaborative research platform, where data can be gathered across Europe and be widely and readily available for analysis by all contributing researchers.

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9. Bibliography

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10. Appendix

10. Appendix

10.1 Supplementary Figures

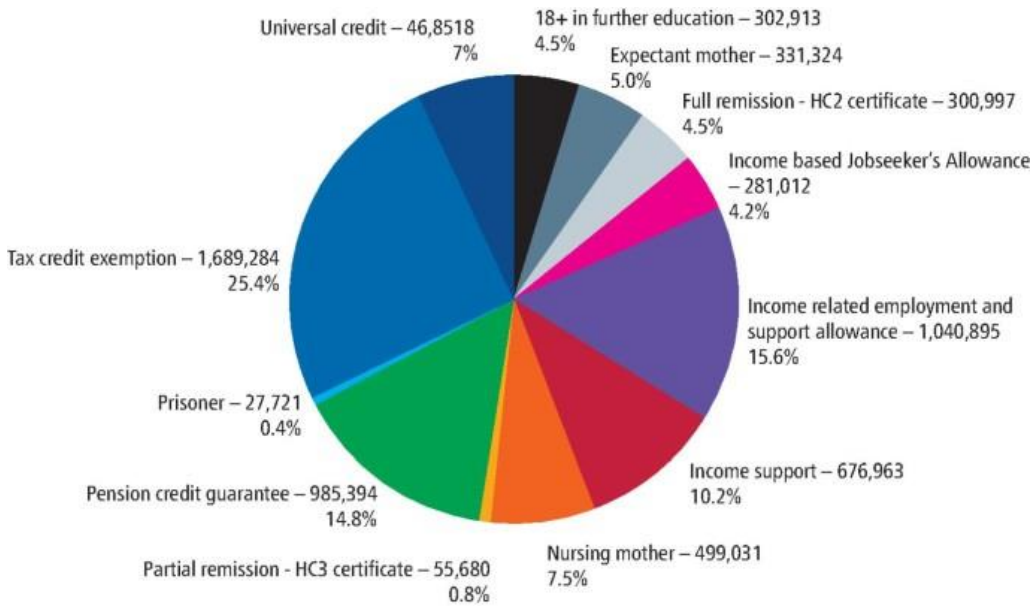


Figure S1: Fee-exempt adult claims by exemption type in 2018-2019 from (90)

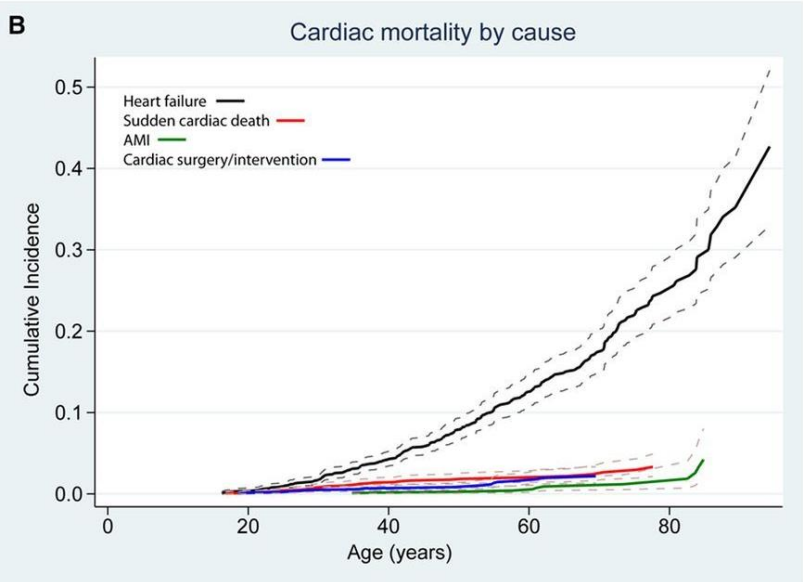


Figure S2: Cumulative incidence of death by fours cardiac causes, including heart failure (black line). Graph by Diller et all (2015), (9)

