An Attention-based Deep Learning Approach for Lifespan Assessment of Heart Failure Risk Among Patients with Congenital Heart Disease

Harry Moroz

Division of Experimental Medicine

Faculty of Medicine

McGill University, Montreal

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English Abstract

Objective—Congenital heart disease (CHD) presents persistent challenges and risks, including long-term comorbidities such as heart failure (HF), necessitating precise delivery of care. This study aims to develop a machine learning method for assessing the lifespan HF risk trajectories by incorporating the comprehensive medical histories of patients with CHD.

Methods—We developed *hART* (heart failure Attentive Risk Trajectory), a deep-learning model to predict HF trajectories in CHD patients. *hART* is designed to capture the contextual relationships between medical events within a patient's history. Specifically, it uses masked self-attention mechanisms to focus on the most relevant segments of the past medical events while not peaking ahead of the future events. To demonstrate the utility of *hART*, we used a retrospective cohort containing healthcare administrative data from the Quebec CHD database (137,493 patients, 35-year follow-up). We evaluated *hART*'s performance by area under the receiver operating characteristic (AUROC) curve and area under the precision-recall curve (AUPRC) in predicting future HF compared to the state-of-the-art methods. We further evaluated the effectiveness of *hART* by examining the differences in HF risk trajectory for patient subgroups, including those with genetic syndrome and severe CHD lesions, as well as patients who died at different ages. Additionally, we computed individualized trajectories and extracted attention weights to assess how specific medical events contribute to rising predicted HF risk. Finally, we extended *hART* by developing *hART-Generative Pre-trained Transformer (GPT)*, which is pre-trained to learn the clinical language of the diagnoses and comorbidities conditions across all patients and then fine-tuned to more accurately predict HF compared to the baseline *hART* that was trained to predict HF from scratch.

Results—*hART* outperformed existing methods, achieving an AUROC of 0.967 and an AUPRC of 0.282 for HF risk prediction. The analysis of computed HF trajectories across different populations revealed that patients with severe CHD lesion consistently exhibited elevated HF risks throughout their lifespan. This indicates the potential for the use of *hART* for effective risk stratification. Patients with the genetic syndrome of CHD exhibited elevated HF risks until the age of 50. Notably, we found a decrease in the impact of the birth condition on long-term risk,

emphasizes how *hART* recognizes the significance of birth conditions and their varying impact on HF risk over different lifespans. Moreover, our study showcased how *hART* captured the importance of the timing of medical events, such as surgery. By analyzing the HF trajectory of individual patients, *hART* demonstrated that the timing of arrhythmic surgery had varying impacts on lifespan HF risk, as we demonstrated that arrhythmic surgery performed at a younger age had minimal long-term effects on HF risk, while surgeries during adulthood had a significant lasting impact. This underscores the model's ability to consider the context and timing of medical events. The *hART-GPT* model demonstrated superior accuracy in predicting comorbidities associated with HF, such as stroke, infective endocarditis, sepsis, MI, and acute kidney disease. Furthermore, after fine-tuning, it demonstrated slightly improved HF prediction over *hART*.

Conclusions—This study demonstrated that attention-based deep learning models can accurately assess lifelong HF risk in patients with CHD. This study developed a model that accurately captures both long—and short-range dependencies in patient histories while offering enhanced interpretability for clinicians through the inclusion of HF trajectories and attention matrices. The interpretable disease trajectories provided by our model have the potential to enable clinicians to identify high-risk individuals, optimize intervention timing, and assess the long-term impact of comorbidities in CHD patients.

French Abstract

Objectif—Les cardiopathies congénitales (CC) présentent des défis et des risques persistants, notamment des comorbidités à long terme telles que l'insuffisance cardiaque (IC), ce qui nécessite une prestation de soins précise. Cette étude vise à développer une méthode d'apprentissage automatique pour évaluer les trajectoires de risque d'insuffisance cardiaque tout au long de la vie en incorporant les antécédents médicaux complets des patients atteints de cardiopathie congénitale.

Méthodes— Nous avons créé *hART* (heart failure Attentive Risk Trajectory), un modèle d'apprentissage profond pour prédire les trajectoires d'insuffisance cardiaque chez les patients atteints de maladies coronariennes. *hART* saisit les liens contextuels entre les événements médicaux dans l'historique du patient. Il utilise des mécanismes d'autoattention pour cibler les segments pertinents des événements passés, sans anticiper les futurs. Pour montrer son utilité, nous avons utilisé des données de soins de santé québécoises (137 493 patients, 35 ans de suivi). *hART* a été évalué en termes d'aire sous la courbe ROC (AUROC) et de précision-rappel (AUPRC) pour prédire l'insuffisance cardiaque future comparé à des méthodes avancées. L'efficacité de *hART* a été examinée pour des sous-groupes, y compris patients génétiques et atteints de lésions cardiaques graves, ainsi que décédés à différents âges. Des trajectoires individualisées et des poids d'attention ont évalué comment des événements spécifiques influent sur le risque prédit d'insuffisance cardiaque. *hART* a été étendu à *hART*-Generative Pre-trained Transformer (GPT), préentraîné pour le langage clinique, puis affiné pour prédire l'insuffisance cardiaque avec plus de précision que la base *hART*.

Résultats—*hART* a surpassé les méthodes existantes, atteignant un AUROC de 0,967 et un AUPRC de 0,282 pour la prédiction du risque d'IC. L'analyse des trajectoires d'IC dans diverses populations a montré que les patients souffrant de lésions coronariennes graves avaient constamment des risques élevés d'IC tout au long de leur vie, soulignant le potentiel de hART pour une stratification précise du risque. Les patients atteints du syndrome génétique de la CC présentaient des risques élevés d'hypertension jusqu'à l'âge de 50 ans. Nous avons notamment constaté une diminution de l'impact de la condition de naissance sur le risque à long terme, ce

qui souligne la façon dont l'étude *hART* reconnaît l'importance des conditions de naissance et leur impact variable sur le risque d'infarctus du myocarde au cours des différentes périodes de la vie. De plus, notre étude a illustré comment *hART* a saisi l'importance du timing des événements médicaux, comme les chirurgies. En étudiant les trajectoires d'IC pour les patients, hART a révélé que la chirurgie arythmique à un jeune âge avait un impact mineur à long terme sur le risque d'IC, tandis que les chirurgies à l'âge adulte avaient un effet important et persistant. Ceci souligne la capacité du modèle à considérer le contexte et le timing des événements médicaux. Le modèle *hART-GPT* a affiché une meilleure précision dans la prédiction de comorbidités liées à l'IC, telles que AVC, endocardite infectieuse, septicémie, infarctus du myocarde et insuffisance rénale aiguë. De plus, après l'ajustement fin, la prédiction de l'IC s'est légèrement améliorée par rapport à *hART*.

Conclusions— Cette étude montre que les modèles d'apprentissage profond basés sur l'attention peuvent précisément évaluer le risque d'IC à vie chez les patients atteints de CC. Le modèle développé capture les dépendances à court et long terme dans l'historique des patients et offre une meilleure interprétabilité pour les cliniciens via des trajectoires d'IC et des matrices d'attention. Les trajectoires interprétables de la maladie permettent aux cliniciens d'identifier les hauts risques, d'optimiser les interventions et d'évaluer les effets à long terme des comorbidités chez les patients atteints de CC.

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I would also like to thank my girlfriend, Leslie Unger, for her endless support and for making the wonderful figures you'll see below.

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Contribution of Authors

Harry Moroz, BSc., MSc candidate.

