DEPARTAMENT OF MATHEMATICS

NOVA SCHOOL OF SCIENCE & TECHNOLOGY

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BSc in Clinical Physiology

SCOPE-15: Syncope Comorbidity Outcomes and Pacemaker Evolution

A 15-Year Retrospective Cohort Study of ILR Interventions

MASTER OF STATISTICS IN HEALTH

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ACKNOWLEDGMENTS

This degree and Thesis have without a doubt been a big journey for me. I have learned many new things and I've adapted to what was expected of me along the way. I would do it all again as it brought me a sense of accomplishment and confidence, I don't normally get to experience. I did have some, well a lot of help, and these people need to be recognized.

First of all, to my teacher and adviser Isabel Natário for putting up with my stress levels and for guiding me through the writing up of this document, my many thanks

To my Chief Celso Camargo and to my colleagues, Laura Pember, Kelly Garrett and Christina Potter, thank you for all the help, be it vetting my initial ideas, helping me create the protocol and guiding me on my journey as a cardiac physiologist.

To Ashford and St. Peter's Hospitals NHS Foundation Trust thank you for letting me use the information I need to be able to do this paper, I am happy to be able to work in a hospital that's prompts the search for further knowledge.

Most Importantly however I want to thank my parents, my sister and my best friend José Portugal, without them lord knows I would have not done this, and I would give up sooner rather than later, thank you for all the support.

ABSTRACT

Introduction
Syncope, a transient loss of consciousness, is a significant healthcare issue due to its high prevalence and diverse causes, leading to substantial morbidity and increased healthcare utilization. Accurate diagnosis and timely intervention are critical to prevent severe outcomes, especially arrhythmias that may necessitate pacemaker implantation.

Methods
This 15-year retrospective cohort study at Ashford and St. Peter's Hospitals NHS Foundation Trust evaluates the impact of various comorbidities and arrhythmias on the timing and likelihood of pacemaker implantation following the use of Implantable Loop Recorders (ILRs). Advanced statistical methods, including the Mann-Whitney U Test and Spearman's rank correlation, logistic regression and time to event analysis, were used to identify key risk factors.

Results
In our study significant associations were identified between comorbidities such as high cholesterol, diabetes, hypertension, and ischemic heart disease and the need for pacemaker implantation. Key arrhythmias, including sinus pauses and Atrioventricular block (AV Block), were found to be critical indicators for pacemaker therapy. The mean duration from ILR implantation to pacemaker Implantation was 364.25 days, with a median of 190 days.

Conclusion
These findings point out the importance of personalized patient management and continuous cardiac monitoring. High cholesterol and previous arrhythmias are significant predictors for the timing of pacemaker implantation, highlighting the need for targeted interventions.

Keywords: Syncope, Pacemaker, Comorbidities, Arrhythmias, Implantable Loop Recorder, Survival analysis, multivariable logistic regression.

RESUMO

Introdução
A síncope, uma perda transitória de consciência, é um problema significativo de saúde devido à sua alta prevalência e causas diversas, levando a considerável morbidade e aumento da utilização de cuidados de saúde. Diagnóstico preciso e intervenção oportuna são críticos para prevenir resultados graves, especialmente arritmias que podem necessitar de implantação de pacemaker.

Métodos
Este estudo de coorte retrospetivo de 15 anos na Fundação NHS dos Hospitais Ashford e St. Peter's avalia o impacto de várias comorbidades e arritmias no tempo e na probabilidade de implantação de pacemaker após o uso de Registradores de Loop Implantáveis (ILRs). Métodos estatísticos avançados, incluindo o Teste U de Mann-Whitney e a correlação de Spearman, foram usados para identificar os principais fatores de risco.

Resultados
O estudo identificou associações significativas entre comorbidades como colesterol, diabetes, hipertensão e doença cardíaca isquémica com a necessidade de implantação de pacemaker. Arritmias como pausas sinusais e bloqueio avançado AV, foram indicadores para a terapia com pacemaker. A duração média desde a implantação do ILR até a instalação do pacemaker foi de 364,25 dias, com uma mediana de 190 dias.

Conclusão
Estes achados ressaltam a importância do gerenciamento personalizado do paciente e da monitorização cardíaca contínua. Colesterol alto e arritmias anteriores são preditores significativos para o tempo de implantação do pacemaker, destacando a necessidade de intervenções direcionadas.

Palavras-chave: Síncope, Pacemaker, Comorbidades, Arritmias, Registradores de Loop Implantáveis, Analise de sobrevivência, Regressão logística multivariada

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GLOSSARY

Atrial Fibrillation (AF)	A common arrhythmia characterized by rapid and irregular beating of the atria.
Atrioventricular Block (AVB)	A type of heart block where the conduction between the atria and ventricles is impaired.
Bradyarrhythmias	Slow heart rhythms that can lead to insufficient blood flow and require medical intervention such as pacemaker implantation.
Cardiac Arrhythmias	Irregular heartbeats caused by abnormalities in the electrical impulses that coordinate the heart's rhythm.
Hypertension	High blood pressure, a condition that can increase the risk of heart disease and stroke.
Implantable Loop Recorders (ILRs)	Medical devices implanted under the skin to continuously monitor the heart's electrical activity over an extended period
Ischemic Heart Disease (IHD)	A condition characterized by reduced blood supply to the heart, often due to coronary artery disease.
Pacemaker	A device implanted in the chest to help control abnormal heart rhythms by delivering electrical impulses to the heart.
Sick Sinus Syndrome (SSS)	A group of heart rhythm disorders involving a faulty sinus node, leading to bradycardia, pauses, or tachy-brady syndrome.
Sinus Pauses/Arrests	Temporary stop of sinus node activity, leading to gaps in the heart's rhythm.

Structural Heart Disease	A category of heart diseases that affect the heart's structure, including conditions like hypertrophic cardiomyopathy and valvular heart disease.
Syncope	A sudden, temporary loss of consciousness followed by spontaneous recovery.
Tachy-Brady Syndrome	A condition where the heart alternates between fast (tachycardia) and slow (bradycardia) rhythms.
Transient Ischemic Attack (TIA)	Often called a mini stroke, a TIA is a temporary period of symptoms similar to those of a stroke, serving as a warning for potential future strokes.
Ventricular Tachycardia (VT)	A fast, abnormal heart rate originating from the ventricles, which can be life-threatening if not managed promptly.

ACRONYMS

AF	Atrial Fibrillation
AVB	Atrioventricular Block
BP	Blood Pressure
CAD	Coronary Artery Disease
CVD	Cardiovascular Disease
ECG	Electrocardiogram
ESC	European Society of Cardiology
HF	Heart Failure
HR	Heart Rate
IHD	Ischemic Heart Disease
ILR	Implantable Loop Recorder
SCD	Sudden Cardiac Death
SSS	Sick Sinus Syndrome
TIA	Transient Ischemic Attack
VT	Ventricular Tachycardia

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INTRODUCTION

1.1 Syncope: A Clinical Overview

Syncope, which is broadly characterized by a sudden, temporary loss of consciousness followed by spontaneous recovery, presents a significant challenge impacting a big portion of healthcare resources every year. Studies estimate that syncope is responsible for 1 to 6% of total hospital admissions and 1-2% of all emergency department visits each year [1] [2].

The causes of syncope are many, ranging from benign conditions like vasovagal syncope to life threatening cardiac arrhythmias, which are major culprits of higher morbidity [3] [4].

The nature of syncope requires a thorough diagnostic approach, including an in-depth patient history, physical examinations, and a series of diagnostic tests, to identify the root cause. Current clinical guidelines recommend detailed risk stratification to identify patients in need of immediate intervention as opposed to those who may benefit from a more conservative approach [2] [3].

The management of syncope is however further complicated by the varied demographics of the affected population and the presence of comorbid conditions, which by themselves need personalized diagnostic and therapeutic strategies. The connection of syncope with comorbidities, especially cardiovascular disease, not only triggers syncope episodes but also worsens the patient's overall status [5] [6].

That being said, recent advancements in diagnostic technologies, particularly the arrival of Implantable Loop Recorders (ILRs), have markedly improved the detection and management of syncope. By allowing for extended cardiac rhythm monitoring with several algorithms tailored to the patient's own rhythm, for example atrial fibrillation (AF) detection or pauses detection algorithms, the use of ILRs adds to the earlier detection of arrhythmic events that may require interventions, such as pacemaker implantation when compared to other exams like Holter monitors or your standard ECG [7] [8].

1.2 Implantable Loop Recorders (ILRs): Diagnostic and Therapeutic Innovations

As said before, ILRs represent an essential modernization in cardiac diagnostics and management, changing the approach to unexplained syncope and transient arrhythmias. These devices enable continuous, long-term monitoring of cardiac rhythms up to 4 years, closing a significant gap in the identification of intermittent arrhythmic events that my cause syncopal episodes and thus would potentially require a pacemaker insertion.

Key Diagnostic and Therapeutic Contributions:

- **Enhanced Diagnostic Capability:** The ILRs capability to continuously monitor cardiac rhythms significantly increases the detection rate of transient arrhythmias, which are often overlooked by conventional exams like a 24h monitor or even a 1-month event recorder [3] [7] [8] [9].
- **Technological Evolution:** The ILRs that are at the moment available in the market now have featured a number of arrhythmia detection algorithms, ie AF detection in Medtronic or artificial intelligence algorithm for pauses detection in Boston, that significantly enhance the diagnostic accuracy. The incorporation of remote monitoring allows the cardiac physiologist to monitor the patient's rhythm without having them come to clinic on a daily basis, this makes the treatment approach to be done as early as possible [4] [7] [8].

The continuous evolution of ILR technology further promises to improve these techniques, ensuring that patients receive timely and tailored treatment interventions at all times.

1.3 ILR-Guided Pacemaker Implantation in Light of Contemporary Guidelines

Our SCOPE-15 study emphasizes the essential role of ILRs in improving diagnostic protocols for unexplained syncope and specific cardiac arrhythmias, highlighting their importance in identifying conditions that will need further device implant. As mentioned previously ILRs shine when it comes to continuous cardiac monitoring, accurately capturing transient arrhythmic events that traditional diagnostic methods often miss. For this reason, ILRs are now one of the gold standard tools in the diagnostic of intermittent arrhythmias as per the European and British guidelines. In our department we use ILRs when the conventional exams such as 24h Holter cannot find any abnormality in the patient's heart rhythm due to having not captured a syncopal episode during the 24 hours.

1.4 Electrophysiological Insights into Cardiac Arrhythmias:

Below is a quick review of the most common arrhythmias that are involved in syncope episodes:

Atrioventricular Block (AVB): AVB occurs when the electrical conduction between the atria and ventricles is impaired. It's categorized into first, second (Type I Mobitz I/Wenckebach and Type II Mobitz II), and third (complete) degrees, based on the severity of conduction delay or blockage [3].

Sinus Pauses/Arrests: Characterized by a temporary cessation of sinus node activity, sinus pauses or arrests can lead to significant gaps in cardiac rhythm, resulting in syncope [8].

Atrial Fibrillation (AF): While AF itself is characterized by rapid, disorganized electrical signals in the atria, it can occasionally lead to syncope due to irregular heartbeats causing reduced blood flow to the brain [3].

Sick Sinus Syndrome (SSS): SSS, or sinus node dysfunction, encompasses a range of disorders resulting from the inability of the sinus node to generate or transmit an appropriate heart rate. Manifestations include sinus bradycardia, sinus arrest, or pauses, often necessitating pacemaker therapy if symptomatic [7] [9].

Tachy-Brady Syndrome: Part of the spectrum of SSS, tachy-brady syndrome is characterized by alternating periods of fast and slow heart rates. Diagnosis is particularly challenging, requiring continuous monitoring to document the arrhythmic episodes accurately [7] [9].

1.5 Influence of Comorbidities on Pacemaker Implementation Decisions

Exploring the connection, between health problems and the need for pacemaker implant after finding abnormal heart rhythms is of course essential for overall patient care. This next section delves into how health conditions such as high blood pressure, smoking, lung diseases, high cholesterol, diabetes, previous stroke, heart diseases and different irregular heartbeats influence the medical choices related to pacemaker implant [3] [10].

Hypertension: This common comorbidity is known to elevate the risk of developing arrhythmias warranting pacemaker intervention. The interaction between elevated blood pressure and the electrical stability of the heart is well known and thus stresses the significance of managing hypertension in patients that maybe be considered for pacemakers [2] [10].

Smoking and Ex-Smoking: Both current and former smokers are found to be at increased risk for arrhythmias due to the detrimental effects of smoking on cardiovascular health. This includes the exacerbation of ischemic and structural heart diseases, which can influence the necessity of a pacemaker implantation [3].