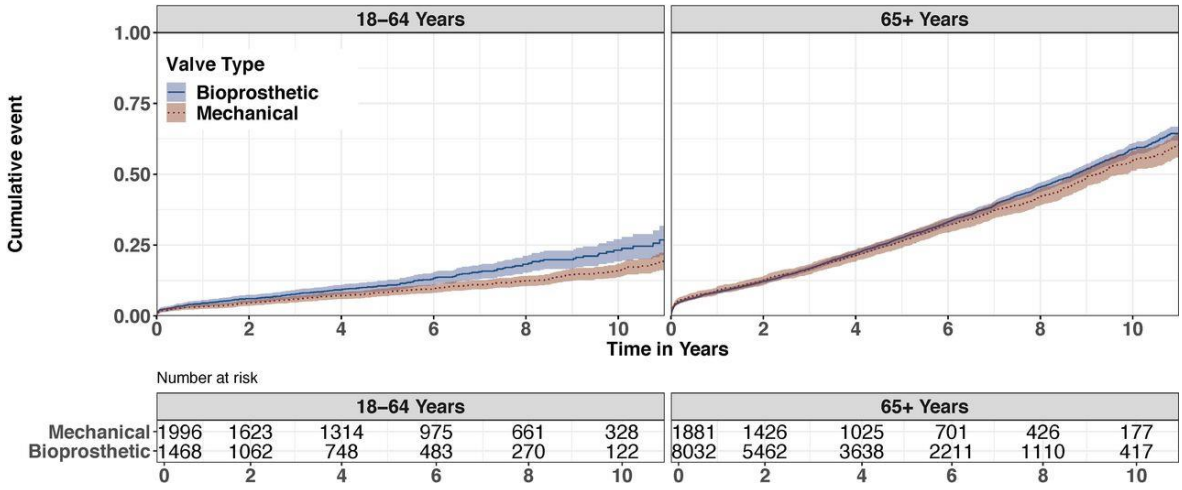


Figure S3: Cumulative incidence of death after valve replacement by age groups. Graph by Sotade et all. (145).

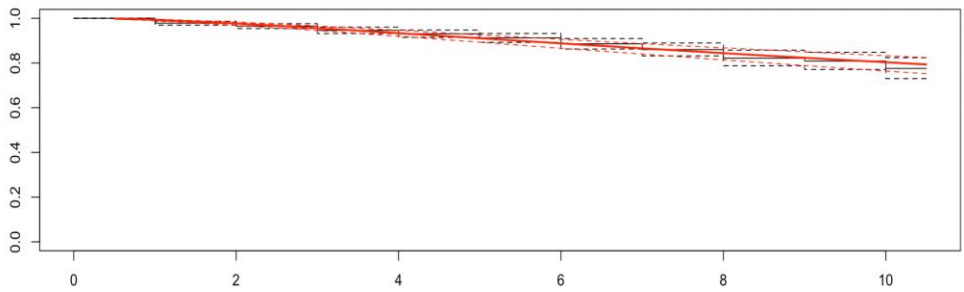


Figure S4: Goodness-of-fit for survival data fitted with a parametric distribution (Log-normal) for patients between 18-64 years old after a valve replacement.

x axis: time (years). y axis: cumulative survival (%).

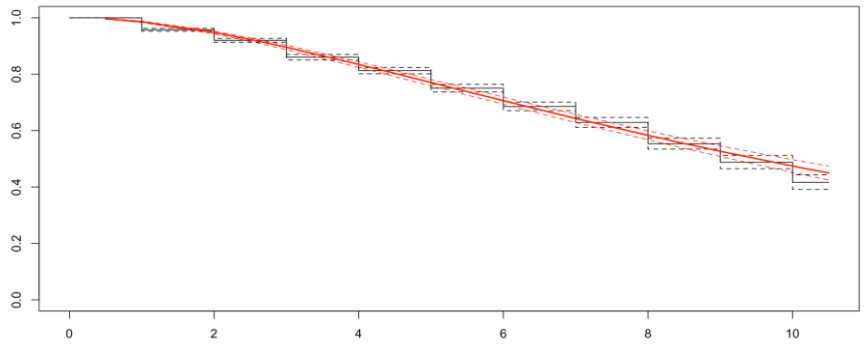


Figure S5: Goodness-of-fit for survival data fitted with a parametric distribution (Generalized Gamma) for patients between ≥65 years old after a valve replacement.

x axis: time (years). y axis: cumulative survival (%).