Harry has led the proposal, developed and writing of this research. He conducted an extensive literature review and has taken the lead in programming and testing the machine learning methods of our study. Lead the experimentation and writing of manuscript. Attended weekly research team meetings and presented findings to the MSc Thesis Committee.

Ariane Marelli, MD, MPH

Primary thesis supervisor. Co-lead the proposal and ideation of the research. Provided the opportunity for funding application to the FRQ-S, the data sources and clinical motivation with continuous guidance on how to structure the project and which direction to pursue. Regularly provided support and feedback reviewing and editing the manuscript.

Yue Li, PhD

Co-Supervisor. Co-lead the proposal and ideation of the research. Supervised the development of methodology, the machine learning methods, design of the study, reviewing and editing of the manuscript. Hosted weekly meetings with himself or his team to assess review results and provide valuable feedback.

Aihua Liu, PhD

Lab Coordinator. Responsible for curating and preparing the dataset crucial for the research project. Additionally, she provided unwavering support and constructive feedback throughout the entire process, while also undertaking the task of editing the thesis.

Robyn Tamblyn, PhD

Academic Advisor. Attended committee meetings and provided feedback on the study findings. Helped to navigate administrative processes.

James Brophy, MD, PhD

Member of thesis committee. Attended committee meetings and provided feedback on the study findings.

Archer Yi Yang, PhD

Member of thesis committee. Attended committee meetings and provided feedback on the study findings.

List of Abbreviations

CHD	Congenital Heart Disease
HF	Heart Failure
ACHD	Adult Congenital Heart Disease
hART	Heart failure Attentive Risk Trajectory
EHR	Electronic Health Records
HFH	Heart Failure Hospitalization
ML	Machine Learning
DL	Deep Learning
RNN	Recurrent Neural Network
LSTM	Long Short-Term Memory
GRU	Gated Recurrent Unit
AI	Artificial Intelligence

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CHAPTER 1: THESIS INTRODUCTION

Congenital heart disease (CHD) is a complex condition characterized by structural abnormalities in the heart that are present at birth (1). It is one of the most prevalent types of birth defects worldwide, affecting 1% of all births (2). With advancements in medical interventions, many patients with CHD now survive into adulthood, presenting unique challenges in managing their long-term health outcomes (3, 4). Among these challenges, the risk of heart failure (HF) remains a significant concern, as it contributes to increased morbidity and mortality in this population (5). Heart failure is one of the most frequent comorbidities of CHD. Accurately assessing and predicting its occurrence over a patient's lifespan is crucial for effective management of improving patient outcomes (6).

The assessment of HF risk in patients with CHD continues to evolve as researchers and clinicians seek to improve risk stratification, identify risk factors, and guide treatment decisions. Initially, the primary focus of risk assessment models in CHD was to identify biomarkers or variables that correlated with negative HF-related outcomes. These models heavily relied on clinical characteristics and anatomical parameters to estimate the probability of developing HF (7, 8). These models had limitations, including their oversight of the dynamic nature of HF risk and the complex interplay between various clinical variables (9, 10). Our laboratory has made significant contributions to HF risk modelling in CHD patients by developing various statistical methods, including regression (11) and survival (12) models, as well as pioneering the use of deep learning (DL) to assess HF risk (13), although the challenges of measuring risk over extended observation periods are evident in these models.

It has become evident that these methods alone have limitations in addressing the long-term prediction required for effective CHD management and a proactive approach to care. Given that HF is a progressive condition that develops over time, early identification of individuals at risk holds great potential for timely interventions and improved outcomes. Specifically, understanding the long-term trajectory of HF risk and the factors influencing it at different stages of life is pivotal in informing resource allocation, specialized care provision, and policy decisions aimed at reducing the overall burden of HF (9). To address the need for accurate long-term risk assessments, researchers have turned to innovative methodologies, including advanced statistical techniques and machine learning algorithms (7). These approaches allow for the

integration of large numbers of patient-specific factors, such as demographic information, genetic predisposition, anatomical complexity, and surgical history, to develop more personalized risk prediction models, improved risk stratification precision and precise treatment planning (9, 13).

The primary objective of this thesis is to develop a novel deep-learning method that leverages electronic health record (EHR) data from patient histories to model the lifespan risk of HF. This method is presented in a manuscript titled "*hART: Deep Learning-Informed Lifespan Heart Failure Risk Trajectories for Patients with Congenital Heart Disease*," which aims to provide a more accurate and personalized assessment of HF risk for individuals with CHD. The thesis also aims to explore the clinical applications of this novel approach, evaluating its potential to inform risk stratification and resource allocation for patients with CHD. The thesis includes a comprehensive literature review to evaluate the evolution of methods used in assessing and modelling HF risk in CHD patients. We will identify the limitations of existing approaches in modelling long-term HF, address the current challenges that persist in achieving accurate lifespan HF risk assessment, and discuss the clinical implications of these findings. Through these objectives, the thesis aims to contribute to the advancement of lifespan risk assessment methodologies and improve the precision of delivery of care, clinical outcomes, and disease burden for individuals with CHD at risk of developing HF.

CHAPTER 2: LITERATURE REVIEW

2.1 Overview of Congenital Heart Disease and Heart Failure

Congenital heart disease (CHD) has now been described as a chronic condition, characterized by structural abnormalities in the heart present at birth, necessitating long-term management and care throughout an individual's lifetime (6). It encompasses a range of conditions, varying in complexity and severity, such as defects in the heart's chambers, valves, or blood vessels. The etiology of CHD is multifactorial and involves a combination of genetic, environmental, and epigenetic factors (14). The clinical manifestations and outcomes of CHD can vary significantly based on the specific defect, its severity, associated anomalies, and the

timing of diagnosis and intervention (15). Advancements in medical technology, such as prenatal screening, diagnostics, and surgical innovations, have enhanced early detection, enabling timely interventions and ultimately resulting in higher survival rates and improved quality of life for individuals with CHD (3). However, despite these advancements, CHD remains a complex and challenging condition. Many patients require multiple surgeries or interventions throughout their lifetime, and the risk of complications and long-term sequelae, including HF, remains a concern (4, 9, 16). The adult CHD (ACHD) population is currently experiencing a significant proportion (approximately 20–50%) of advanced HF cases, making it the primary cause of death in this population. Furthermore, this trend is projected to continue, resulting in a rising number of ACHD patients with advanced HF in the future (17-19).

Heart failure in CHD patients can arise due to the underlying structural abnormalities, resulting in impaired heart function over time (20). The pathophysiology of heart failure in adults with CHD is more complex and intricate compared to the general population (21). The complex nature of disease progression and the wide heterogeneity in outcomes make it crucial to develop accurate prognostic models that can estimate lifespan risk trajectories at both population and individual levels (22). By understanding the underlying pathophysiological mechanisms and identifying key risk factors specific to patients with CHD, clinicians and researchers can better tailor treatment strategies, and allocate healthcare resources more effectively (6). Therefore, developing a reliable predictive model for lifespan HF risk in CHD patients is of utmost importance and can significantly contribute to improving patient care and outcomes in this population (9).