Respiratory Diseases: Some chronic respiratory conditions such as Chronic Obstructive Pulmonary Disease (COPD) may aggravate the severity of arrhythmias or contribute to their onset, which can potentially contribute to the need for a pacemaker [3].

High Cholesterol: Elevated cholesterol levels are a known risk factor for atherosclerosis and subsequent ischemic heart disease, which can predispose patients to rhythm disturbances. [2].

Diabetes Mellitus: As a factor that can destabilize cardiac electrical activity, diabetes mellitus requires careful evaluation in patients with cardiac arrhythmias, an unbalance sugar level may further contribute to the need for a pacemaker [3].

Stroke History and Other Arrhythmias: A history of stroke or the presence of other arrhythmic conditions forms a critical part of a patient's cardiac profile, influencing the decision-making process for pacemaker therapy, in the majority of cases the type of pacemaker to be implanted, ie single chamber versos dual chamber [3].

Ischemic Heart Disease (IHD): Patients with IHD are prone to arrhythmias due to compromised blood flow and subsequent myocardial damage, their medical managing need to be continually reviewed to minimize the need for further arrhythmic treatment [3].

Structural Heart Diseases: Conditions such as hypertrophic cardiomyopathy or valvular heart disease can predispose patients to rhythm disturbances that may be alleviated with pacemaker therapy [3].

In conclusion we can see that comorbidities play a significant role in the decision-making process for pacemaker implantation following documented cardiac arrhythmias. This is also where we can see that a tool such as the ILR plays an important role in making sure the patients get the appropriate treatment at the correct time.

2

METHODS

2.1 Study Design

The SCOPE 15 study, carried out at the Cardiology Department of Ashford and St. Peters Hospitals NHS Foundation uses information from January 2008 to December 2023. Our focus is on exploring the outcomes, diagnostic pathways and long-term treatment approaches involving Implantable Loop Recorders (ILRs) in a group of patients experiencing unexplained fainting and dizziness.

This study was conducted to address the challenges and effectiveness of ILRs in today's NHS. With information collected over 15 years we aim to offer insights into how ILR technology has contributed to a better understanding of syncope causes and its medical management.

The study methodology involves an analysis that enabled our team to meticulously collect and analyze data from patient records. The review of these data was focused particularly on patient's history and the time between ILR implant and if needed pacemaker insertion.

The retrospective approach was selected to outline the results, treatment choices and patient care plans without dealing with the practical challenges of a prospective study.

Carried out at Ashford and St. Peter's Hospitals NHS Foundation Trust our study not only assesses the primary impacts of ILRs but also explores secondary effects such as how comorbidities influence treatment decisions and overall handling of syncope and dizziness in cardiology.

By combining data from healthcare databases such as Prism Healthcare Solutions, Surrey Safe Care and the Evolve EMR system we created a strong database.

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Throughout its design and implementation, SCOPE 15 study aims to provide insights that could potentially reshape future guidelines.

2.2 Data Source and Collection

The SCOPE-15 study relies on a robust data gathering framework, drawing its primary dataset from the medical records maintained at Ashford and St. Peter's Hospitals NHS Foundation. The focal point of this data collection revolves around patients who were implanted with ILRs from January 2008 to December 2023.

To ensure the study's data integrity and range as mentioned before we have used multiple healthcare databases, including Prism Healthcare Solutions, Surrey Safe Care, and the Evolve Electronic Medical Records (EMR) system.

These systems were crucial in providing a comprehensive view of each patient's history and follow-ups. This included any prior diagnostic tests, treatments, and any related healthcare interactions that provide context to each patient's condition before and after receiving an ILR.

The data collection process is structured to be as inclusive as possible while maintaining strict criteria for data quality and relevance. Regular checks and cross-checks were performed to ensure that the data meets the standards required.

2.3 Patient Cohort

In our study we have firmly examined a specifically defined group of patients within the cardiology service of Ashford and St. Peter's Hospitals NHS Foundation. The initial cohort consisted of 929 patients who underwent ILR implantation between January 2008 and December 2023. This group was narrowed down to a focused subset of 469 patients after applying inclusion and exclusion criteria, aimed at ensuring the study's relevance and precision in addressing its research objectives.

2.4 Inclusion and Exclusion Criteria

Inclusion Criteria:

- Patients who underwent ILR insertion due to unexplained syncope or episodes of dizziness.
- Patients with complete and accessible medical records that provide detailed information on medical history, treatment outcomes, and follow-up data.
- Patients who were monitored using ILRs between January 2008 and December 2023 at Ashford and St. Peter's Hospitals NHS Foundation Trust.

Exclusion Criteria:

- Patients who received ILRs for reasons other than syncope or dizziness, such as managing palpitations or atrial fibrillation for example.
- Records with incomplete or missing data, such as lack of follow-up details or incomplete documentation.
- Patients that pass away by non-cardiac causes before the ILR was explanted.

2.5 Refinement of the Patient Cohort

As mentioned earlier, our study's selection process involved analysis of data, from various healthcare databases. The information was cross-checked when possible in different platforms to ensure that all the information was accurate. This enabled us to categorize and study the remaining patients based on their background and more importantly how the ILR findings directly impacted the selection for pacemaker insertion.

By defining the study population in this manner, our goal was to produce findings that are relevant and practical in today's practice.
As we can see on the image bellow from the initial 929 ILR implanted for syncope, we used 469 on our study, from these only 157 patients had a pacemaker implanted. On the remaining 312 patients it was decided that at the time of ILR explanted there was no need for further invasive procedure to be done.

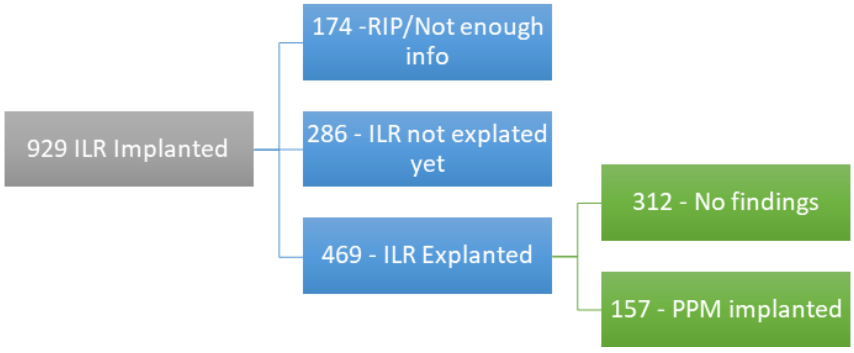

Figure 1 - Inclusion Criteria for Patients with ILR Implants

2.6 Variables and Operational Definitions

2.6.1 Variables Collected

The SCOPE-15 study collected an extensive display of data as we can see below:

- **Demographic Data:** Age and gender statistics were crucial for demographic trend analysis and to gauge the prevalence of our study results.
- **Medical History:** A detailed account of each patient's medical background, emphasizing prior cardiovascular issues and treatments was done.
- **Comorbidities:** Detailed recording of co-existing conditions, such as cardiovascular disorders and metabolic syndromes for example was performed on all available subjects.
- **ILR-Detected Arrhythmic Events:** All recorded arrythmias were analyzed with focus on those that were identified as being severe enough to need further treatment, i.e. a pacemaker implant.

2.6.2 Operational Definitions

To keep track with the current guidelines in practice in the NHS our study used rhythm definitions from the British Heart Rhythm Society (BHRS):

ILR-Detected Arrhythmia Requiring Pacemaker Implantation: Defined as any arrhythmia detected by the ILR that necessitates pacemaker implantation, this includes:

- **High-grade AV Block:** A severe form of atrioventricular block where the communication between the atria and ventricles is significantly impaired, often requiring immediate pacing intervention.
- **Symptomatic Pauses due to Sinus Node Dysfunction:** These are significant interruptions in the normal pacing function of the heart's sinus node, visible on an ECG as a missing P-wave, lasting long enough to cause symptoms.

Electrophysiological Definitions:

- **Atrioventricular (AV) Block:**
  - **First-degree:** A minor delay in the electrical conduction between the atria and ventricles without missed beats [11] [12].
  - **Second-degree (Type I and II):** Type I (Wenckebach) shows progressively lengthening conduction until a beat is dropped; Type II (Mobitz) is characterized by a sudden drop without prior lengthening of the conduction time [11] [12].
  - **Third-degree (Complete):** A complete disconnection in atrial and ventricular activities [11] [12].
- **Sinus Pauses:** Defined as transient interruptions of sinus node activity, these pauses disrupt the regular rhythm of the heart and can lead to symptoms of syncope if prolonged [11] [12].
- **Atrial Fibrillation (AF):** AF, characterized by rapid and disorganized atrial depolarizations, can often lead to significant hemodynamic instability and transient loss of consciousness when not managed appropriately [11] [12].
- **Sick Sinus Syndrome (SSS):** Encompasses a spectrum of intrinsic sinus node dysfunction disorders, ranging from sinus bradycardia to arrest [12] [10].
- **Tachy-Brady Syndrome:** This variant of sick sinus syndrome involves alternating episodes of tachycardia and bradycardia heart rates [10] [12].

These operational definitions are the backbone of our study's methodology, ensuring each case is evaluated with a high degree of clinical accuracy and consistency, thereby enhancing the reliability of our study's findings and recommendations.

2.7 Primary Outcomes

The primary outcome measures of the SCOPE-15 study are:

- **Type of Arrhythmias Leading to Pacemaker Implantation:** By documenting each case where an ILR-detected arrhythmia results in pacemaker implantation we can conclude which conditions most frequently justify pacemaker implantation.
- **Impact of Comorbid Conditions on Pacemaker Therapy:** Assessing how existing comorbidities influence the team's decision to proceed with pacemaker therapy.

The secondary outcome measures of the SCOPE-15 study are:

- **Immediate vs. Delayed Pacemaker Implantation**: Investigating situations where immediate implantation occurs versus cases where decisions are delayed.
- **Time Interval Analysis from ILR Implantation to Pacemaker Decision:** Determining the median time and the average time between ILR implantation and the decision to implant a pacemaker.
- **Guideline Adherence and Clinical Decision-Making:** Investigating the adherence to established clinical guidelines in the treatment process and how ILR data influences clinical decisions.

By systematically measuring these outcomes, the SCOPE-15 study aims to contribute valuable data to the optimization of current treatment protocols and to improve patient outcomes.

2.8 Statistical Analysis

The statistical analysis, in the SCOPE 15 study was designed to analyze the collected data and gain insights from the observed trends and patterns. For that reason, we employed:

Descriptive Statistics: We used descriptive statistics to summarize the data, clinical features and results of the study group. Central tendency measures, like mean and median were used as dispersion measures, standard deviation and interquartile range were utilized for continuous variables. Categorical variables were described using frequencies and percentages.

Inferential Statistics:

- **Time-to-Event Analysis:** The timing of pacemaker implantation from ILR implantation was examined using Kaplan-Meier estimator and Cox proportional hazards models as survival analysis techniques. These methods took into consideration censored observations , for example patients who did not get a pacemaker during the study period or were lost to follow-up.
- **Multivariable Regression Analysis**: We used multivariable logistic regression without and with the inclusion of comorbidities to analyze patient risk factors regarding pacemaker usage. The strength of these associations was quantified by odds ratios (ORs) with 95% CI.
- **Subgroup Analyses:** Was used to investigate the differential effects of ILR data on pacemaker implantation in multiple cohorts (age groups, sex and comorbidity categories).
- **Software employment:** We used R Studio to conduct the statistical analyses.
- **Null hypothesis testing:** Null hypotheses were tested at a pre-defined significance level of 0.05 for all tests with similar clinical presentations.

2.8.1 Welch's t-test:

The Welch's t test is a variation of the students t test. It is used to assess whether there are disparities, between the averages of two sets even when they have varying variances and sample sizes. This method comes in handy when assuming variances in the source populations of the samples is not feasible [13][14][15][16].

Hypotheses

In the context of analysis, the null hypothesis (H0) suggests that there is no distinction, in the two groups. In terms it is expressed as: H0; $\mu 1 = \mu 2$, where $\mu 1$ represents the mean of the first group and $\mu 2$ signifies the mean of the second group.

Contrariwise the alternative hypothesis (H1) proposes that there exists a difference in the means of these two groups. Formally stated as: H1; $\mu 1 \neq \mu 2$, with $\mu 1$ denoting the mean of the group and $\mu 2$ representing the mean of the group.

Test Statistics

The Welch's test statistics given by:

$$t = \frac{\bar{x}_1 - \bar{x}_2 - d}{\sqrt{\frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}}}$$

Where:

- $\bar{X}_1 and\ \bar{X}_2$ are the sample means of groups 1 and 2, respectively.
- S_1^2 and s_2^2 are the unbiased estimators of the variances of groups 1 and 2 , respectively.
- n_1 and n_2 are the sample sizes of groups 1 and 2, respectively.