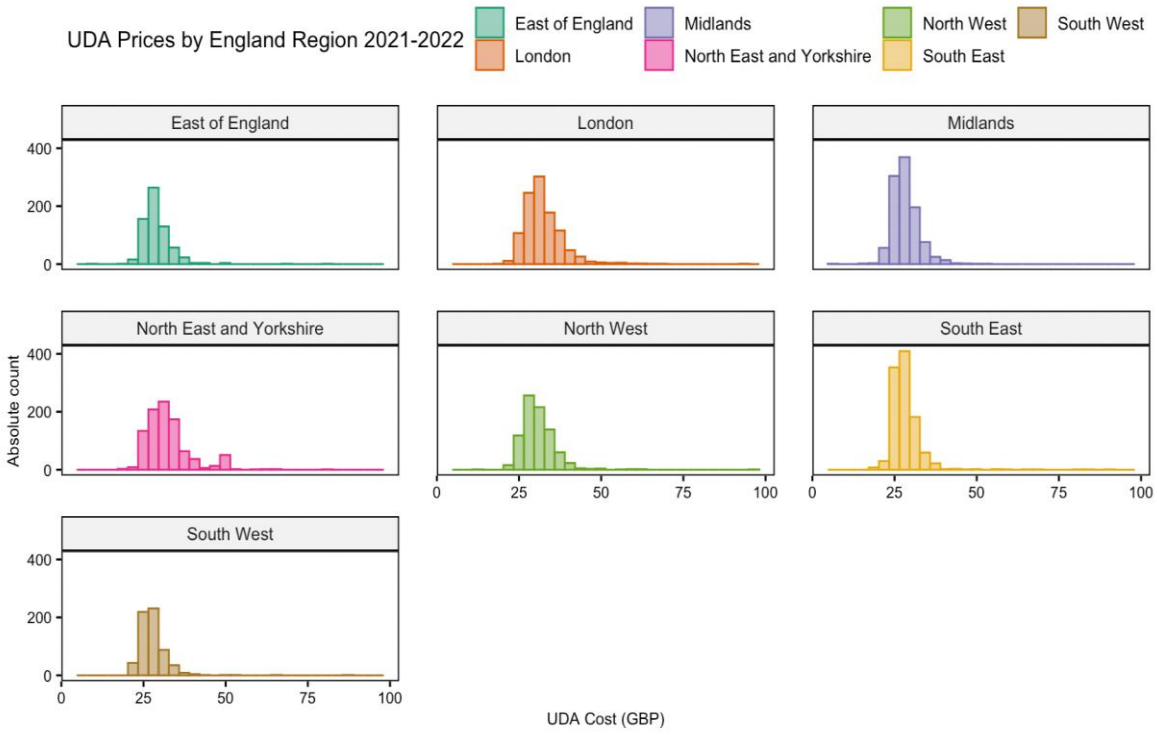


Figure S6: Histograms displaying the costs of UDAs (in GBP, £) by England Region in 2021-2022.