2.2 Evaluating Risk Factors for Heart Failure in Congenital Heart Disease Patients

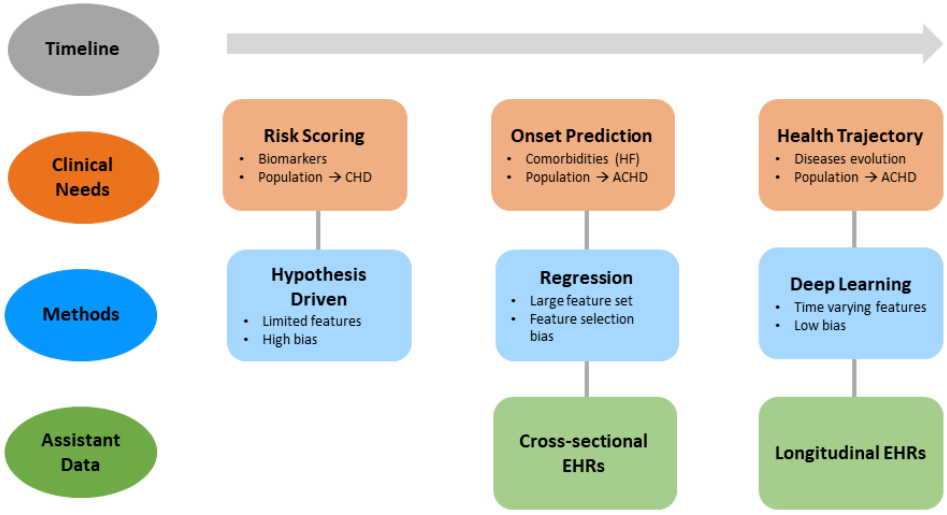
Risk factors for HF in CHD patients differ from those in individuals without CHD. While risk factors for HF reported in the general population, such as hypertension, diabetes, and obesity, also apply to CHD patients, there are additional factors specific to this population (10). The underlying structural abnormalities of CHD play a significant role in increasing the risk of HF (23). The type, severity, and complexity of the congenital heart defect, along with residual lesions and the need for surgical interventions, contribute to the heightened risk. Additionally, the presence of associated anomalies, abnormal heart rhythms, pulmonary hypertension, and the

timing of interventions can impact the likelihood of developing HF in CHD patients (24). Overall, the presence of a variety diverse and interconnected risk factors for HF in CHD, combined with the inherent heterogeneity of the CHD population, poses significant challenges in accurately assessing and managing HF risk (25). Thus, developing model to understand the risk factors and risk of comorbidities unique to patients with CHD is essential to precision delivery of care for this patient population (6).

2.3 Methods for Assessing Risk of Heart Failure in Patients with Congenital Heart Disease

Over the years, a variety of prognostic models and predictive approaches have emerged (7, 26), each with its own set of strengths and limitations. Some of the most common methods include traditional statistical approaches (27, 28), regression-based models (8, 10, 11), survival models (12, 29), and deep learning approaches (13, 30, 31). Ongoing research in this area, driven by the need to tackle the new challenges presented by the aging and increasing complexity of care for the population (32), has led to the adoption of new methods that offer unique insights into the assessment of risk factors associated with heart failure in CHD patients. Figure 1 illustrates the progressive evolution of methods in response to the evolving clinical needs of the CHD population. Over time, there has been a shift in focus, transitioning from risk scoring to disease onset prediction and, more recently, emphasizing the importance of lifespan health trajectories. This shift reflects the changing management strategies in CHD. As a result, we observe a corresponding advancement in modelling techniques, starting from hypothesis-driven approaches and progressing to regression models, with the recent emergence of deep learning methods. The utilization of both cross-sectional and longitudinal electronic health records (EHRs) has made the development of these sophisticated models possible. In the subsequent sections, we will delve deeper into each of these methods and examine their capacity to capture the intricate relationships among medical events associated with HF in patients with CHD.

Figure 1: Overview of the Evolution of Methods of Modelling HF for CHD patients



2.3.1 Heuristic Modelling

Traditional statistical methods used in clinical trials and clinical risk prediction scenarios test hypotheses related to one or many independent variables. These approaches based on prior knowledge select features to assess the correlation of biomarkers on various CHD-related outcomes (27, 28, 33). The biomarkers identified in studies using hypothesis driven methods have identified significant risk factors for HF-related admissions (27), and helped classify adult patients at higher risk of HF (28, 34). However, their simplistic design limits their ability to capture complex relationships between variables and the wide range of possible outcomes, making long-term risk estimates using traditional statistical techniques less comprehensive and less accurate (33). This is most prominent for the aging population with CHD, which has greater heterogeneity and complexity of diseases, along with an increased prevalence of comorbidities, particularly due to prior surgeries (34-36).

2.3.2 Regression Modelling

Regression analysis has become a prominent method for developing risk scores in the context of HF among patients with CHD. This multivariable approach estimates coefficients,

such as log odds or hazard ratios, for each predictor and adjusts them in relation to other predictors within the model, offering a quantitative measure of each variable's contribution to the outcome's risk (37). Several studies have successfully utilized regression analysis to create risk scores which stratify high- and low-risk patients (8, 32). Additionally, facilitated by the availability of large medical databases and Electronic Health Records (EHR), these methods identify how specific medical events and factors contribute to a higher likelihood of HF, such as age, sex, CHD lesion severity, recent 12-month HF hospitalization (HFH) history, and comorbidities (10, 11). While researchers can easily validate and interpret risk scores developed using regression models, the static nature of predictors and outcomes, along with the linear nature of regression, limits the ability of these models to capture complex relationships among predictors. (8, 10, 11, 32).

2.3.3 Survival-Based Modelling

Unlike linear-based regression, survival models consider the time until the occurrence of an event, such as the onset of HF. Thus, they can capture the temporal aspect of risk prediction, allowing for an understanding of disease progression and time-dependent factors (38). Several studies have successfully identified risk factors and biomarkers which contribute to 1-year HF risk, such as age ≥ 50, male sex, recent 12-month HFH history, pulmonary arterial hypertension, chronic kidney disease, coronary artery disease, systemic arterial hypertension, and diabetes and several other comorbidities (11, 12, 17, 29). Additionally, these methods can identify critical short-term periods in subsets of a patient's lifespan when the risk of HF may increase, enabling targeted interventions and monitoring strategies (11, 12, 39). However, the current models developed for predicting outcomes in the aging CHD population have primarily focused on short-term risk assessment (1-year risk) (11, 12, 29), leaving long-term relationships largely unaddressed (9) and limited (40, 41). Although various studies have demonstrated comparable performance between survival approaches and machine/deep learning techniques in certain contexts (42, 43), our team's prior research indicates that survival approaches such as Cox regression may yield suboptimal accuracy in modeling CHD outcomes (44). Furthermore, modelling time-to-event data in the context of CHD presents significant challenges due to the heterogeneity and dynamic nature of the condition. The complex interplay of diverse disease

presentations and evolving patient profiles further complicates the accurate prediction of long-term outcomes using survival models (7, 13, 38).

2.3.4 Deep Learning-based Modelling

Deep learning (DL) is a subfield of machine learning (ML) that focuses on training artificial neural networks with multiple layers to identify complex patterns and relationships within data, without relying on predefined assumptions, linearity or bias of feature selection (45). Deep learning models excel at handling high-dimensional and unstructured longitudinal data, such as medical imaging, text from medical records and event-based diagnosis codes. These methods capture evolving risk and personalize predictions over time, thereby modelling long-term hidden patterns that regression and survival models may not capture (46-48). This adaptability is particularly crucial given the variability in disease progression and treatment response among individuals with CHD (9, 49). The use of DL to model CHD-related outcomes is an emerging topic (49). Diller et al. (2019) demonstrated the utility of deep learning networks by combining convolution networks and dense networks to build a disease severity score based on clinical data, diagnosis data, imaging, medications, and other variables (30). Lu et al. (2020) presented the first use of DL in HF modelling for adult patients with CHD by employing recurrent neural networks (RNNs), specifically long-short-term-memory (LSTM) and gated recurrent unit (GRU) models, to capture long-range non-linear dependencies in sequential events (13). Their supervised longitudinal GRU model accurately predicted HF and other comorbidities associated with the patient's history, surpassing traditional statistical models such as Cox proportional hazard models (13). Despite the promising potential of deep learning methods like convolutional neural networks and RNNs in modelling the progression of HF risk over a lifespan (13, 50), there are still notable limitations to address. These studies reported relatively poor accuracy for longer prediction periods (13, 51). There is also the need to develop methods for forecasting continuous HF risk estimates in diverse CHD populations (6, 9). Additionally, the challenge of limited interpretability and the "black box" nature of deep learning algorithms remains a significant concern, particularly when developing tools for clinicians that require a clear understanding of the underlying mechanisms (52).