The degrees of freedom for Welch's t-test, which are used to determine the critical value from the t-distribution, are approximated using the Welch–Satterthwaite equation:

$$df \approx \frac{\left(\frac{s_1^2}{n_1}+\frac{s_2^2}{n_2}\right)^2}{\frac{\left(s_1^2/n_1\right)^2}{n_1-1}+\frac{\left(s_2^2/n_2\right)^2}{n_2-1}}$$

This estimation of the degrees of freedom enables the test to adjust for the varying variances and sample sizes of both groups resulting in a t test when dealing with heteroscedasticity.

Interpretation

The calculated t-value from Welch's test is then compared against the critical t-value from the t-distribution table at the desired level of significance, using the approximated degrees of freedom. A significant result (typically $p < 0.05$) indicates that there is a statistically significant difference in means between the two groups being compared.

Application in Research

In our research we used Welch's t test to compare the ages between patients who received ILR only and those who later had a pacemaker installed. Since the initial analysis showed that there were differences in variances, between these two groups, Welch's t test was considered a reliable approach, for comparing the means compared to the traditional Students t test.

2.8.2 Pearson's Chi-squared Test with Yates' Continuity Correction

The Pearson's Chi-squared test with Yates' continuity correction is a modification of the standard Chi-squared test of independence, tailored for 2 by 2 contingency tables. This correction is intended to adjust for the continuity of the Chi-squared distribution, which is particularly useful when dealing with small sample sizes, as it reduces the approximation error that occurs in the discrete probability distribution of small samples [13] [14] [15] [16].

Hypotheses

In this analysis, the **null hypothesis (H_0)** states that there is **no relationship** between the two categorical variables. This means that any differences observed between them are simply due to chance. In formal terms: H_0: The two variables are independent.
On the other hand, the **alternative hypothesis (H_1)** suggests that there **is a relationship** between the two variables — meaning that changes in one are associated with changes in the other. Formally expressed as: H_1: The two variables are not independent.

Test Statistics

The Chi-squared statistic with Yates' continuity correction is:

$$\chi^2 = \sum_{i=1}^{r} \sum_{j=1}^{c} \frac{(|O_{ij} - E_{ij}| - 0.5)^2}{E_{ij}}$$

Where:

- O_{ij} represents the observed frequency in each cell (i, j) of the table.
- E_{ij} is the expected frequency under the null hypothesis of independence, calculated as:

$$E_{ij} = \frac{(Row\ Total_i \times Column\ Total_j)}{Grand\ T}$$

Where:

- r is the number of rows and c is the number of columns of the table

Under the null hypothesis, this statistic follows a qui-square distribution, being the degrees of freedom for a 2 by 2 contingency table with 2 rows and 2 columns, with Yates' correction, always 1:

$$df = (\mathrm{r} - 1) \times (\mathrm{c} - 1) = (2 - 1) \times (2 - 1) = 1$$

Interpretation

A high value of the Chi-squared statistic after applying Yates' correction suggests that the observed frequencies differ significantly from the expected frequencies, accounting for continuity. This typically means that the variables are associated rather than independent. If the calculated Chi-squared statistic exceeds the critical value from Chi-squared distribution table at the chosen significance level, the null hypothesis of independence is rejected. This indicates that a statistically significant association exists between the variable under investigation.

Application in Research

In our research we utilized a version of the Chi test to explore the link, between having an implanted device and various health conditions such as Structural Heart Disease, Diabetes or High Cholesterol. By applying Yates correction, we adjusted the test to better suit the size and distribution of our data.

For instance, when studying how having a pacemaker (Device = Yes or No) relates to the presence of Structural Heart Disease the test helps us determine if there is a connection between patients with heart disease and those that had a pacemaker.

2.8.3 Kaplan-Meier Curves

The Kaplan Meier estimator is used in statistics to estimate the survival rate based on information. In studies these graphs play a role in illustrating the likelihood of a patient surviving beyond a specific time. The Kaplan Meier technique is especially valuable, for examining data related to the time until an event occurs when not all individuals experience said event and observations may conclude or be limited [16] [17] [18] [19].

The Kaplan-Meier estimator is given by:

$$\widehat{S}(t) = \prod_{i:\, t_i \leq t} \left(1 - \frac{d_i}{n_i}\right)$$

Where:

- $\hat{S}(t)$ is the estimated probability of surviving beyond time t.
- t_i are the times at which each event (e.g., death, pacemaker implantation) or censoring occurs.
- d_i is the number of events (e.g., deaths, pacemaker Implantations) that occur at time t_i.
- n_i is the number of individuals known to have survived (not had the event or censored) up to time t_i.

Survival Probability and Censoring

In the Kaplan-Meier method, the survival probability at each time t_i is calculated as the product of the probabilities of surviving each earlier time t_j, multiplied by the probability of surviving at time t_i given survival up to t_j. This approach accounts for censored data, which occurs when a study ends before the event has occurred for some individuals, or they are lost to follow- up.

Interpretation

The Kaplan Meier graph gives a representation of how survival chances change over time. Each dip, in the graph signals an event and the height at each point shows the probability of survival up to that moment. Contrasts in survival outcomes among groups can be shown by creating Kaplan Meier graphs for each group. This approach enables a comparison of survival rates between groups revealing any differences or similarities, in their chances of survival.

Application in Research

In our research we used Kaplan Meier graphs to study the duration, from ILR implantation to pacemaker insertion. By illustrating survival trends for patient categories, we could visually compare how likely it was for patients to remain without needing a pacemaker over time based on their heart rhythm issues or other health conditions. This not only helped us grasp the patterns but also shed light on how certain medical conditions influenced the timing of requiring a pacemaker.

2.8.4 Log-rank Test

The Log rank Test is a method that is often applied in survival analysis to compare the survival outcomes of groups. It is utilized to assess whether there are differences, in survival rates among the groups being studied by examining the hypothesis $H0$ suggesting no disparity in survival and the alternative hypothesis $H1$ proposing variations, in survival [16] [17] [18] [19].

Mathematically, the hypotheses can be stated as:

- **Null Hypothesis ($\boldsymbol{H_0}$) :** $S_1(t)$=$S_2(t)$, where $S_1(t)$and $S_2(t)$ are the survival functions of the two groups at time t.
- **Alternative Hypothesis ($\boldsymbol{H_1}$):** $S_1(t) \neq S_2(t)$, indicating that at least one time point t exists where the survival functions differ between the groups

Test Statistics

The Log rank Test examines the survival durations, against the predicted survival durations assuming there is no variance between groups. The computation of the test statistic, for the Log rank Test is done in the manner:

$$\chi^2 = \frac{(O_1 - E_1)^2}{V(O_1 - E_1)}$$

Where:

- O_1 are the total number of events (e.g., deaths, failures) in group 1 at each time point.
- E_1 are the expected number of events in group 1 at each time point, calculated under the assumption of equal survival curves.

The estimated quantity of occurrences, in each category at every moment is determined by considering the event frequency seen in all categories combined at that time relative, to the size of each category.

The degrees of freedom for the Log-rank Test statistics $\chi 2$ distribution are typically $k-1$, where k is the number of comparison groups. For two groups, the test has one degree of freedom.

Interpretation

The result of the Log-rank Test is given as the observed value of the test statistics along with a p-value. A p-value < 0.05 indicates that there is a statistically significant difference in the survival distributions between the groups. The larger the $\chi 2$ value, the stronger the evidence against the null hypothesis of no difference in survival.

Application in Research

In our study we used the Log rank Test to compare the survival curves created from Kaplan Meier estimates among groups of patients grouped by clinical traits, like the presence or absence of certain arrhythmias. This analysis helped us determine if these traits had an impact on the duration until pacemaker placement.

2.8.5 Cox Proportional Hazard Model

Sir David Cox introduced the Cox Proportional Hazard Model back, in 1972. This model is commonly applied in studies to explore how different factors influence the time it takes for a specific event to occur. Known as the Cox model it is especially valuable, in studying survival data allowing researchers to analyze how survival time relates to predictors or explanatory variables even when dealing with censored data [17] [18] [19] [20] .

Model

The model is formulated as follows

$$h(t, X) = h_0(t)e^{(\beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p)}$$

Where:

- $h(t,X)$ is the hazard function at time t for a given individual with a vector of explanatory variables X.
- $h_0(t)$ is the baseline hazard function, representing the hazard for an individual with all explanatory variables equal to zero.
- $\beta_1, \beta_2, \ldots, \beta_p$ are the coefficients of the explanatory variables $X_1, X_2, \ldots, X_p$ which measure the impact of these variables.
- $e^{\beta_1 X_1 + \beta_2 X_2 + + \beta_p X_p)}$ is the exponential term that relates the covariates to the hazard.

Estimation and Interpretation

The coefficients β are estimated using maximum likelihood estimation. The exponential of any given coefficient, $exp(\beta_i)$, can be interpreted as the proportional change in hazard for a one-unit increase in the i the explanatory variable, holding all other variables constant. This is why the model is termed "proportional hazards": it assumes the effect of the covariates proportionally scales the hazard function.

Application in Research

In our study, the Cox Proportional Hazards Model was employed to analyze the time from ILR implantation to pacemaker insertion, considering various covariates such as age, presence of specific arrhythmias, and comorbid conditions.

2.8.6 Logistic Regression

Logistic regression is a technique employed to predict the likelihood of an outcome by considering one or more predictor variables. This method proves beneficial, in scenarios where the result variable's categorical and binary like in contexts where decisions on procedures such, as “pacemaker implantation: yes or no" are made based on different risk factors [15] [16] [21] [22] [23].

Model

The logistic model is expressed as:

$$Y \sim \text{Bernoulli}(p)$$
$$\text{logit}(p) = log\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \cdots + \beta_p X_p$$

Where:

- Y is the binary outcome/response variable.
- p is the probability of the event of interest (e.g., undergoing pacemaker implantation).
- $\frac{p}{1-p}$ is the odds ratio of the event occurring.
- $\beta_0, \beta_1, \ldots, \beta_p$ are the coefficients of the model.
- $X_1 X_2, \ldots, X_p$ are the predictor variables (e.g., age, comorbidities).

The coefficients are estimated using maximum likelihood estimation, aiming to find the set of coefficients that best fit the model to the observed data [14].

Interpretation

The exponential values of the coefficients (exp(β_j)) in regression indicate the odds ratio when the predictor Xj increases, by one unit keeping all predictors unchanged. This simplifies understanding how variations, in predictor variables impact the likelihood of the event taking place [14].

Application in Research

Our study used regression to investigate the impact of factors, like age and various health conditions on the chances of a patient needing a pacemaker after ILR insertion. By including these variables in the regression model, we were able to evaluate how each one separately and together influences the decision to proceed with a pacemaker offering measurable odds ratios that aid, in decision making.

2.8.7 Mann-Whitney U Test

The Mann Whitney U Test, also referred to as the Wilcoxon Rank Sum Test is a method that is often applied to compare differences between two groups when the variable being studied is ordinal or continuous but does not follow a normal distribution. This test is especially handy in evaluating whether there are variations, between two populations based on a characteristic or criterion [16][24].

Test Statistics

The Mann-Whitney U Test is based on the ranks of the data rather than the data values themselves. The test statistic, U, is calculated by:

1. Combining all observations from both groups into a single dataset.
2. Ranking all observations from lowest to highest, taking the average rank in case of ties.
3. Summing the ranks for the observations from each of the two groups separately, denoted as R_1 and R_2.
4. Calculating the U statistic for each group, where:

- n_1 and n_2 are the sample sizes for each group.
- The smaller of U_1 and U_2 is the final U statistic used for the test.

$$U_1 = n_1 \times n_2 + \frac{n_1(n_1 + 1)}{2} - R_1$$

$$U_2 = n_1 \times n_2 + \frac{n_2(n_2 + 1)}{2} - R_2$$

Interpretation

In the Mann Whitney U Test the null hypothesis suggests that both groups distributions are the same. On the other hand the alternative hypothesis implies that one group tends to exhibit distinct values compared to the other. When p-value <0.05 it signifies a significant distinction, in distributions, between these two separate groups.

Application in Research

In our research we used the Mann Whitney U Test to analyze the time it took for patients to receive pacemaker implants based on whether they had heart rhythm conditions, like Sinus Pauses, AVB, VT and more. By comparing these groups, we aimed to see if having specific arrhythmias was linked to slower pacemaker implantation times helping us identify factors that could impact treatment schedules.