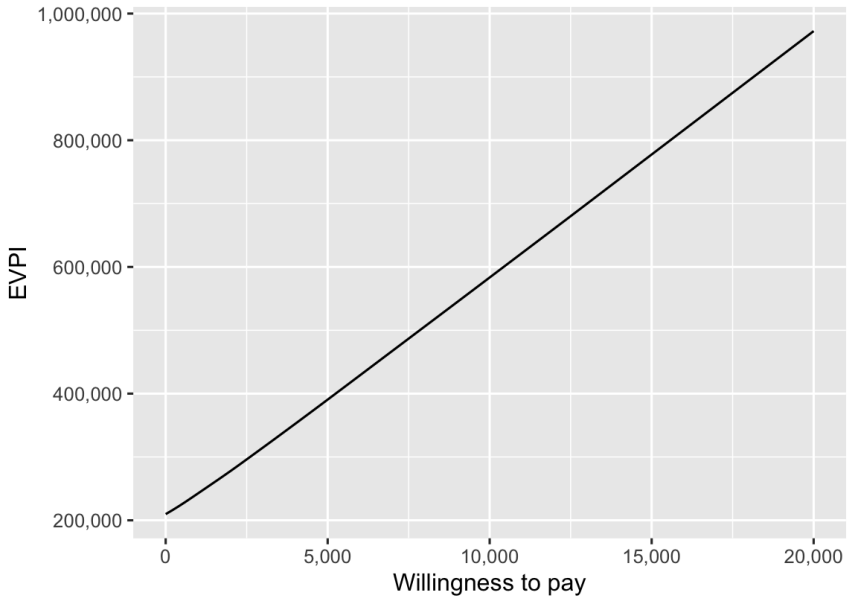
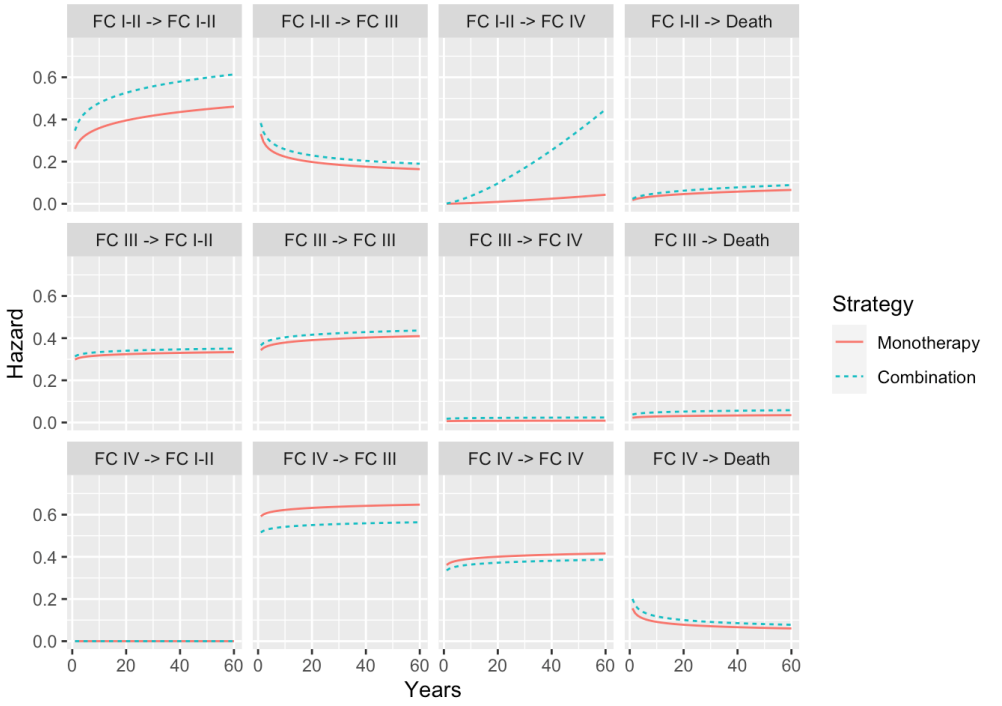
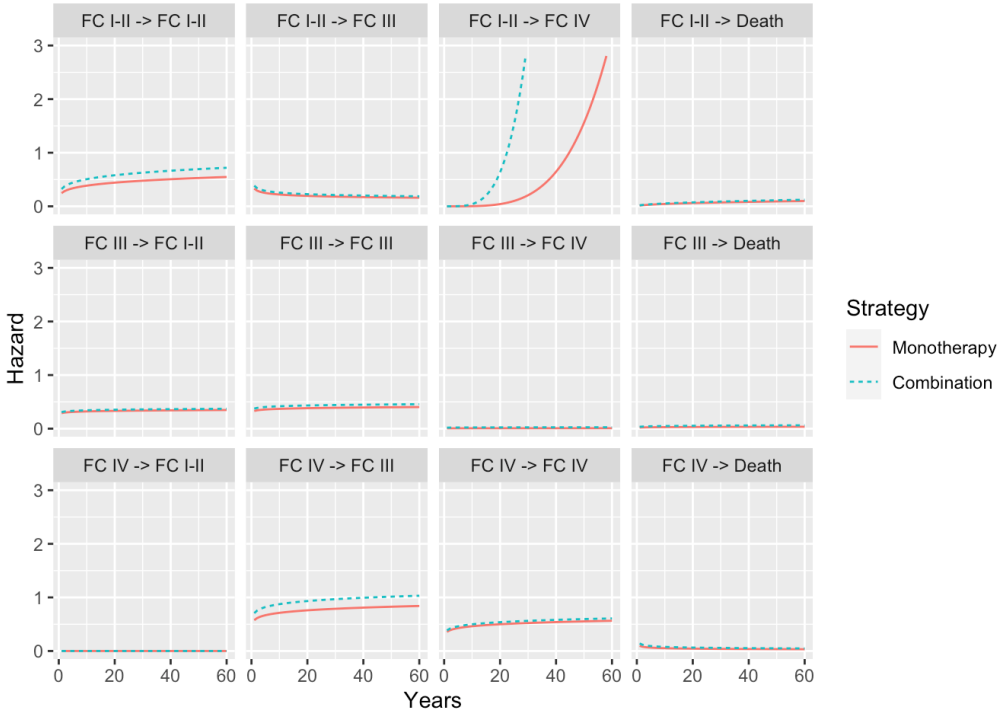