2.4 Current challenges for long-term HF risk assessment

While assessing HF in CHD patients, it is important to recognize the remaining limitations and challenges associated with the various employed modelling methods presented above. This section summarizes key limitations that researchers have encountered in the existing literature, hindering the accurate and comprehensive modelling of HF risk in CHD patients.

2.4.1 Modelling the Long Dependencies between Medical Events

One major limitation in HF risk assessment modelling is the difficulty in capturing long-range dependencies among variables (13, 49). Many traditional models struggle to effectively capture and incorporate complex relationships that extend over extended periods of time, leading to suboptimal predictions for long-term HF risk trajectories. This limitation hinders the ability to accurately forecast HF outcomes and develop personalized intervention strategies for CHD patients (13, 49).

2.4.2 Utilizing Longitudinal Electronic Health Records (EHR)

The utilization of EHR data presents unique challenges in HF risk assessment modelling. While EHRs offer vast amounts of patient information, including diagnoses, treatments, and medical events, effectively harnessing this data for modelling purposes is a complex task. Issues such as missing data, data quality, and heterogeneity among EHR systems can impact the accuracy and reliability of risk assessment models. Additionally, integrating diverse types of EHR data, such as clinical notes, imaging data, and laboratory results, requires sophisticated methods to ensure meaningful and comprehensive modelling (9, 46, 50, 53).

2.4.3 Interpretability

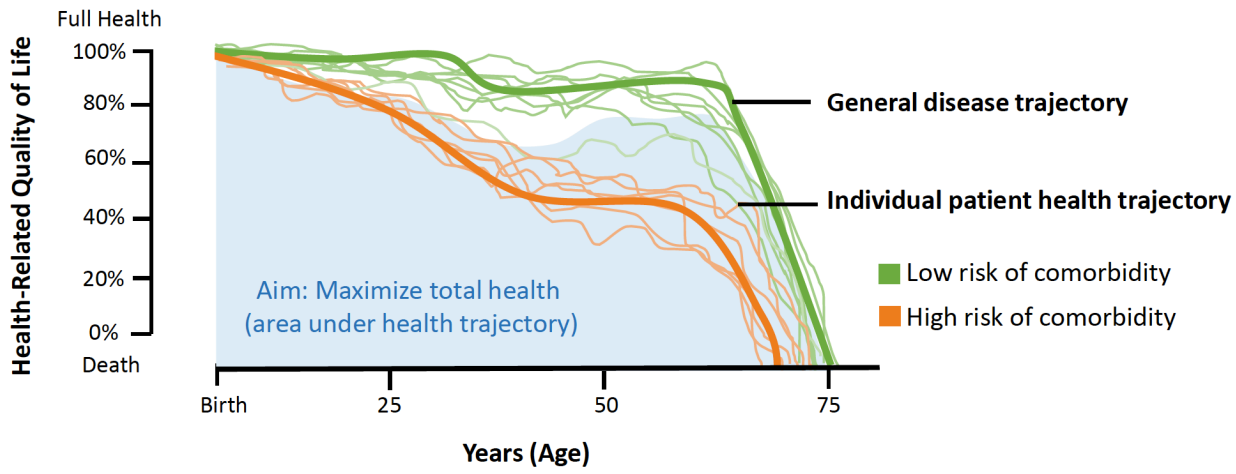
The interpretability of a predictive model refers to its capacity to provide human-understandable justifications for its output, allowing for insights into its inner workings (54). DL models often lack interpretability as their complex architectures and high-dimensional

representations make it challenging for non-specialists to discern the reasoning behind their predictions, limiting the ability to provide clear and understandable explanations (52, 54). Interpretability is essential for many tasks, such as medical diagnosis, as it leads to trust in the model. As artificial intelligence (AI) methods expand into healthcare, significant restructuring is required between the models developed by computer scientists and their application and use by clinicians to inform clinical interventions. This is a multifactorial challenge that requires improving factors related to clinician acceptability and understanding of AI-based solutions, human engineering factors as well as the ability to migrate models into user-friendly informative tools to facilitate applied knowledge translation (52).

2.5. Current goals in heart failure risk assessment for patients with congenital heart disease

A state-of-the-art review conducted by prominent researchers in the field of CHD emphasized the importance of understanding the lifespan evolving risk of comorbidities, due to the changing demographics of the population (6, 9). They discussed the need of modelling disease trajectories, depicted in Figure 2, which provide a long-term view of a specific dimension of an individual's life over time. When applied to CHD, trajectories are a construct that "moves beyond the notion of episodic illness and towards a dynamic composite measure of disease burden" (9). In existing literature, few studies have investigated the modelling of complex disease trajectories over a patient's lifespan outside of survival-based approaches (7, 13). This is mainly due to the challenges discuss in section 2.4. However, the availability of longitudinal medical databases and recent advancements in DL methods have paved the way for future breakthroughs in the field. Therefore, the primary objective in assessing HF for patients with CHD is to establish a robust and interpretable lifespan HF prediction model (9, 49). Furthermore, future research endeavours should focus on developing models capable of capturing long-term patterns in patient histories, while maintaining interpretability and user-friendliness.

Figure 2: Disease and Health Trajectory (9)



2.6 Proposed Direction

Based on publications from other fields in healthcare, a possible course of research is to implement models using an attention-based DL method. The attention mechanism was introduced by Bahdanau et al. to address the limitation of previous models in modelling a long sequence of data (55). Attention has recently gained popularity due to its success within transformers-based model, such as *ChatGPT* (56). Attention enables the outputted representation to have full access to all parts of the input sequence rather than only the "close" time steps, allowing for a deeper understanding of the available data. Furthermore, the architecture of the attention mechanism facilitates the intuitive interpretation of the model's outputs using attention weights/scores which represent the relative importance between data points (55, 57). This method has already seen promise when applied to medical records. Song et al. developed an attention-based architecture for processing clinical time-series data which showed better results than RNNs (58). An et al. used attention-base neural networks to predict cardiovascular disease and comorbidities, such as HF (59). Furthermore, Chen et al. demonstrated that the incorporation of attention into a deep learning model can improve both the performance and interpretability of predicting readmissions for heart failure patients (60). The hopes are that using attention-based model will allow personalize, interpretable models and accurate of prediction of HF trajectories for CHD patients.

2.7 Clinical Implications

The clinical implications are far-reaching and have the potential to significantly impact healthcare practices, leading to improved patient outcomes. Accurate assessment of long-term HF risk in patients with CHD based on their past medical history carries substantial clinical implications. Figure 3 depicts the clinical usage of this approach. This approach not only enables researchers to uncover distinct HF trajectories within sub-populations but also identifies specific medical events occurring at times that significantly contribute to individual patient risk.