Determining Comorbidities for Comparison

In order to decide which pre-existing conditions to compare in terms of their effect, on the timing of pacemaker insertion we used a mix of assessments and insights drawn from our findings. By conducting an exploration of the data and examining statistics we were able to pinpoint conditions with high prevalence and potential significance. Subsequently we employed methods like Chi tests and Kaplan Meier survival analysis to identify conditions that exhibited noteworthy relationships with pacemaker insertion.

2.8.8 Spearman's Rank Correlation

Spearmans Rank Correlation Coefficient, also referred to as Spearmans rho is a measure used to determine the correlation, between two variables X and Y based on their ranks. It is particularly valuable when working with data that is unstructured or does not meet the criteria, for Pearsons correlation coefficient, like needing a linear relationship and interval scaling [16][13].

Coefficient

The coefficient is calculated based on the ranked values for each variable rather than the raw data. The formula for Spearman's rho is:

$$\rho = 1 - \frac{6 \sum d_i^2}{n\,(n^2 - 1)}$$

Where:

- d_i is the difference between the ranks of corresponding variables X_i and Y_i.
- n is the number of observations.

Interpretation

Spearman's rho values range from -1 to +1:

- **+1** indicates a perfect positive correlation: as one variable increases, the other variable also increases.
- **-1** indicates a perfect negative correlation: as one variable increases, the other variable decreases.
- **0** indicates no correlation: increases or decreases in one variable do not predict changes in the other.

Application in Research

In our research we used Spearmans Rank Correlation to investigate how heart rhythm issues, like AVB or VT relate to the time, between ILR implantation and pacemaker placement. By analyzing Spearman's rho, we could understand how these heart rhythm problems impacted when further treatment is needed.

2.9 Ethical Considerations

The SCOPE-15 study was conducted with strict adherence to ethical standards and considerations. Approval was granted by the Ashford and St. Peters Hospital Ethics Committee, ensuring compliance with ethical guidelines for the protection of patient privacy and the responsible use of medical records in research. This retrospective analysis was performed with a commitment to uphold the confidentiality and dignity of all patient data collected.

Prior to start, the study protocol, including the data extraction and analysis methods, was thoroughly reviewed to ensure alignment with the ethical principles of beneficence, nonmaleficence, and justice. Patient identifiers were removed or anonymized to maintain confidentiality, and the data was stored securely, accessible only to those directly involved in the study.

Informed consent, which is typically a prerequisite for prospective studies, was not applicable in this retrospective design. However, the protocol was designed to minimize any risk of harm to the patients whose records were included in the study. The ethical review also confirmed that the study met the requirements for patient data usage and was in compliance with relevant data protection and privacy regulations.

3 RESULTS

3.1 Descriptive Statistics

All statistical analyses were ran using R-project (version 4.3.2) under R-studio (version 2023.12.1+402) environment.

3.1.1 Age Analysis

Homogeneity of Variances Assessment

To make sure we have measures, for comparing our groups of patients we first looked at whether the variances between the groups were equal, which is important for certain types of t tests. We used a Bartlett test to check if the variances between the ILR group and the pacemaker group were similar. The test showed a K square value of 7.850 with 1 degree of freedom and the p value was 0.005 indicating differences in variance. Based on these findings we decided to use Welch's t test for comparing ages moving forward because it can handle variations in variances, between groups giving us an evaluation despite these differences.

Age Distribution and Comparative Analysis

The age of patients was a primary variable of interest. The Welch's Two Sample t-test was utilized to compare mean ages between the ILR-only group (n = 312) and those who progressed to pacemaker implantation (n = 157). The analysis revealed a notorious age difference between the groups, with a t-value of -7.465 and degrees of freedom approximately equal to 369.61, emphasizing the significant effect ($p < 0.001$). The older cohort, who received pacemakers, had a mean age of 70.705 years, distinctly higher than the mean age of 59.269 years in the ILR-only group.

This stark age disparity highlights the correlation between advanced age and the likelihood of progressing to pacemaker implantation, which aligns with clinical observations suggesting that older patients often require more invasive interventions.

Visual Representation of Age Distribution

The histograms were used to show the age distribution of patients, in groups. In Figure 2 and 3 we can see the histograms for both the ILR group and the pacemaker group, respectively.

For the ILR group the histogram shows an even distribution across various age ranges with peaks around 50 and 70 years old. This indicates that there is a range of ages among patients who only had an ILR implanted without any interventions.

On the other hand, the histogram for the pacemaker group reveals a shift towards older ages. The data is skewed to the left with a peak, around 75 years.

These results indicate a trend where older patients are more likely to receive pacemakers compared to younger patients who typically will only have an ILR implanted.

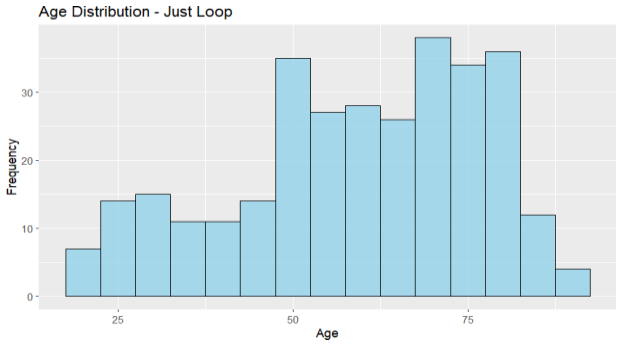

Figure 2 - Age Distribution – Just ILR

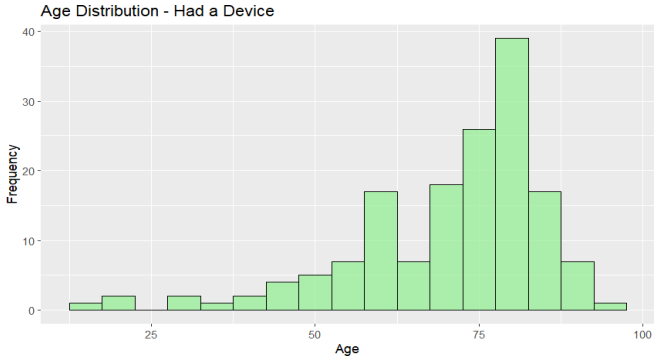

Figure 3 - Age Distribution – Had a Device

3.1.2 Prevalence of Comorbidities and Other Conditions

The prevalence of various comorbidities was compared between the two groups to understand the potential impact of these conditions on the progression to more invasive treatments.
This comparison aimed to understand how certain conditions might influence the need for further treatment. We used a Chi-squared test to analyze if the differences in occurrence rates between the two

groups were statistically significant. Before conducting this test we calculated the expected frequencies for each category to ensure that the tests assumptions were satisfied.

Table 1 - Prevalence of Comorbidities and Other Conditions in ILR-Only vs. Device Implanted Patients

Variables	Total (n=469)	Just ILR (n = 312)	Device Implanted (n =157)
Gender Male , n (%)	55.7	52.9	60.5
Hypertension, n (%)	39.8	33	52.9
Smoker / ex-smoker n (%)	18.4	18.9	17.2
Respiratory disease n (%)	13.5	12.2	15.9
High cholesterol n (%)	12.4	9.94	17.2
Diabetes mellitus, n (%)	13.1	8.97	21
Previous stroke, n (%)	7.49	7.69	7.01
Other arrhythmias, n (%)	23.3	18.6	32.5
IHD, n (%)	19.9	10.6	38.2
Structural heart disease, n (%)	12.4	6.09	24.8
No relevant information n (%)	8.99	12.8	1.27
Others n (%)	9.85	10.9	8.28

Upon examination of the table 1 , we concluded:

Hypertension: The pacemaker group exhibited an uptick, in hypertension prevalence at 52.9% compared to the ILR group at 33%. This hints at a link between hypertension and the clinical choice for a pacemaker. In our study we defined hypertension as s defined as persistently high blood pressure of 135/85 mmHg or higher.

Diabetes Mellitus: Likewise, diabetes mellitus showed prevalence in the pacemaker group at 21% versus the ILR group at 8.97% suggesting it could contribute to worsening cardiac symptoms leading to pacemaker insertion. In our study we defined Diabetes as a persistently high blood glucose levels, a fasting plasma glucose of ≥ 7.0 mmol/l,

Other Arrhythmias: There was a significant contrast in the prevalence of other arrhythmias with the pacemaker group displaying a notably higher rate at 32.5% compared to the ILR only groups 18.6%. This emphasizes how arrhythmic conditions can impact the need for pace- maker placement.

Ischemic Heart Disease (IHD): A substantial variation was observed in IHD prevalence with the pacemaker group having more than tripled the rate at 38.2% and the ILR group at 10.6%. This emphasizes IHD as a comorbidity necessitating advanced intervention.

High Cholesterol: Patients in the pacemaker group were more likely to have high cholesterol, with 17.2% affected compared to 9.94% in the ILR-only group. This suggests that raised cholesterol levels might be contributing to a higher overall cardiovascular risk, which in turn could make these patients more likely to progress from simple monitoring to needing a pacemaker. In our study we defined high cholesterol as total cholesterol level equal to or greater than 5 mmol/L.

Structural Heart Disease: Structural heart disease was much more common in those who went on to have a pacemaker — 24.8% versus 6.09% in the ILR-only group. This clear difference highlights how existing structural problems in the heart can increase the likelihood of developing rhythm disturbances that eventually require pacing.

Table 2 -Chi-Square Test Results for Comorbidities and Device Implantation

Comorbidity/Condition	Chi-Squared	Degrees of Freedom	P-Value	Conclusion
Transient Ischemic Attack (TIA)	0.005	1	0.943	No significant association
Structural Heart Disease	32.369	1	1.275e-08	Significant association
High Cholesterol	4.493	1	0.034	Significant association
Diabetes	12.458	1	0.001	Significant association
Previous Arrhythmias	10.678	1	0.001	Significant association
Respiratory Disease	0.985	1	0.321	No significant association
Hypertension (HTN)	16.661	1	4.468e-05	Significant association
Ischemic Heart Disease (IHD)	48.795	1	2.842e-12	Significant association
Smoking Status (Ex-smoker/Smoker)	0.097	1	0.756	No significant association

Upon examination of table 2, the comorbidities prevalence and Chi-squared results we concluded overall that:

The results highlight significant associations between the insertion of cardiac devices and the conditions structural heart disease, high cholesterol, diabetes, previous arrhythmias, hypertension, and ischemic heart disease. No significant associations were found for TIA, respiratory disease, and smoking status. These findings could suggest that patients with more severe cardiac conditions are more likely to receive devices, potentially as a management strategy for their conditions.

3.1.3 Specific Arrhythmias Leading to Pacemaker Implantation

Within our study's pacemaker group, we analyzed the occurrence of specific arrhythmias that necessitated the transition from ILR monitoring to pacemaker implantation. The study revealed that some arrhythmias appeared more frequently:

- **Sinus Pauses:** Representing the most prevalent arrhythmia in this cohort, sinus pauses were observed in 46.2% of the patients who received pacemakers. This high prevalence suggests that sinus pauses are a critical indicator for healthcare workers to consider when deciding on the escalation of care to pacemaker implantation.
- **Atrioventricular Block (AVB):** With a prevalence of 17.3%, AVB stands out as a significant cardiac event often requiring intervention with a pacemaker.
- **Tachy-Brady Syndrome/Sick Sinus Syndrome (SSS):** This syndrome was present in 15.4% of the cases, highlighting the known challenge of managing patients that present with both tachycardia and bradycardia.
- **Slow Conducted Afib:** Occurring in 10.3% of patients, slow-conducted atrial fibrillation demonstrates the relationship between atrial fibrillation and Bradyarrhythmias that can at times lead to syncope.
- **Ventricular Tachycardia (VT):** VT was the least common yet significant arrhythmia, with a prevalence of 5.7%

Table 3 illustrates the prevalence of these specific arrhythmias within the group of patients who underwent pacemaker implantation.

Table 3 - Prevalence of Specific Arrhythmias Leading to Pacemaker Implantation

Variables	Observed
Sinus Pauses	46.2
Slow Conducted Afib	10.3
AVB	17.3
VT	5.77
Tachy-Brady / SSS	15.4

Understanding how common and significant these issues are in individuals experiencing fainting spells can enhance the accuracy of diagnosis and promptness of treatments which in the end leads to better outcomes for patients.

3.1.4 Time Interval from ILR Implantation to Pacemaker Implantation

Another important point of our study was to quantify the duration between ILR implantation and subsequent pacemaker implant. This interval is fundamental in understanding the timeline and urgency of progression to more advanced treatment within our patient cohort.