Figure S7: Graph displaying the Expected Value of Perfect Information (EVPI) for free dental care strategy.

A


FC I-II -> FC I-II
FC I-II -> FC III
FC I-II -> FC IV
FC I-II -> Death
FC III -> FC I-II
FC III -> FC III
FC III -> FC IV
FC III -> Death
FC IV -> FC I-II
FC IV -> FC III
FC IV -> FC IV
FC IV -> Death
Hazard
0.0
0.2
0.4
0.6
0
20
40
60
Years
Strategy
Monotherapy
Combination

B


FC I-II -> FC I-II
FC I-II -> FC III
FC I-II -> FC IV
FC I-II -> Death
FC III -> FC I-II
FC III -> FC III
FC III -> FC IV
FC III -> Death
FC IV -> FC I-II
FC IV -> FC III
FC IV -> FC IV
FC IV -> Death
Hazard
0
1
2
3
0
20
40
60
Years
Strategy
Monotherapy
Combination

C

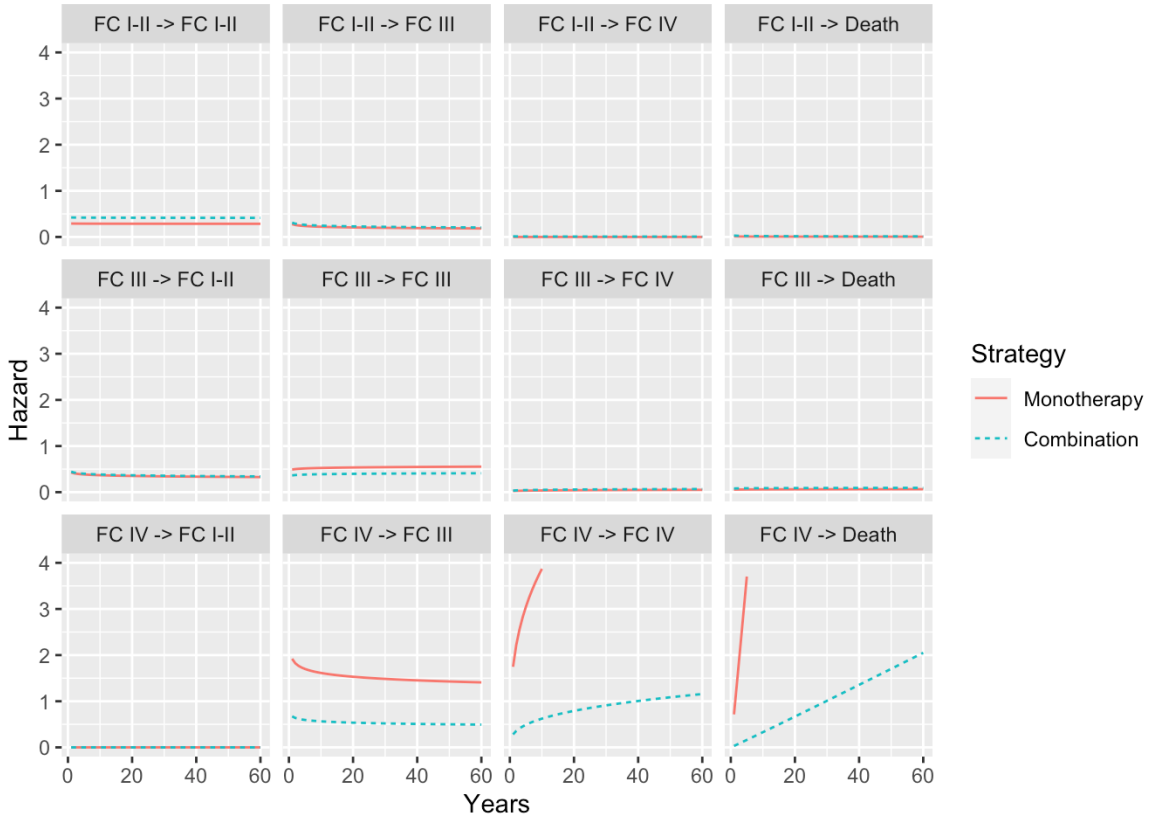


Figure S8: Graphs displaying the derived Hazard Rate for each transition according to treatment strategy for all the PAH-CHD groups. **A) Model 1**: All PAH-CHD population. **B) Model 2:** Unrepaired PAH-CHD subgroup. **C) Model 3**: PAH after CHD Defect Closure Group.

10.2 Supplementary Tables

Table S1: PH Standards, from the National Audit of Pulmonary Hypertension Great Britain, 2020-21(106)

Quality Standards
1. PH centres should participate in the Audit
2. PH centres should see a sufficient number of patients
3. New patients should be diagnosed within 6 months
4a New patients should be seen or discharged within 30 days
4b New PAH/CTEPH patients should be seen or discharged within 30 days
5. Patients receiving a PH drug should have pre-treatment cardiac catheterization
6a Patients should have pre-treatment WHO functional class and an exercise test recorded
6b Patients should have pre-treatment WHO functional class recorded
7. Patients should have a pre-treatment vasoreactivity study recorded