2.7.1. Risk Stratification

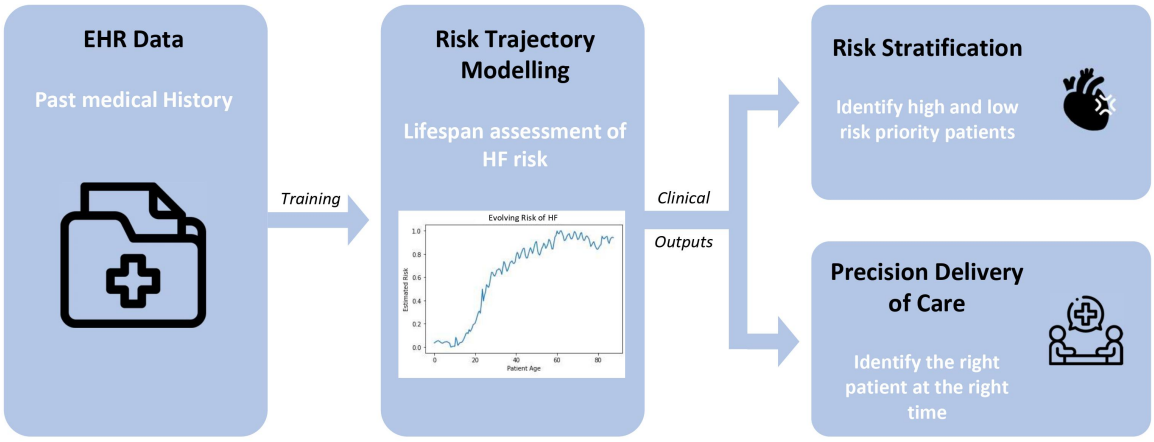
Risk stratification refers to the process of categorizing individuals into different risk groups based on their likelihood of developing an outcome. Risk stratification allows for the tailoring of follow-up protocols based on the individual patient's risk profile. High-risk patients can be scheduled for more frequent and comprehensive evaluations, including diagnostic tests, imaging studies, and specialist consultations. Despite limited availability of specialized care for CHD patients (61), regular monitoring and proactive management can help detect early signs of heart failure and enable timely interventions, leading to improved outcomes (5, 62). Specifically, risk stratification is commonly used to identify patients with CHD needing cardiac operations (63).

2.7.2 Precision Delivery of Care

Precision delivery of care refers to the concept of tailoring healthcare interventions and treatments to individual patients based on their specific characteristics, needs, and risk profiles. It involves utilizing personalized information, such as the patient's medical history, genetic markers, and clinical data, to guide decision-making and optimize the allocation of resources and timing of interventions. CHD patients have diverse disease presentations and comorbidities, variable disease progression rates, and unique response patterns to interventions. Precision delivery of care allows healthcare providers to identify optimal timings for interventions based on each patient's specific needs (6). Additionally, integrating advanced technologies, such as

predictive modelling and AI, can facilitate the precision delivery of care into clinical practice (9). These tools can leverage large datasets, including patient medical records and genomic data, to generate personalized risk assessments and treatment recommendations. This enables healthcare providers to make more precise and individualized decisions regarding the delivery of care (6, 49).

Figure 3: Clinical Workflow of Risk Trajectory Modelling



CHAPTER 3: MANUSCRIPT TO BE SUBMITTED

hART: Deep Learning-Informed Lifespan Heart Failure Risk Trajectories

Harry Moroz (1), Yue Li (2,3), Ariane Marelli (1,3)

(1 Department of Medicine, McGill University of Health Centre, Montreal, QC, Canada

(2) School of Computer Science, McGill University, Montreal, QC, Canada

(3) Co-correspondence: yueli@cs.mcgill.ca, ariane.marelli@mcgill.ca

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None.

Abstract

Objective—Heart failure (HF) results in persistent risk and long-term comorbidities. This is particularly true for patients with lifelong HF sequelae of cardiovascular disease (CVD) such as patients with congenital heart disease (CHD). This study aims to develop a machine learning method for assessing the lifespan HF risk trajectories by incorporating medical histories using a large CHD population to develop our models.

Methods—We developed *hART* (heart failure Attentive Risk Trajectory), a deep-learning model to predict HF trajectories in CHD patients. *hART* is designed to capture the contextual relationships between medical events within a patient's history. Specifically, it uses masked self-attention mechanisms to focus on the most relevant segments of the past medical events while not peaking ahead of the future events. To demonstrate the utility of *hART,* we used a retrospective cohort containing healthcare administrative data from the Quebec CHD database (137,493 patients, 35-year follow-up). We evaluated *hART*'s performance by area under the receiver operating characteristic (AUROC) curve and area under the precision-recall curve (AUPRC) in predicting future HF compared to the state-of-the-art methods. We further evaluated the effectiveness of *hART* by examining the differences in HF risk trajectory for patient subgroups, including those with genetic syndrome and severe CHD lesions, as well as patients who died at different ages. Additionally, we computed individualized trajectories and extracted attention weights to assess how specific medical events contribute to rising predicted HF risk. Finally, we extended *hART* by developing *hART*-Generative Pre-trained Transformer (GPT), which is pre-trained to learn the clinical language of the diagnoses and comorbidities conditions across all patients and then fine-tuned to more accurately predict HF compared to the baseline *hART* that was trained to predict HF from scratch.

Results—*hART* outperformed existing methods, achieving an AUROC of 0.967 and an AUPRC of 0.282 for HF risk prediction. The analysis of computed HF trajectories across different populations revealed that patients with severe CHD lesion showed a consistently elevated HF risks throughout their lifespan. Patients with genetic syndromes and CHD exhibited elevated HF risks until the age of 50. Notably, we found a decrease in the impact of the birth condition on

long-term risk, emphasizes how *hART* recognizes the significance of birth conditions and their varying impact on HF risk over different developmental stages of life. By analyzing the HF trajectory of individual patients, *hART* demonstrated that the timing of interventions such as arrhythmia surgery had varying impacts on lifespan HF risk, as we demonstrated that arrhythmic surgery performed at a younger age had minimal long-term effects on HF risk, while surgeries during adulthood had a significant lasting impact. This underscores the model's ability to consider the context and timing of medical events. The *hART-GPT* model demonstrated superior accuracy in predicting comorbidities associated with HF, such as stroke, infective endocarditis, sepsis, myocardial infarction, and acute kidney disease. Furthermore, after fine-tuning, it demonstrated slightly improved HF prediction over *hART*.

Conclusions—This study demonstrated that attention-based deep learning models can accurately assess lifelong HF risk in patients as developed in patients with CHD. We developed a model that accurately captures both long—and short-range dependencies in patient EHR history, while offering enhanced interpretability for clinicians through the inclusion of HF trajectories and attention matrices. The interpretable disease trajectories we generated have the potential to enable clinicians to identify high-risk individuals, optimize intervention timing, and assess the long-term impact of comorbidities in patients with lifelong comorbidities such as CHD patients.

Introduction

The delivery of care for chronic illnesses has become increasingly complex as patients age and their medical histories expand (1). The lifetime risk of heart failure (HF) ranges from 20-45% after the age of 45years in the United States (2). With advances in medical and interventional therapies, patients with congenital heart disease (CHD), the most common birth defect (3) are now surviving to adulthood (4). In patients with CHD, we have shown that HF is the leading cause of death with a cumulative incidence rate of 25% by age 65 (5, 6). Adult CHD (ACHD) patients face potential lifelong comorbidities. The demographic changes in the CHD population have motivated a paradigm shift in disease management with an increasing focus on a lifespan perspective and a proactive approach to care (7-9). This shift has refocused attention on the study of the comorbidities that affect the disease outcomes of ACHD. Improved management of comorbidities such as HF are pivotal to improving health outcomes and optimizing the associated healthcare resource utilization for ACHD patients (9-11). While we and others have contributed to understanding the prevalence and risk factors of HF in CHD (12-14), there remains the need to better understand and measure the long-term trajectory of disease progression in this patient population to optimize the timing of medical interventions and available resources (15). Incorporating large datasets to optimize the precision delivery of care, disease trajectories can provide a framework to assess the impact and relationship of different patient presentations, time-varying risk factors and comorbidities on the evolving risk of specific outcomes, such as heart failure.