The descriptive statistics showed:

- **Mean Duration**: On average, patients underwent pacemaker Implantation 364.25 days after receiving their ILR.
- **Median Duration:** The median time to intervention however was 190 days, indicating that half of the patients received a pacemaker within approximately six months post-ILR implantation.
- **Distribution**: The time interval exhibited a right-skewed distribution, reflecting that while a subset of patients quickly progressed to pacemaker therapy, others remained under ILR monitoring for a more extended period before intervention was deemed necessary.

The histogram below demonstrates the frequency of patients across different time intervals from ILR implantation to pacemaker Implantation. It distinctly shows a peak within the earlier months, tapering off as time progresses, which visually reinforces the variability in treatment progression. Such a distribution suggests that while some patients may exhibit early signs that prompt quick action, others may have slower courses that allow for longer periods of monitoring before a pacemaker is warranted.

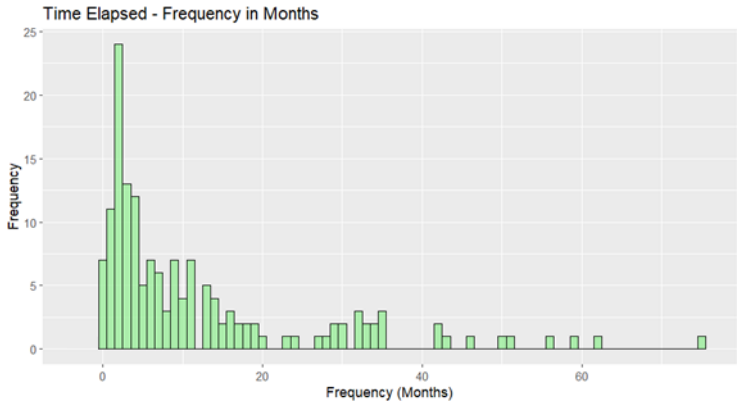

Figure 4 - Time Elapsed from ILR Implantation to Pacemaker Implantation (days)

It's important to analyze the paths of patients, with syncope and cardiac arrhythmias. By studying the time span, between ILR insertion and pacemaker placement we can better understand how arrhythmias progress and how they are treated.

3.2 Time-to-Event Analysis

3.2.1 Kaplan-Meier Survival Analysis

The Kaplan-Meier survival analysis was used in our study to evaluate the time in days from ILR implantation to pacemaker Implantation across various patient subgroups.

Age Group Comparison

- **Observation**: The survival curves across different age groups do not show a statistically significant difference (p-value: 0.49).
- **Implication**: This suggests that age may not be a critical factor influencing the need for pacemaker implant.

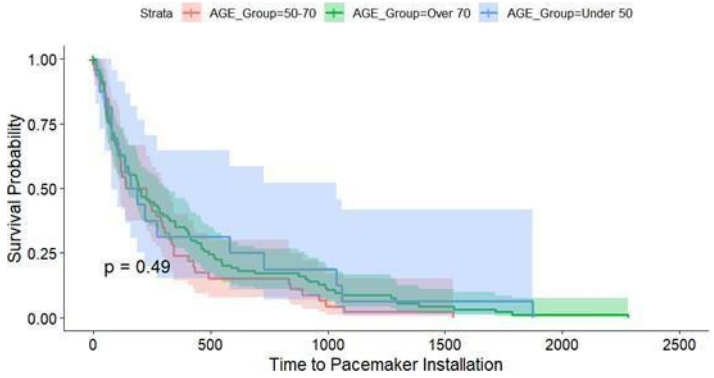

Figure 5 - Kaplan-Meier Survival Analysis by Age Group

Smoking Status Comparison

- **Observation**: Similar survival probabilities are observed between ex-smokers/smokers and non-smokers (p-value: 0.48).
- **Implication**: Smoking status alone does not appear to significantly impact the timing of pacemaker implant.

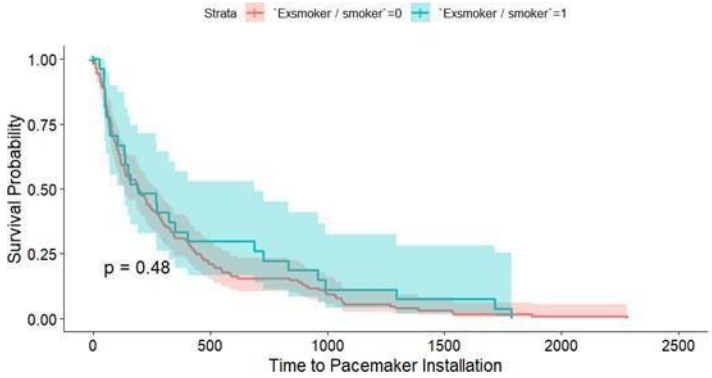

Figure 6- Kaplan-Meier Survival Analysis by Smoking Status

IHD Comparison

- **Observation**: Patients with and without IHD have closely overlapping survival curves (p-value: 0.38).
- **Implication**: The presence of IHD is not a distinct determinant for the timing of pacemaker implant in this cohort.

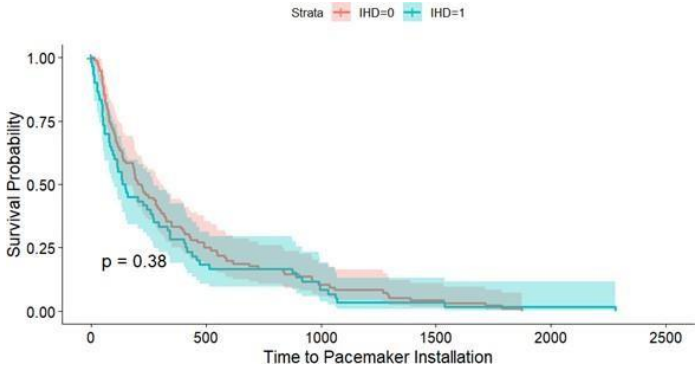

Figure 7 - Kaplan-Meier Survival Analysis by Ischemic Heart Disease (IHD)

Hypertension Comparison

- **Observation**: There is an initial divergence but eventual convergence of survival curves for patients with hypertension compared to those without (p-value: 0.097).
- **Implication**: Hypertension may influence early pacemaker implant, but the effect diminishes over time.

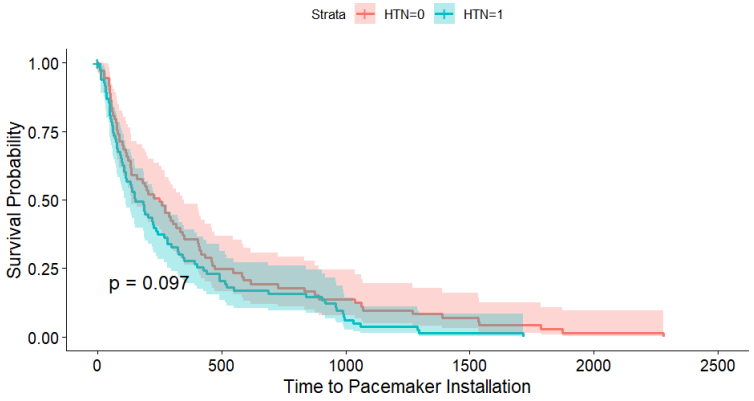

Figure 8 -Kaplan-Meier Survival Analysis by Hypertension (HTN) Status

Previous Arrhythmias Comparison

- **Observation**: No significant difference in survival probabilities based on the history of previous arrhythmias (p-value: 0.37).
- **Implication**: The historical occurrence of arrhythmias does not significantly alter the timeline for pacemaker implant.

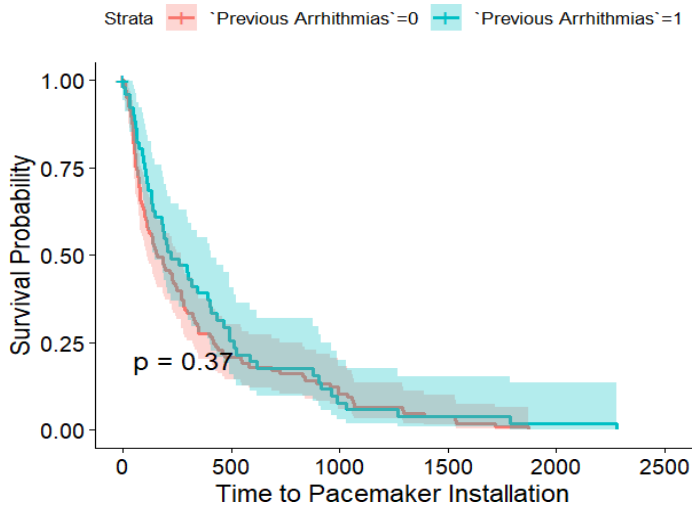

Figure 9 - Kaplan-Meier Survival Analysis by Previous Arrhythmias

High Cholesterol Comparison

- **Observation**: A notable difference in survival curves is observed between patients with and without high cholesterol (p-value: 0.014).
- **Implication**: High cholesterol is identified as a significant factor, potentially accelerating the progression to pacemaker implant.

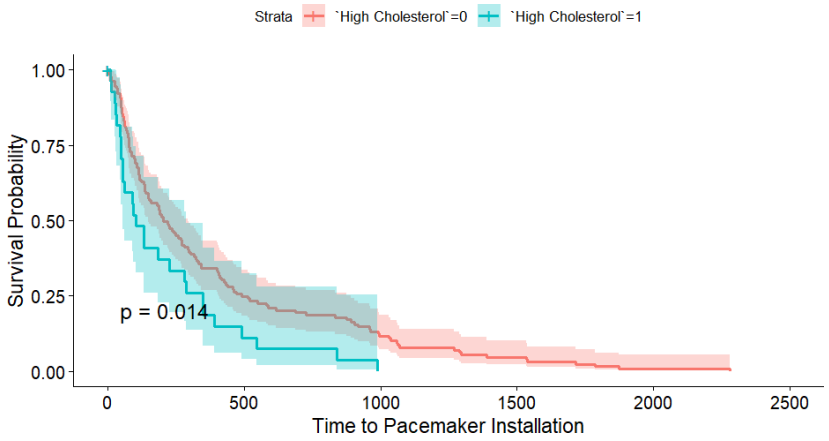

Figure 10 - Kaplan-Meier Survival Analysis by High Cholesterol

Diabetes Comparison

- **Observation**: Similar survival probabilities between diabetics and non-diabetics (p-value: 0.14).
- **Implication**: Diabetes mellitus does not appear to be a significant independent factor for the timing of pacemaker implant.

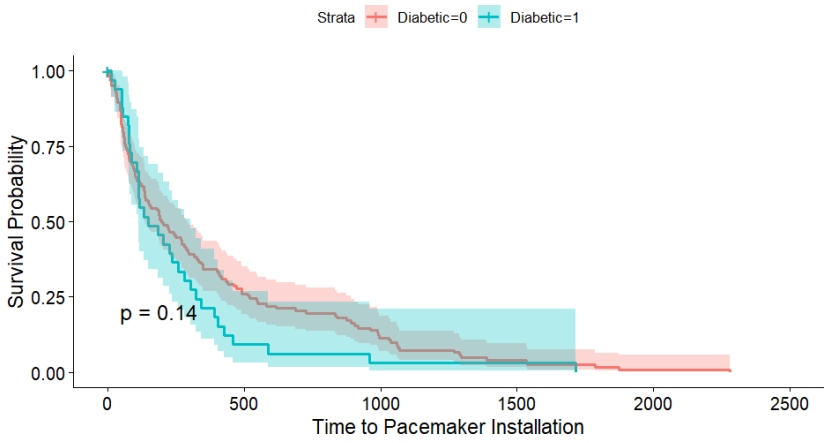

Figure 11 -Kaplan-Meier Survival Analysis by Diabetic

TIA (Transient Ischemic Attack) Comparison

- **Observation**: No notable difference in survival times between patients with a TIA history and those without (p-value: 0.91).
- **Implication**: A history of TIA does not seem to affect the timing of pacemaker implant.

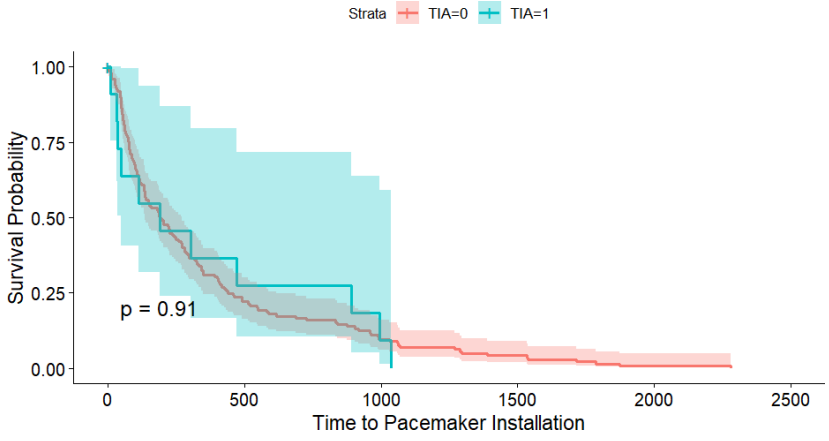

Figure 12 - Kaplan-Meier Survival Analysis by TIA

Structural Heart Disease Comparison

- **Observation**: Overlapping survival curves for patients with and without structural heart disease (p-value: 0.45).
- **Implication**: Structural heart disease does not significantly alter the timeline for pacemaker implant.