8. New patients should begin drug therapy within 12 weeks of referral
9. Patients receiving a PH drug should have had a PH diagnosis recorded
10. 1st line drug therapy for PAH should be a phosphodiesterase 5 (PDE5) inhibitor
11. Patient quality of life should be recorded
12. Patients receiving a PH drug should have an annual consultation
13. Waiting times for pulmonary endarterectomy should be <4 months
14. Waiting times for BPA should be <18 weeks
15. PH centres should record patient participation in research

Tables S2-S4: Goodness-of-fit parameters from survival curves used in the Dental Care Model

S2: Extrapolate Survival 18-64 years old after valve replacement:

	Parameters	**Log-likelihood**	**AIC**
Weibulll	Shape = 1,46 Scale = 26,71	-564,42	1.132,83
Weibull PH	Shape = 1,46 Scale = 0,008	-564,42	1.132,83
Exponential	Rate = 0,0190	-575,38	1.152,76

Gompertz	Shape = 0,14 Rate = 0,011	-567,30	1.138,61
Log-Logistic	Shape = 1,52 Scale = 24,06	-564,47	1.132,95
Log-Normal	**Meanlog = 3,51** **Sdlog = 1,41**	**-563,81**	**1.131,61**
Generalized Gamma	Mu = 3,49 Sigma = 1,31 Q = 0,14	-563,78	1.133,56

S3: Extrapolate Survival after valve replacement ≥65 years old after valve replacement:

	Parameters	**Log-likelihood**	**AIC**
Weibulll	Shape = 1,67 Scale = 11,55	-6083,12	1.2170,23
Weibull PH	Shape = 1,67 Scale = 0,02	-6083,12	1.2170,23
Exponential	Rate = 0,06	-6362,45	1.2726,90
Gompertz	Shape = 0,19 Rate = 0,03	-6.148,64	1.2301,28
Log-Logistic	Shape = 1,87 Scale = 9,59	-6.089,83	1.2183,65
Log-Normal	Meanlog = 2,32 Sdlog = 1,01	-6.092,31	1.2188,61
Generalized Gamma	**mu = 2,41** **sigma= 0,76** **Q = 0,60**	**-6.079,01**	**1.2164,02**

S4: Extrapolate Survival after IE (Data from Netzer 2002) medical & surgical arm used:

	Parameters	**Log-likelihood**	**AIC**
Weibulll	Shape = 0,75 Scale = 351,74	-259,41	522,83
Weibull PH	Shape = 0,75 Scale = 0,01	-259,41	522,83
Exponential	Rate = 0,003	-261,55	525,01

Gompertz	**Shape = 0,0062** **Rate = 0,00583**	**-258,36**	**520,72**
Log-Logistic	Shape = 0,89 Scale = 213,69	-258,87	521,74
Log-Normal	Meanlog = 5,40 Sdlog = 2,01	-258,91	521,83
Generalized Gamma	Mu = 5,53 Sigma = 1,86 Q = 0,24	-258,86	523,71

Table S5: Yearly healthcare consultations in the PH Service by initial WHO FC

WHO FC initially	Type of Healthcare Interaction	Average of number / Year
WHO FC I	Daycase	2,70
	Inpatient	2,14
	Outpatient	2,02
WHO FC II	Daycase	3,03
	Inpatient	3,54
	Outpatient	2,32
WHO FC III	Daycase	2,72
	Inpatient	3,00
	Outpatient	2,31
WHO FC IV	Daycase	5,30
	Inpatient	3,49
	Outpatient	3,43

Acronyms: WHO FC, functional class from the World Health Organization scale.

Table S6: The goodness-of-fit AIC for each transition fitted to the Weibull distribution for the 3 models.

Transition	Model 1: All PAH-CHD Population	Model 2: Unrepaired PAH-CHD	Model 3: Corrected PAH-CHD
1	1832,73	1446,31	388,91
2	1732,93	1400,36	343,81
3	46,58	29,66	16,70
4	313,21	270,04	146,86
5	2272,38	1936,06	340,02
6	2579,22	2227,05	353,85
7	461,87	400,74	67,39
8	684,24	584,48	109,87
9	14,66	12,71	6,00
10	84,42	72,81	13,64
11	84,83	76,55	13,54
12	56,24	47,57	12,21

Acronyms: CHD, congenital heart disease; PAH, pulmonary arterial hypertension.

Table S7: Average life-years gained in each state, by treatment strategy.

		Model 1: All PAH-CHD Population		Model 2: Unrepaired PAH-CHD		Model 3: Corrected PAH-CHD	
		Mono	Comb	Mono	Comb	Mono	Comb
State	dr	Life-years		Life-years		Life-years	
WHO FC I-II	0	14,19	9,54	11,67	8,69	9,46	6,96
WHO FC III	0	8,50	6,58	8,25	6,49	4,36	3,38
WHO FC IV	0	1,10	1,42	1,40	1,56	0,03	0,01
WHO FC I-II	0,035	8,24	6,20	6,92	5,57	5,74	4,94
WHO FC III	0,035	5,12	4,32	5,12	4,34	2,59	2,34
WHO FC IV	0,035	0,40	0,61	0,61	0,72	0,01	0,01

Acronyms: CHD, congenital heart disease; comb, combination therapy; dr, discount rate; FC, functional class; mono, monotherapy; PAH, pulmonary arterial hypertension; WHO, World Health Organization.

Table S8: Detailed sum of costs, QALYs and time spent in each health state for sample = 1 (n = 561) in the model of "All PAH-CHD".

Strategy	WHO State	Cost category	Costs sum	QALYs sum	LYS sum	Nº transitions	Total time
Monotherapy	FC I-II	Drug	37.578.453,00	4.940,45	6.915,34	4248	6915,34
		Medical	49.314.356,00				
	FC III	Drug	22.088.431,00	2.358,50	4.064,80	3563	4064,80
		Medical	102.876.197,00				
	FC IV	Drug	2.547.080,00	243,85	468,72	571	468,72
		Medical	5.787.405,00				
Combination	FC I-II	Drug	26.436.738,00	2.796,06	3.913,75	4002	3913,75
		Medical	27.909.529,00				
	FC III	Drug	27.962.353,00	2.401,90	4.139,60	3828	4139,60
		Medical	104.769.268,00				
	FC IV	Drug	5.400.900,00	415,97	799,56	1306	799,56
		Medical	9.872.284,00				

Acronyms: CHD, congenital heart disease; FC, functional class; LYS, life-years; PAH, pulmonary arterial hypertension; QALY, Quality-Adjusted Life years; WHO, World Health Organization.

All costs are in £.