Assessing the evolving risk of HF in patients with CHD remains a challenging task due to the complexity and the heterogeneity of patient presentations and difficulties in capturing long-range dependencies among variables (5, 12, 13). For many chronic illnesses, such as CHD, modelling the high-dimensional irregular time-varying nature of Electronic Health Record (EHR) data has been limited in its capacity to capture temporal patterns of the disease progression (5, 13, 16). However, recent advancements in deep learning (DL) have provided highly flexible frameworks that can accurately model long-term sequential patient data, including complex longitudinal clinical and epidemiological presentations of chronic diseases such as CHD (17, 18). Although DL techniques have been shown to be effective in modeling the trajectory of HF in lifespan CHD patients (18), capturing long-term temporal patterns of CHD,

and generating interpretable trajectories continue to pose a challenge. DL models that use Transformer architecture such as Bidirectional Embedding Representations by Transformers (BERT) and Generative Pre-trained Transformer (GPT)-3 (19) (i.e., the same framework used in the recently popularized *ChatGPT*) have produced remarkable results in natural language processing (NLP) tasks and outperformed recurrent neural networks in modeling sequential data (20-22). This is primarily because Transformers can capture long- and short-range temporal dependency by computing attention between all pairs of time points in an entire sequence (21, 23). In the context of our study, it is crucial to model the evolving chronic comorbidity conditions caused by CHD (which develops at birth) throughout a patient's lifespan, requiring the inclusion of the patient's complete medical history for accurate prediction of disease progression (24). Additionally, from an interpretability standpoint, one motivation for using attention-based learning to model patient medical data is that it allows for a more comprehensive and contextual understanding of the data. Just like how the GPT learns the contextual information within a sentence (19), medical events may have different importance and meaning within a patient's medical history. Attention-based models can use their attention mechanisms to focus on specific aspects of a patient's medical history and other relevant data, allowing them to consider the context and individual characteristics of the patient. This can provide a more accurate and nuanced understanding of the patient's health and can be used to improve treatment planning and decision making. By considering the full context of a patient's medical history, attention-based models can make more informed and personalized predictions or recommendations, which can ultimately lead to better patient outcomes. Several studies have investigated the use of self-attention in deep learning for patient representation learning, clinical decision support, and predicting future clinical events, and have shown promising results (23, 25-27).

In patients with CHD with a high lifespan risk of HF, our objectives were to: (1) Develop an attention-based deep learning model, *hART* (heart failure Attentive Risk Trajectory), using longitudinal EHR data to accurately predict lifespan HF risk and compare its performance to existing methods. (2) Assess *hART*'s ability to differentiate HF trajectories across populations based on CHD severity, genetic syndromes, and age of death. (3) Explore *hART*'s utility in evaluating individual patients' HF risk by analyzing the impact of specific medical events over time.

Methods

Data Sources

In Quebec, Canada, a unique Medicare number is assigned to individuals in their first year of life, enabling comprehensive tracking of diagnoses and health services throughout their lifetime. This study utilized administrative databases, including physicians' services and drug claims, hospital discharge summaries, and the Quebec Health Insurance Board and Death Registry. These databases contain vital statistics, demographic information, and diagnostic and procedure codes (ICD-9 and ICD-10) recorded since 1983. The Quebec CHD Database, one of the largest of its kind worldwide, was created by merging and cleaning data from these sources, identifying CHD patients using validated algorithms and optimizing the accuracy of diagnoses through manual audits (4).

The resulting dataset is from the Quebec CHD database, comprising 137,493 patients with up to 35 years of follow-up from 1983 to 2017. It includes demographic information, inpatient and outpatient diagnoses, surgical history, and vital status. HF events were identified based on hospitalizations with heart failure (HFH) as the admission and/or discharge diagnosis. The dataset includes demographic variables (sex and age), diagnoses (CHD lesion type, pulmonary hypertension, and coronary artery disease), hospitalizations (acute kidney injury and sepsis), and surgeries (percutaneous procedures, congenital surgeries, and surgical arrhythmia procedures). These variables were selected based on their relevance as potential predictors and common confounding factors associated with HF.

Study Population

The study population cohorts were obtained from the Quebec CHD database. For the training and evaluation of our models, we applied two exclusion criteria. Firstly, patients who entered the study after the age of 75 were excluded. Secondly, patients with less than 6 months of available data were excluded. Following these criteria, a total of 134,446 patients were included in the training and evaluation of our models. Out of these patients, 11.74 % experienced at least one HFH with the average age of HF being 62.97.

Study Design

This study comprises three phases aimed at developing and evaluating a novel longitudinal HF risk prediction model, *hART*, and exploring its application in clinical practice.

The first phase involves a retrospective cohort study designed to develop and evaluate the performance of the *hART* model in predicting the lifespan risk estimation of HF. An attention-based deep learning model is developed to accurately incorporate patients' entire medical histories using longitudinal EHR data from the Quebec CHD database. The following research question guides this phase: How does the performance of the novel *hART* model compare to existing methods and baseline models in predicting the lifespan risk estimation of HF?

The second phase focuses on analyzing the predicted HF trajectories obtained from *hART* are analyzed to explore the added value it provides in understanding patient populations and individualized risk trajectories. One of the key aspects of this phase is the interpretability of the DL model, enabling both clinicians and researchers to make informed clinical decisions and interventions. We investigate the question: Can *hART* discern variations in lifelong HF risk across diverse patient populations and characteristics? Additionally, we explore *hART*'s potential in assessing individual HF risk over time, investigating how distinct medical events influence predicted risk.

In the third phase, the focus shifts towards transforming the developed *hART* model into a more generalizable model (*hART-GPT*) capable of predicting all medical events associated with a patient's next medical visit. The research question guiding this phase is: Can the incorporation of a GPT architecture effectively enhance patient representation learning in *hART*, enabling accurate prediction of a wide range of medical events beyond HF?

hART (heart failure Attentive Risk Trajectory Model)

This section describes *hART*, a self-attention model for multivariate sequence modeling that predicts a patient's risk of heart failure based on their medical history. The proposed method employs a variation of the transformer encoder, which uses a self-attention mechanism to model dependencies among events through the assignment of attention scores (21). The transformer

architecture and attention networks have been found to achieve superior performance on many sequential NLP (Natural Language Processing) benchmarks and to be significantly faster in training compared to recurrent networks (21, 26, 28). Furthermore, the context vector and attention weights of the transformer architecture allow for the interpretation of how medical events contribute to the model's output (29) and provide clinicians with retrospective risk trajectories. An overview of the model is depicted in Figure 1. Our *hART* has four major components—input padding, positional encoder, masked multi-head self-attention layers and residual connections.