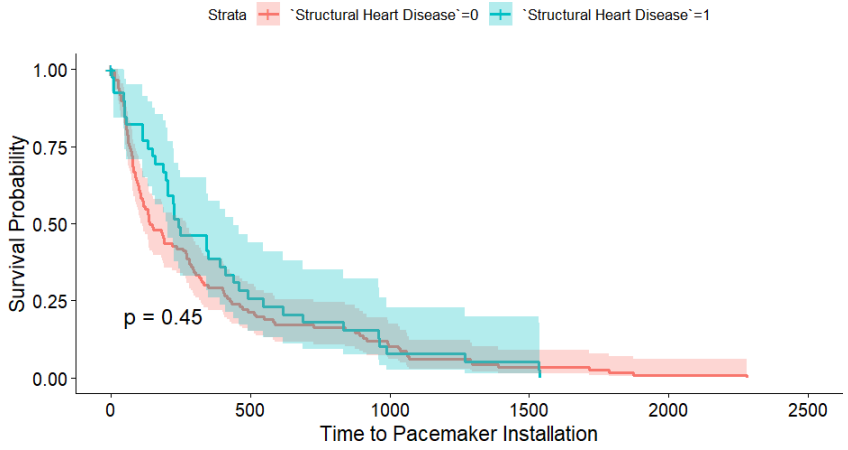

Figure 13 - Kaplan-Meier Survival Analysis by Structural Heart Disease

"No relevant history " Group Comparison

- **Observation**: The presence or absence of a relevant medical history does not significantly impact survival probabilities (p-value: 0.22).
- **Implication**: The defined 'relevant history' does not significantly influence the timing for pacemaker implant.

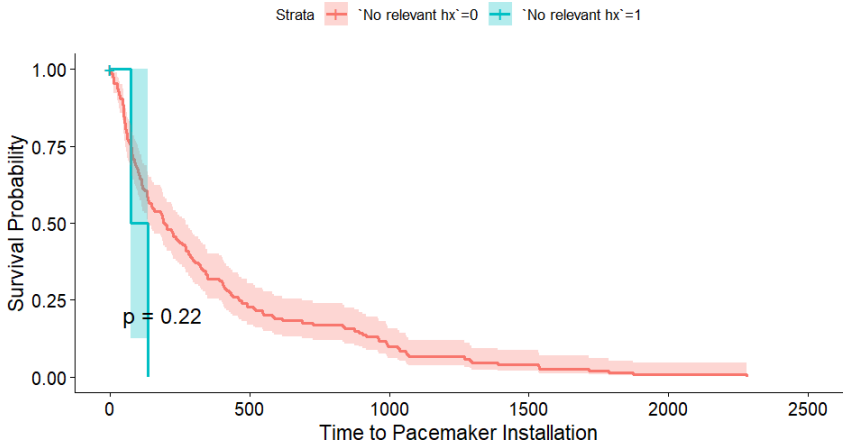

Figure 14 - Kaplan-Meier Survival Analysis by "No relevant Hx"

"Others" Group Comparison

- **Observation**: Similar survival probabilities between the "Others" groups with no significant differences in the timing of pacemaker Implantation (p-value: 0.29).
- **Implication**: The categorization as 'Others' does not have a significant impact on pacemaker implant timelines.

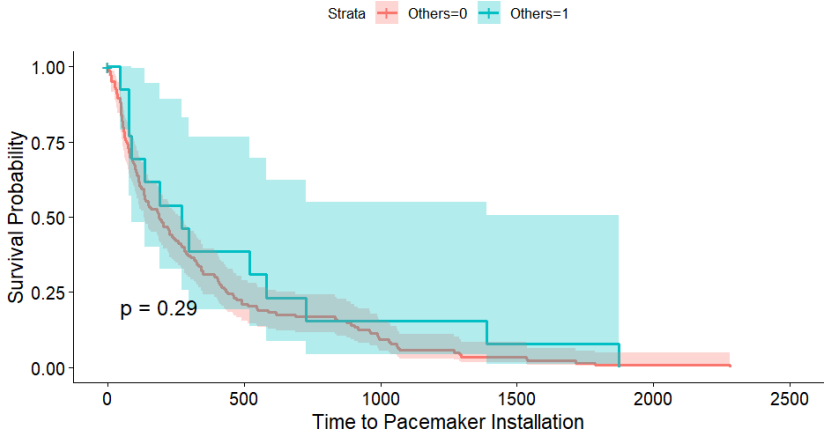

Figure 15 - Kaplan-Meier Survival Analysis by "Others"

Gender Comparison

- **Observation**: A visible divergence in survival curves between genders, with a trend indicating potential influence on pacemaker Implantation timing (p-value: 0.053).
- **Implication**: There may be gender-related factors affecting the timing of pacemaker necessity, warranting further investigation.

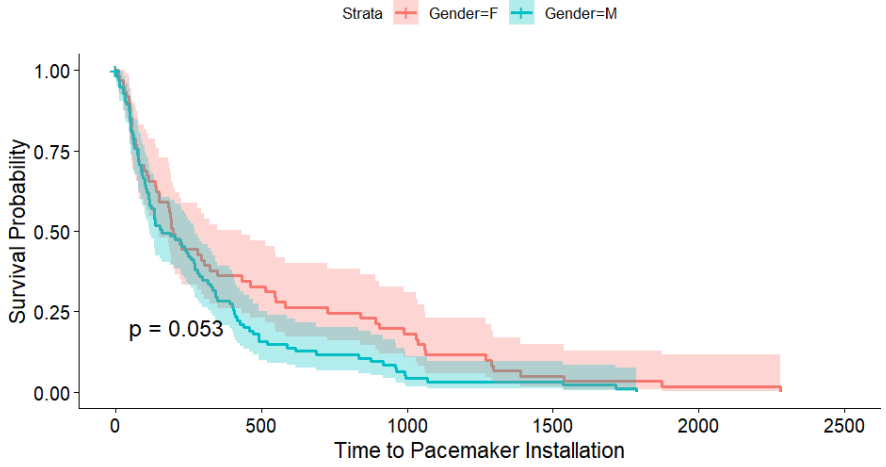

Figure 16 - Kaplan-Meier Survival Analysis by Age

3.2.2 Log-rank Test Results

After observing the previous graphic representations and the descriptive statistics we proceeded to use the Log rank test, to confirm how specific clinical factors impacted the timing of pacemaker placement on the comorbidities that showed potential influence.

Table 4 - Chi-Square Test Results for Various Comorbidities and Pacemaker Implant Timing

Comparison	Chi-Squared	Degrees of Freedom	p-value
Gender -Male	3.7	1	0.05
Structural Heart Disease	0.6	1	0.5
High Cholesterol	6.1	1	0.01
Ischemic Heart Disease (IHD)	0.8	1	0.4
Hypertension (HTN)	2.7	1	0.1
Previous Arrhythmias	0.8	1	0.4
Diabetes Mellitus	2.1	1	0.1

Analysis:

- **Gender:** The results suggest a possible trend where gender might influence the timing of pacemaker implant, with males potentially requiring a pacemaker slightly earlier than females. This finding, being at the threshold of statistical significance (p-value: 0.05), warranted further investigation.
- **Structural Heart Disease:** There was no significant difference between the two groups ($p = 0.5$), suggesting that structural heart disease on its own doesn't seem to influence how soon patients progress to needing a pacemaker in this cohort.
- **High Cholesterol:** There is a statistically significant difference (p-value: 0.01), suggesting that patients with high cholesterol are likely to require pacemaker placement sooner than those without, highlighting the importance of managing cholesterol levels in patients with hx of syncope.
- **Ischemic Heart Disease (IHD):** The lack of a significant difference (p-value: 0.4) suggests that IHD does not significantly alter the survival times to pacemaker implant in our cohort.
- **Hypertension (HTN):** The results indicate a non-significant trend (p-value: 0.1) that may imply an early but diminishing impact of hypertension on pacemaker implant.
- **Previous Arrhythmias:** No significant impact (p-value: 0.4) of previous arrhythmias on the timing for pacemaker placement was observed, suggesting other factors may be more influential.
- **Diabetes Mellitus:** Although not statistically significant (p-value: 0.1), there is a trend where diabetes mellitus may contribute to an earlier need for a pacemaker, meriting additional research.

3.2.3 Cox Proportional Hazards Model Analysis

In our study we used the Cox Proportional Hazards Model to identify the factors that significantly affect the time from ILR implantation to pacemaker implant. The model studied a range of covariates including age, gender, presence of specific arrhythmias, comorbid conditions, and other clinical characteristics.

Overall Model Significance

Table 5 - Overall Model Significance for Cox Proportional Hazards Analysis

Test	Statistic	Degrees of Freedom	p-value
Likelihood Ratio Test	22.620	13	0.046
Wald Test	22.680	13	0.050
Score (logrank) Test	23.320	13	0.040
Global Test	15.885	13	0.255

After analysis we determined that the model shows significance based on various tests, this indicates that the model aligns well with the data and highlights factors affecting the time required for pacemaker implant.

Individual Variable Analysis

Table 6 - Cox Proportional Hazards Model Analysis Results

Variable	p-value	Analysis
Age	0.84512	Not significant
Gender (Male)	0.02731	Significant
IHD	0.26818	Not significant
Hypertension	0.17099	Not significant
Previous Arrhythmias	0.26191	Not significant
Structural Heart Disease	0.15180	Not significant
TIA	0.93332	Not significant
High Cholesterol	0.00659	Significant
Diabetes Mellitus	0.27114	Not significant
No Relevant History	0.13022	Not significant
Others	0.63194	Not significant
Ex-smoker / Smoker	0.16936	Not significant.
Respiratory Disease	0.15689	Not significant.

Concordance

The concordance statistic of 0.618 indicates the moderate predictive power of the model.

Overall Analysis:

The Cox Proportional Hazards model reveals that gender (with males at higher risk) and high cholesterol are significant predictors of earlier pacemaker Implantation. Other factors, including age, IHD, hypertension, previous arrhythmias, structural heart disease, TIA, diabetes mellitus, smoking status, and respiratory disease, do not show significant influence on the timing of pacemaker Implantation.

3.2.4 Logistic Regression Analysis

We used the logistic regression model in our study to identify factors significantly influencing the likelihood of requiring pacemaker implantation after ILR placement. The model considered several covariates, including age, gender, specific arrhythmias, comorbid conditions, and other clinical characteristics.

Overall Model Significance

Model Summary:

- Null deviance: 594.97 on 466 degrees of freedom
- Residual deviance: 460.11 on 453 degrees of freedom
- AIC: 488.11
- Number of Fisher Scoring iterations: 5

Upon analysis the logistic regression model shows a decrease, in deviance compared to the model indicating a strong alignment with the data. The AIC value reflects the model's ability to strike a balance, between quality and complexity.

Individual Variable Analysis

Table 7 - Logistic Regression Analysis of Factors Influencing the Timing of Pacemaker Implantation

VARIABLE	ESTIMATE	STD. ERROR	Z VALUE	PR(>|Z|)	OR	95% CI FOR OR
(Intercept)	-3.882	0.609	-6.374	1.84e-10	0.021	0.006 - 0.066
Age	0.027	0.008	3.165	0.002	1.027	1.011 - 1.045
Gender (m)	-0.173	0.245	-0.707	0.480	0.841	0.519 - 1.357
IHD	1.635	0.296	5.528	3.24e-08	5.127	2.901 - 9.272
HTN	0.863	0.254	3.398	0.001	2.370	1.449 - 3.930
P. Arrhythmias	0.702	0.278	2.527	0.012	2.018	1.174 - 3.497
SHD	1.397	0.349	3.998	6.39e-05	4.043	2.065 - 8.168
TIA	-0.263	0.441	-0.596	0.551	0.769	0.314 - 1.791
High cholesterol	0.847	0.348	2.436	0.015	2.333	1.180 - 4.636
Diabetic	0.955	0.334	2.860	0.004	2.597	1.353 - 5.028
No relevant history	-0.482	0.787	-0.612	0.541	0.618	0.093 - 2.384
Others	1.138	0.434	2.621	0.009	3.120	1.317 - 7.307
Ex/ smoker	0.128	0.304	0.420	0.674	1.137	0.621 - 2.056
R.disease	0.584	0.345	1.692	0.091	1.793	0.908 - 3.527

Analysis:

- **Significant Predictors**: Age, IHD, HTN, Previous Arrhythmias, Structural Heart Disease, High Cholesterol, Diabetes Mellitus, and Others.
- **Non-significant Predictors**: Gender, TIA, No Relevant History, Ex-smoker/Smoker, and respiratory disease.
- **Odds Ratios (OR)**: Provides a measure of the change in odds of pacemaker implantation associated with a one-unit change in the predictor variable. For instance, we observed that having IHD increases the odds of pacemaker implantation by approximately 5.13 times compared to not having IHD.

The logistic regression model detected factors that predict the need, for a pacemaker implant. Factors such as age, heart disease, high blood pressure, past arrhythmias, heart structural issues, high cholesterol levels, diabetes and other health conditions notably raise the chances of needing a pacemaker.

3.2.5 Mann-Whitney U Test Analysis on Arrhythmias

The Mann-Whitney U Test was used in our study to analyze the time distributions to pacemaker implantation for patients categorized by the presence or absence of specific arrhythmias. This test helped us to determine whether the occurrence of specific arrhythmias was associated with faster or slower times to pacemaker implantation, thus identifying potential risk factors.

Individual Variable Analysis

Table 8 - Mann-Whitney U Test Results for the Timing of Pacemaker Implantation Based on Specific Arrhythmias

Variable	W (test statistic)	P-value	Analysis
AVB	1769.5	0.898	Not significant difference
VT	717	0.676	Not significant difference
Slow conducted AF	1118.5	0.995	Not significant difference
Tachy-brady / SSS	1438	0.475	Not significant difference
Sinus pauses	3117	0.742	Not significant difference

Analysis:

The findings, from the Mann Whitney U Test suggest that there was no variance in the timing of pacemaker implantation among the arrhythmias that were selected for this study, i.e. AVB, VT, Slow Conducted AF, Tachy Brady/SSS and Sinus Pauses. This indicates that the occurrence of these arrhythmias by themselves might not consistently predict when a pacemaker should be implanted.

3.2.6 Mann-Whitney U Test Analysis on Comorbidities

Once again, we used the Mann-Whitney U Test, this time to analyze the time distributions to pacemaker implantation for patients grouped by the presence or absence of comorbidities.

Individual Variable Analysis Selected

Comorbidities Based on Previous Results

Table 9 - Mann-Whitney U Test Results for the Timing of Pacemaker Implantation Based on Specific Comorbidities

Variable	W (test statistic)	P-value	Analysis
Structural heart disease	1896.5	0.116	Not significant difference
High cholesterol	2186	0.038	Significant difference
HTN	3388.5	0.203	Not significant difference
Diabetic	2190	0.488	Not significant difference
IHD	3313	0.115	Not significant difference
Previous arrhythmia	2186	0.038	Significant difference

Analysis

The analysis showed no significant differences in the time to pacemaker implantation for patients with SHD, HTN, diabetes, or IHD compared to those without these conditions. However, significant differences were found for patients with high cholesterol and those with previous arrhythmias. This suggests that high cholesterol and previous arrhythmias may influence the timing of pacemaker implantation. On the other hand, conditions like SHD, HTN, diabetes, and IHD do not appear to affect the timing of this procedure.

3.2.7 Spearman's Rank Correlation Analysis on Arrhythmias

The Spearman's rank correlation test was used in our study to analyze the relationship between the time to pacemaker implantation and the presence of specific arrhythmias. As we know Spearman's rank correlation assesses the strength and direction of association between two ranked variables.

Individual Variable Analysis

Table 10 - Spearman's Rank Correlation Results for the Timing of Pacemaker Implantation Based on Specific Arrhythmias

VARIABLE	S	P-VALUE	RHO	ANALYSIS
VT	655308	0.658	-0.036	Not significant correlation
Slow Conducted Afib	633749	0.984	-0.002	Not significant correlation
AVB	641519	0.863	-0.014	Not significant correlation
Sinus Pauses	644815	0.813	-0.020	Not significant correlation
Tachy-Brady / SSS	597762	0.493	0.055	Not significant correlation

In summary the results of the Spearmans rank correlation tests suggest that there is no correlation between the arrhythmias and the timing of pacemaker implantation. This once again implies that these arrhythmias alone may not be predictors, for when a pacemaker should be implanted.

4

DISCUSSION AND IMPLICATIONS

4.1 Summary of Key Findings

As said previously, SCOPE 15 study was aimed to study and tackle the issues, in managing fainting episodes by assessing how today's ILRs work in detecting arrhythmias that may require pacemaker insertion. Through an analysis of a 15-year patient data set we investigated the links between certain health conditions, specific arrhythmias and when at which point in time does the patient might need a pacemaker. The primary and secondary outcomes of the study were modeled to provide insights into the factors that influence decisions and patient outcomes.

Primary Results

Through reviewing all information obtained, we discovered trends and connections that could shape future medical recommendations and patient care plans.

Impact of Specific Comorbidities on Pacemaker Implantation

From all the comorbidities that were chosen to be studied in our study, cholesterol, diabetes, HTN, SHD and IHD were found to be patient predictors for pacemaker implants.

This shows us that managing these conditions is rather important in the overall picture of the typical cardiac patient, who, as we know, tends to present more than one condition at the same time. For example, patients with heart disease, be it SHD or IHD, tend to also exhibit other conditions like hypertension or high cholesterol levels.

The cardiac patient is someone who requires a multidisciplinary team approach to their treatment. When not applied properly, we may see a decline in the overall health, which puts these patients at risk of needing a pacemaker.

Here is also when the ILR plays an important role as monitoring tool, as it monitors the heart rhythms 24/7 and has the capacity to alert the team when a new or worsen arrhythmia is found, making it easier to tailor treatment plans for each individual patient

Arrhythmias Leading to Pacemaker Implantation:

- **Sinus Pauses:** Sinus pauses were the most prevalent arrhythmia leading to pacemaker implantation, occurring in nearly half of the cases.
- **Atrioventricular Block:** AVB was another significant arrhythmia that often-necessitated pacemaker intervention.
- **Tachy-Brady Syndrome/Sick Sinus Syndrome (SSS):** This syndrome was notable among patient's requiring pacemakers, highlighting its relevance in clinical evaluations.
- **Slow Conducted Afib:** Although less common, slow-conducted atrial fibrillation was significant enough to warrant pacemaker therapy on some cases.
- **Ventricular Tachycardia (VT):** VT was the least common arrhythmias requiring pacemaker implantation.

With these results, we can conclude that the real-time monitoring provided by the ILR is very important in the management of severe cardiac arrhythmias. Conditions like sinus pauses and AVB that can cause severe bradycardia are more associated with pacemaker insertion compared to another arrhythmias. This might be due to the fact the clinicians are happy with the close monitoring of the patient's heart rhythm that the ILRs give and are reassured that if needed, for example in a case of a slow conducted AFib that causes the patient to either feel dizziness or have in fact an episode of syncope, the clinician can quickly refer the patient for a pacemaker implant without causing any delays in treatment.

Time Interval Analysis from ILR Implantation to Pacemaker Insertion

- **Mean Duration:** On average, patients underwent pacemaker implantation approximately one year after ILR implantation. This suggests a significant period of monitoring and decision-making before progressing to pacemaker therapy.
- **Median Duration:** The median time to pacemaker Implantation was around six months, indicating that a good number of patients required pacemakers within a relatively short period post-ILR implantation.
- **Distribution:** The distribution of time intervals was right-skewed, reflecting variability in the urgency and timing of pacemaker implantation. This variability underscores the diverse progression rates of underlying conditions in patients and highlights the need for personalized monitoring and intervention strategies.

Conclusion

In summary, the SCOPE 15 results show that not only are arrhythmias essential in deciding whether to insert a pacemaker, but also specific comorbidities likewise play a significant role. While it is always important to act quickly on new findings, in cardiology, it is particularly crucial. We want to avoid implanting pacemakers in all patients who experiences a syncopal episode as sometimes there is underlying conditions we can treat.

Nevertheless, monitoring those with cardiac-related syncope for any changes in their condition is essential whenever possible. Since it can be challenging to pinpoint the cause of syncopal episodes, tools like the ILRs are truly important in nowadays clinical practice.

With ILRs, doctors do not feel pressured to implant a pacemaker sooner than expected because the patients' cardiac rhythms are monitored 24/7. This gives doctors time to look for better ways to manage not only the arrhythmias but also the comorbidities we have seen as predictive factors.

Half of the cohort received a pacemaker within six months. However, the average time for pacemaker implantation was close to 1 year, indicating that in some patients,

doctors were willing to monitor the situation further before pursuing a more invasive treatment.

4.2 Comparison with Existing Literature

Comorbidities and Pacemaker Implantation

Our study identified several comorbidities, including cholesterol, diabetes, hypertension, the presence of heart disease, and even gender, as factors influencing the likelihood and timing of pacemaker implantation. These findings aligned with existing research, as we can see below:

In the study *"Risk factors and a 3-month risk score for predicting pacemaker implantation in patients with atrial fibrillation*" [25], similar risk factors were highlighted, and a risk score incorporating these comorbidities was established. This study emphasizes the significance of these conditions such as high cholesterol in predicting the need for pacemaker therapy, supporting our own findings.

Additionally, the negative impact of comorbidities on patient outcomes is well-documented in many papers. For instance, the study "*Sex differences and long-term outcome in patients with pacemakers*" [26] found that gender played an important role in long-term outcomes of pacemaker patients, with women showing different complication rates compared to men. Once again, this study aligns with our own findings in that we also found differences between female and male patients.

The study "*Long-term outcomes associated with permanent pacemaker implantation after surgical aortic valve replacement*" [27] highlights the importance of continuous follow-up for patients with multiple comorbidities. Although this paper talks about post-pacemaker insertion follow-up, it does depict a similar point that we stress in our study: monitoring not only the arrhythmias but also optimizing the treatment plans for comorbidities found in each patient, as this ensures optimal patient outcomes.

Further supporting our findings, "*Bradyarrhythmias and pacemaker indications in elderly patients*" [28] , discuss how elderly patients with conditions like diabetes and hypertension are more likely to experience bradyarrhythmias necessitating pacemaker implantation. This corroborates our study's results, emphasizing the significant impact of these comorbidities on the clinical management of older adults.

In another study, "*The use of an implantable loop recorder in the investigation of unexplained syncope in older people*" [29], the role of ILRs in diagnosing underlying arrhythmic events in

patients with comorbidities are highlighted. This study supports our approach of using ILRs to closely monitor patients with high cholesterol, diabetes, and hypertension.

Moreover, the study "*Diagnostic yield of implantable loop recorders in patients with unexplained syncope: single-center experience*" [30], found that the diagnostic yield of ILRs is significantly influenced by the presence of comorbidities such as ischemic heart disease and hypertension. These findings are in line with our results, reinforcing the importance of considering comorbid conditions in the diagnostic process and subsequent treatment planning.

Lastly, the study "*Clinical electrophysiology of the aging heart*" [31], emphasizes the increasing prevalence of arrhythmias and the need for pacemaker therapy in older adults with comorbid conditions. This study once again aligns with our findings, stressing the critical role of comprehensive management strategies that address both the primary arrhythmic condition and the associated comorbidities.

Diagnostic Strategies

The use of ILRs was a common theme across multiple studies, supporting the diagnostic strategies employed in our SCOPE-15 study.

The study "*Diagnostic usefulness of implantable loop recorder in patients with unexplained syncope or palpitation*," [32] demonstrated the diagnostic utility of ILRs, accentuating similar to our own study the importance of continuous monitoring in identifying patients at risk of requiring a pacemaker.

The *"2018 ESC Guidelines for the diagnosis and management of syncope"* [3] and the paper "*Indications for the use of diagnostic implantable and external ECG loop recorders*" [10] both emphasize the essential role of ILRs in diagnosing syncope and guiding patient management. These guidelines support our approach of utilizing ILRs for continuous patient monitoring.

In the study "*Unexplained syncope: Implications of age and gender on patient characteristics and evaluation*," [33] it was reported that ILRs significantly increase the detection rates in cases of unexplained syncope, particularly in older adults. Once again, this study aligns with our on decision of using ILRs to improve diagnostic accuracy. Similarly, the study "*Diagnostic Yield of Implantable Loop Recorders in Patients with Unexplained Syncope*" [30] found ILRs to also be highly effective in diagnosing unexplained syncope.