Firstly, padding is applied to each patient to extend all inputs to the size corresponding to the oldest age of any patient in the dataset, and masking is used to ignore these special tokens in loss calculation and predictions. Secondly, in contrast to approaches like RNNs, the attention mechanism does not utilize any recurrence or convolutions for sequence modeling. Instead, we pass the data through a positional encoder to translate the notion of time within the time steps of our sequences (21). The positional encoder is commonly used in NLP problems where the transformer is employed. We selected to use the same discrete positional encoder as described in the original Transformer paper (21), however, Time2Vec (30), a trainable encoding layer, was also tested and yielded inferior results. Positional encoding describes the location or position of an entity in a sequence so that each position is assigned a unique representation. Thirdly, we pass our data through the attention layers. The attention mechanism was introduced in 2014 to address the limitation of previous models in modelling a long sequence of data (31). The self-attention mechanism's architecture facilitates the context vector to account for the importance of all past-time steps and the relationship between them. In the medical context, this implies that when predicting HF, the model considers the entire patient's history as well as the relationship between each visit. Specifically, we utilize a masked multi-head attention mechanism (21), to improve the ability of our model to capture various aspects of the data simultaneously and can help to improve the model's performance and interpretability (32). A masked matrix is added to the scaled dot product equation to ensure that the attention weights only consider points before the predicted time step to be included in the calculation of the context vector (Fig 1.). Each masked multi-head attention mechanism is followed a normalization layer and a dropout layer to form an attention block. Our proposed model uses two layers of the attention blocks described above, where each layer is applied on top of the previous one. This allows the model to build up a

hierarchical representation of the input data, with each layer focusing on a different level of abstraction. This can help the model to better capture the complex relationships and dependencies in the data and can also improve its performance and interpretability (21, 26). Finally, the implementation of a residual connection between the two attention blocks in the model mitigates the vanishing gradient problem during backpropagation and provides the outputted representation with knowledge of the original state of the input, ensuring contextual representations of a patient's medical risk assessment represent their medical history (33).

The output sequence from the attention layers is a context-aware representation of a patient's health progression, such that each time step's representation has only considers the past medical history. Furthermore, the representation is computed with respect to the future occurrence of HF and thus is associated to the evolving risk of HF of a patient. The final representation is passed through a final dense layer with a SoftMax activation function. This computes a single value HF risk estimate for each time-step. This works as a classification layer for each time steps. The output is a sequence of risk score predictions for each 6-month interval. Ultimately, our model has combined a patient's medical history and the future occurrence of HF into a deep learning-informed lifespan HF risk trajectory.

hART-GPT (hART - Generative Pre-Trained Transformer)

hART-GPT is an extension of the *hART* architecture described earlier, where we replace the final dense layer to outputs the 11 time-varying variables that make up a patient's 6-month medical visits. By doing so, we can create a generalized patient representation that can be fine-tuned to predict any outcome, such as heart failure. To this end, we fine-tune the fixed output of the attention blocks of the pre-trained *hART-GPT* by appending a dense layer with one output node to predict the HF variable. This approach allows us to leverage GPT's ability to predict the next word in a sentence to *hART*'s ability to predict the next medical event. In our case, we are fine-tuning the model to predict the next HF event. This combination allows for a more accurate and personalized prediction of HF risk based on a patient's medical history, ultimately leading to better patient outcomes.

Statistical Analysis

In phase one of the study, we utilized a sequence-to-sequence supervised approach to predict future HF risk and generate a continuous lifespan trajectory of HF risk. Patient records were partitioned into six-month intervals, with each interval comprising a 23-dimensional vector encompassing static variables reflecting the patient's condition at birth (such as sex and genetic syndrome), a continuous variable (age), and binary-encoded indicators denoting the occurrence of particular medical events and medical conditions (such as surgeries and comorbidities). We opted for 6-month intervals to enhance the representation of medical events and positive HF labels during model training, while also maintaining consistency with our earlier developed models (18). The labels were generated using a 1-step sliding window technique based on HF hospitalization. This approach enabled us to predict the future 6-month risk of HF at each time step, creating a continuous prediction of HF risk based on past patient data. To ensure consistency, patient sequences were masked with values of -1, resulting in all sequences being standardized to 150 time-steps, which corresponds to the maximum age of 75 years. We compared the performance of the proposed model, *hART*, with three baseline models: logistic regression (LR), Support Vector Machine (SVM) and our previously published Deep Heart-Failure Trajectory Model (DHTM) (18), which utilizes Gated-Recurrent Units (GRU). Additionally, to assess the significance of the order of medical events within a patient's medical history, we have randomized the time steps and re-evaluated *hART* (34). We divided our patient dataset into a training set and a testing set, with 80% used for training and 20% for evaluation. Out of the 80% training set, we further split 15% as a validation set for hyperparameter tuning using the Adam optimizer (35). The optimal parameters for each model are listed in Online Supplementary Table 1. The As the dataset labels were heavily skewed towards negative examples due to the limited number of recorded HF hospitalizations per patient, we employed focal loss to improve the precision of our model on the imbalanced dataset. Focal loss down-weights well-classified examples and focuses on misclassified examples (18, 36). To evaluate the performance of our models, we calculated two metrics: Area Under the Precision Recall Curve (AUPRC) and the Area Under the Receiver Operating Characteristic (AUROC). AUPRC evaluates our model's accuracy and recall, while AUROC measures the balance between true positive and false positive rates. In our binary classification task, we utilize the optimized

threshold described in (18), which is applied to determine whether a predicted outcome should be classified as positive or negative.

In the first section of phase two of the study, we compare the predicted lifespan risk of HF (HF trajectory) between different patient populations. We examine the average HF trajectory and confidence interval of patients in different subgroups of CHD and compute the significant difference between the sequences of predicted risk using the Kolmogorov-Smirnov test. Specifically, we considered 3 types of subgroups: genetic syndrome, severe CHD (encompassing conditions such as tetralogy of Fallot, truncus arteriosus, transposition complexes, endocardial cushion defects, or univentricular heart), and age of death. For unbiased analysis, we computed the HF trajectories on the held-out patients (testing set), which were not used to train *hART*. Alongside the predicted HF trajectories, we visualize the *hART*-generated attention weights for the exposure group as a heat maps. Finally, we compute the distribution of actual occurrences of HF for each subpopulation. Table 1 summarized the characteristics of each population. The Fisher's exact test is used to determine the significance of differences between characteristics of each patient profile.

The ability to personalize treatment for patients with risk of HF is critical for achieving better patient outcomes. However, it can be challenging for clinicians to identify the impact of specific medical events on an individual's predicted HF risk. In the second section of phase two of the study, we address this challenge by exploring the impact of the timing of medical events on the HF risk of two patients with CHD who had similar characteristics, but underwent the same arrhythmic surgery at different ages (33 and 3 years old, respectively). We display the attention scores computed by *hART* as heat maps for these two representative patients. Moreover, we examined the individualized HF risk trajectories of both patients produced by *hART* and compared them to a baseline trajectory calculated from patients with similar initial medical profiles. Notably, the baseline trajectory was derived from female patients with non-genetic syndrome and non-severe CHD, who lived past the age of 75.

In the third phase of the study, we evaluate the performance of the *hART-GPT* model in predicting the 11 medical events which were binary encoded in phase one. These variables include myocardial infarction (MI), Stroke, infective endocarditis (IE), arrhythmia (ARR), ventricular arrhythmia (VARR), congenital surgery (Congsx), arrhythmic surgery (ARRsx), Percutaneous Coronary Intervention (PCI), Sepsis, acute kidney disease (AKD), and HF. The

labels for these variables were generated using a 1-step sliding window technique, allowing the model to predict the occurrence of these events within the subsequent 6-month period. To assess the performance of *hART-GPT*, the AUROC and AUPRC for each variable was compared against a GRU-based model (18). Additionally, we compare the AUROC and AUPRC of the fine-tuning of *hART-GPT* against *hART* for predicting HF.