Lastly the Meta-Analysis " *Predictors of Pacemaker Requirement in Patients Receiving Implantable Loop Recorders for Unexplained Syncope: A Systematic Review and Meta-Analysis*," [34] provided a comprehensive review of ILRs' effectiveness in predicting pacemaker needs in syncope patients that further proved our use of ILRs in our clinical day to day.

Conclusion

In conclusion, the existing literature supports most of our study's findings. Comorbidities were found to influence arrhythmias and, therefore, pacemaker therapies. ILR was broadly found to be the best tool for diagnosing unexplained syncope, which corroborates our study findings.

That being said, we could not find a study with a similar protocol to ours. Therefore, we were unable to determine if some of our findings, like the time from ILR implant to pacemaker implant or which types of arrhythmias were more commonly seen, could be reproduced in other centers or hospitals.

Moreover, most of the studies we found on the relationship between comorbidities and pacemaker implants focused on post-pacemaker implant follow-ups rather than pre-pacemaker workups like ours. As the healthcare system increasingly embraces a preventive medicine policy, we anticipate that future studies will shift their focus to the preventive aspects, offering hope for improved patient care.

4.3 Clinical Significance and Impact on Patient Management

As said before, managing the underlying causes of syncope poses a challenge in the field of healthcare due to the fact that it can be caused by an array of causes, i.e. cardiac, neurological, etc... It is crucial to diagnose and act to prevent bad outcomes.

Our SCOPE 15 study highlighted the importance of identifying individuals at risk of cardiac syncope by monitoring and addressing, when possible, their underlying health conditions.

Our study showed a clear connection between the existence of comorbidities and the increasing likelihood of patients requiring pacemakers in the future. Effectively managing these conditions could potentially delay the need for a pacemaker. For instance, controlling diabetes can decrease the risk of the patient developing arrhythmias that cannot be controlled with simple medications. Understanding these correlations allows the cardiac team to design personalized treatment plans for each patient instead of following guidelines that do not consider patients' underlying comorbidities.

The use of ILRs and, as such, 24/7 rhythm monitoring in patients with unexplained syncope and known comorbidities is beneficial in optimizing the time to treatment and determining which treatment is best for each patient.

In conclusion, this study's clinical relevance lies in its potential to enhance treatment protocols and patient outcomes. By stressing the importance of managing health conditions in individuals experiencing syncope episodes, our findings support a more beneficial method of patient care.

4.4 Limitations

The SCOPE 15 research although thorough has limitations that may affect how we interpreted the findings:

- **Retrospective Approach:** Because it looks back at data, the study relies on information that was recorded previously which could have some flaws in terms of accuracy and extensiveness.
- **Patient History Information:** The accuracy of histories taken from databases could rely on how detailed and precise the notes were, by various healthcare providers.
- **Applicability:** Since the study was carried out within one healthcare system its conclusions may not directly apply to other NSH Trust or different healthcare systems.
- **Changes:** Over a period of 15 years covered by the study there have been advancements in ILR technology and clinical guidelines. These changes, in technology and methodology could affect how we compare data across time points during the study period.

The SCOPE 15 study's approach aimed to minimize these issues as possible. However it is important to acknowledge that these limitations are inherent in the study design and should be taken into account when interpreting the research findings.

4.5 Future Research Directions

Future studies should concentrate on overcoming the limitations highlighted in our research through carrying out studies involving larger and more varied participant groups.

Examining the lasting effects on patients with ILRs and pacemakers concerning accompanying health conditions can grant deeper insight into the efficacy of these treatments. Understanding how diverse health issues affect patients long term outcomes will aid in refining protocols and enhancing patient care strategies.

Moreover, delving into the integration of emerging technologies like heart monitors and artificial intelligence (AI) algorithms could improve precision and patient care. Wearable monitors provide real time data gathering that when paired with AI powered analysis could enhance detection of heart rhythm irregularities and streamline decision making processes for pacemaker placements. In some cases, this is already been done with device companies like Medtronic using AI algorithms on their devices.

Future studies could also investigate patient focused outcomes, such as quality-of-life functional ability and patient satisfaction to assess the effects of ILR and pacemaker therapy beyond measures. By including these perspectives in research, we can ensure that upcoming interventions align with needs and preferences contributing to the development of a more personalized treatment.

Collaboration among other medical centers and healthcare systems would also be essential. Through sharing data and expertise researchers can overcome a number of limitations.

To sum up addressing these research routes will advance tailored medicine. Enhance the provision of care for individuals, with syncope and arrhythmias ultimately leading to better patient outcomes and increased healthcare efficiency.

5

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APPENDIX – ETHICS APPROVAL

Thesis Data Approval

CORREIA, Laura (ASHFORD AND ST PETER'S HOSPITALS NHS FOUNDATION TRUST) <l.correia@nhs.net>

Fri 05/01/2024 13:45

To:CAMARGO, Celso (ASHFORD AND ST PETER'S HOSPITALS NHS FOUNDATION TRUST) <celso.camargo@nhs.net>
Cc:POTTER, Christina (ASHFORD AND ST PETER'S HOSPITALS NHS FOUNDATION TRUST) <christinapotter@nhs.net>

From: JONES, Yvonne (ASHFORD AND ST PETER'S HOSPITALS NHS FOUNDATION TRUST) <yvonne.jones11@nhs.net>
Sent: 05 January 2024 08:42
To: CORREIA, Laura (ASHFORD AND ST PETER'S HOSPITALS NHS FOUNDATION TRUST) <l.correia@nhs.net>
Subject: FW: Thesis Data Approval

Hi Laura,

Please see email trail below which confirms that the Medical Director, research, and IG leads are all happy for you to go ahead on the understanding that the data is anonymised with no data that could identify an individual leaving the Trust.

I hope your study goes well, if I can be of any further help, please let me know.

Kind regards,

Yvonne

Yvonne Jones
Head of Clinical Effectiveness
Quality Department
St Peter's Hospital

From: TOWNSEND, Jane (ASHFORD AND STPETER'S HOSPITALS NHS FOUNDATION TRUST) **<janetownsend@nhs.net>**
Sent: Wednesday, January 3, 2024 2:43PM
To:FLUCK, David (ASHFORD AND STPETER'S HOSPITALS NHSFOUNDATION TRUST) <david.ffuck@nhs.net>;JOHN, Isaac (ASHFORD ANDSTPETER'S HOSPITALS NHSFOUNDATION TRUST) <Isaac.John@nhs.net>;JONES, Yvonne (ASHFORD AND STPETERS HOSPITALS NHSFOUNDATION TRUST) <yVOnne.jonesll@nhs.net>
Cc:DHALIWAL, Kam (ASHFORD ANOST PETER'S HOSPITALS NHSFOUNDATION TRUST) <kam.dhaliwall@nhs.net>
Subject:RE: Thesis Data Approval

Hi Isaac,

Many thanks for your email. Unfortunately,there was no '1n1tial protocol' attached to the email. However, I understand that cardiac loops record heart rhythms so I assume that it would be simple to anonymisc these cg. sendraw data only. Aslongas thereisnoidentifiable information being shared, thenIGhavenoob;ection.

KlrdRegards, Jane

I do not work on Fridays

Jane Townsend | Information Governance Manager & Data Protection Officer
IGTeam at Ashford & St Peter's Hospitals NHS Foundation Trust
Phone: 01932 722384 / 07SI0 38327S
Email: laoetownseod®nhsnet/ iliP·tcIG@nhsnet
Website: https:/fwww.ashfordstoeters.info/patient-information
Int(anet: Info(mation Governaoce (asP.:h.nhs.uk).

Isyour Pata Secudtv & Awareness trainingup to date?

From:FLUCK, David (ASHFORD ANOST PEHR'S HOSPITALS NHS FOUNDATION TRUST) <david.ffuck@nhs.n•t>
Sent: 03 January 2024 09:40
To:JOHN,Isaac (ASHFORD AND STPETERS HOSPITALS NHSFOUNDATION TRUST) <i5aac.inhn@nh5.net>; JONES, Yvonne (ASHFORD ANDSTPETER'S HOSPITALS NHS FOUNDATION TRUST) <vvonne.jonesl l@nhs.net>; TOWNSEND, Jane (ASHFORD AND ST PETER'S HOSPITALS NHSFOUNDATION TRUST) <Janotownsend@nhs.net>
Subject: Re:Thesis Data Approval

thank you Isaac

From:JOHN, Isaac {ASHFORDAND ST PETER'SHOSPITALSNHS FOUNDATION TRUST) <isaac.john@nhs.net>
Sent: 03 January 2024 09:22
To:FLUCK, David (ASHFORD ANO STPETER'SHOSPITALSNHSFOUNDATION TRUSn <david.fluck@nhs.net>; JONES, Yvonne (ASHFORD ANDST PETER'SHOSPITALSNHS FOUNDATION TRUST) <.v.vonn•.Jonesll@nhs.net>;

2'1/0S/24, "16:51 E«w • CORREIA, Laura(ASHFORDANOSTPETER·s HOSPffALSNHS!=OUI\"OATIONTRUST}- Outloak

TOWNSEND, Jane (ASHFORD ANDST PETER'S HOSPITALSNHSFOUNDATION TRUST) <janetownsend@nUi.IIil:.

Subject: RE: ThesisData,\pproval

Dear David

It is a retrospective data collection andanalysis.If the datais anonymised, thenno consent wouldbe required. Ana Laura Correla our cardiac phys olog1st1sregistered in Portugal not in the UK. Thus, data willbesubmitted for a degree in Portugal. I hope it should be fine as ongas Jane is content with this arrangement

Isaac

From:FLUCK, David (ASHFORD ANDST PETER'S HOSPITALS NHS FOUNDATION TRUST) <david.fluck@nhs.net>
Sent: Wednesday, January 3, 2024 9:09 AM
To:JONES, Yvonne(ASHFORDMD STPETER'S HOSPITALS NHS FOUNDATION TRUST) <.Y.J!onne.jones1l@nhs.net>; JOHN, Isaac (ASHFORD ANO ST PETER'S HOSPITALS NHS FOUNDATION TRUST) <Isaac.j2h!!@.nhs.net>; TOWNSEND, Jane {ASHFORD ANDSTPETER'SHOSPITALS NHSFOUNDATIONTRUST) <janetowosend@ohs.net>
Subject:RE: Thesis Data Approval

Be good to get your advice tsaac andjane'sbut I would besupportive as long aswe havethe right consent/ethics in place and the right IGarrangements

david

From:JONES, Yvonne (ASHFORD AND ST PETER'S HOSPITALS NHS FOUNDATION TRUST)
<.V=nll,j=11@.Jl.bi.nel>
Sent: Wednesday, January 3, 2024 8:37 AM
To:HUCK, David (ASHFORD ANO STPETER'S HOSPITALS NHSFOUNDATION TRUST) <davld.Ruck@nhs.net>; JOHN, Isaac (ASHFORD ANO STPETER'SHOSPITALS NHSFOUNDATION TRUST) <isaac.j2hn.@.nhs.net>
Subject:FW: Thesis Data Approval

Hi David andIsaac,

Areyou ableto advise on the attacned please, as it is not a din calaudit or research what approval process would we follow? I havenot beeninvolved with the ethics committee but this seems to be more of a request to use data in an anonymised way. Does this corr,e under the Caldicon guardian role?

Kindregards,

Yvonne

Yvonne Jones
Head of Clinic.a Effectiveness
Quality Department
St Peter's Hospita

From: CORREIA, Laura (ASHFORD ANDST PETER'S HOSPITALS NHSFOUNDATION TRUST) <l.corrcia@nhs.net>
Sent:Monday, January 1, 2024 4:17 PM
To: JONES,Yvonne (ASHFORD ANDSTPETER'S HOSPITALS NHS FOUNDATION TRUST) <.v=j=11@
Subject: Th s, Data Aproval

Good Afternoon,

My name is Ana Laura Correia, I'm currently working asa Band 6 Cardiac Physiologist at St Peters.
At the s.ame time, I'm doing a Master in Health statistics at the Institute of Hygiene and Tropical Medicine Universidade Nova Oe Lisboa, aspart or my final thesis I would like to request permission to use the data **from the loop recordersthat were explantedinthishospital.**
I have attached a copy of my initial protocol.
All the patient data will be anonymized per the ethics guidelines of the NHSand my University.
If the ethics committee needs more information about the study I'm more than happy to give it.

Kind Regards
Laura

Laura Corrcial Band 6 Cardiac Physiologi.sl
RCCP Registered!Ashfordand St. Peter's NHS FoundationTrust
E.:l.oorrcia@nhi1.net | W: W\\'\\-.ai1hford!!!P.:£tcr.i.nhs.11\-