Results

HF Prediction Performance

In terms of predicting the next HF event at time t + 1 based on the sequence up to time t, *hART* achieved an AUPRC score of 0.282 and an AUROC score of 0.967, which outperformed the baseline models (Fig. 2). Particularly noteworthy, it outperformed our previously established GRU-based model, which attained an AUPRC score of 0.210 and an AUROC score of 0.961. The improvements are most pronounced at the 1% recall rate, where our model achieved over 80% precision outperforming the other models by 10%, signifying that our model predicts the occurrence of HF within a 6-month period with 80% accuracy. This is promising given the high class imbalance, where HF instances account for only roughly 1% of time steps. The attention model trained on the randomized time steps conferred an AUPRC score of 0.2097 and an AUROC score of 0.9563, which are much lower compared to the *hART* trained on the original time step sequence. This implies that *hART* can leverage the temporal order to improve HF prediction.

Population-based HF Trajectories: Severity

The results of our study demonstrate a significantly higher estimated risk of HF for patients with severe CHD compared to those with non-severe CHD throughout their entire lifespan ($p < 0.05$, KS-test) (Fig. 3a). Specifically, out of 124,898 patients with non-severe CHD, 11.56% had HF, whereas out of 9,548 patients with severe CHD, 14.04% had HF ($p < 0.05$, Fisher's exact test). Additionally, the *hART* model effectively predicted the actual distribution of HF among severe patients, with the predicted HF trajectory indicating a significant rise in risk 10

years earlier than the actual incidence of HF. The highest risk in severe CHD patients begins at 30 years of age, while the incidence of HF rises at 40 years of age. The computed attention matrix for patients with severe CHD highlights the most important time steps for risk prediction, with significant attention given to the time of birth and the period from 10 to 40 years of age.

Population-based HF Trajectories: Genetic Syndrome

In this study, we analyzed the impact of genetic variants associated with CHD on the risk of HF using our *hART* model. Our results showed that patients with known genetic syndrome associated with CHD have a higher risk of developing HF until the age of 50 ($p < 0.05$, KS-test), after which the risk trajectories intersect with those of non-genetic patients ($p > 0.05$, KS-test). The comparison between predicted HF trajectories and actual HF distribution in genetic and non-genetic patients reveals similar deviations in both groups, with *hART* predicting the intersection of HF occurrence earlier. This suggests that the predictive model is effective in identifying the risk of HF in genetic patients more than 10 years earlier than the actual occurrence. The most important timesteps for predicting HF in genetic patients were found to be from birth to 20 years of age, with decreasing importance until age 50. Interestingly, the initial condition became less important for rises in risk over time, which is supported by the intersection of risk mentioned above. Our *hART* model demonstrates the ability to identify early rises in HF risk in genetic CHD patients and highlights the importance of early interventions in this patient population.

Population-based HF Trajectories: Age of Death

We also examined the correlation between increased risk of mortality and HF (Fig. 4). Our CHD dataset contains 2598 patients who died before 40 years old, 4031 which died between 40 and 70 and 11541 who died after 70, of which 19.25%, 43.81% and 56.44%, respectively, had HF ($p<0.05$, Fisher's exact test). By taking the reciprocal of the predicted HF risk and scaling the trajectory with respect the HF risk at age of death, we can illustrate the depreciation of overall health. First, we find that the initial medical condition of patients who die younger is associate in a lower initial predicted overall health. Secondly, *hART* model predicts that the estimated risk of

HF for CHD patients who die younger have significantly earlier decreases in overall heath in predicted HF risk. As expected, the average age of the first HF was lower for patients who had earlier death (p-value < 0.05, KS test). Furthermore, the patient who died before 40 had a significantly higher proportion of surgeries (19.71% vs 9.90% for patients who died between 40 and 70 vs 5.09% for patients who died after 70) ($p < 0.05$, Fisher's exact test). By looking at the attention matrix of our population who died before 40, we find that the patient history from birth to the age of 10 contribute significantly to the rapid depreciation of overall health. Although the indication of death was not included in the training of *hART*, we identified a strong association between predicted HF risk and mortality, indicating the potential use of *hART* as a tool for mortality risk stratification and survival analysis in CHD patients.

Connecting the dots backward: using the event-based attention to associate HF hospitalization with past medical events in the CHD patient records

We investigated the impact of the timing of medical events on the individualized HF risk trajectories for two representative CHD patients. Patient A had arrhythmic surgery at the age of 33, and their risk trajectory deviated from the baseline after the surgery. The attention scores computed by *hART* indicated that the surgery remained important to the HF trajectory for the rest of the patient's life, contributing to the deviation from the baseline (Figure 5a). Patient B had arrhythmic surgery at the age of 3, and their risk trajectory had a significant deviation from the baseline from the age of 4 to 45. However, *hART's* attention scores showed that the importance of the surgery in predicting HF decreased over time, and its impact was minimal around the age of 45 (Figure 5b). These findings suggest that *hART* can capture the understanding of how the context and timing of past medical events affect the lifespan trajectories of individual patients. Such knowledge can be beneficial in designing personalized treatment regimens for CHD patients.

Pre-training on future comorbidities and fine-tuning on HF prediction

In this section, we aimed to evaluate the performance of our extended attention-based model, *hART-GPT*, in predicting the complete next time step for CHD patients and compare it to the GRU-based model. Figure 6a illustrates that *hART-GPT* outperformed the GRU model for all variables and was particularly effective at predicting comorbidities associated with HF, such as stroke, infective endocarditis, sepsis, myocardial infarction, and acute kidney disease. This could be attributed to the fact that the selection of variables was made to include confounding variables for HF. Additionally, we examined the performance of fine-tuning *hART-GPT* on predicting the next HF and compared it to *hART* and other baseline models (Figure 6b). We observed that *hART-GPT* slightly outperformed *hART* with an AUROC of 0.979 and an AUPRC of 0.2900. These results suggest that *hART-GPT* is a promising tool for predicting the risk of HF and associated comorbidities in patients.

Discussion

HF trajectories enables the assessment of the progression of chronic diseases and comorbidities throughout a patient's life. By analyzing long-term sequential patient data, this approach can provide insight into the evolution of a disease over time, including the impact of several factors such as age, sex, and individual patient characteristics. This valuable capability holds the potential to inform precision delivery of care, leading to improved patient outcomes and optimized resource allocation for individuals with CHD (9). In this study, we present the first use of attention-based deep learning. Our developed approach called heart-failure Attentive Risk Trajectories (*hART*) is a step towards a deep understanding of the lifespan disease progression of CHD, and specifically the leading comorbidity, HF. We demonstrate the capacity of *hART* on modeling sequential administrative diagnostic data from Quebec CHD patients and its ability to accurately predict their HF trajectories. The remarkable performance of *hART* compared to existing approaches demonstrates the efficacy of the attention mechanism in effectively modeling long-term sequential patient data. It allows for contextualization and focused attention on specific medical events within a patient's comprehensive medical history. Moreover, we showed that the temporal order is important to achieve the highest prediction accuracy of *hART*, implying its ability to learn hidden semantics from the sequential medical data. Additionally, we showed the potential of a GPT framework (*hART-GPT*) to improve the

accuracy of predicting the risk of HF and associated comorbidities in patients, suggesting that these models could be valuable tools for patient representation learning and can be fine-tuned to tackle a wide array of medical problems (23).

Furthermore, we demonstrate the use of predicted HF trajectories to gain a deeper understanding of patient's HF risk and medical profile. Our model has captured how different medical events and patient population of CHD patients can lead to different level of long-term HF risk. Assessing HF trajectories based on population reveal substantial findings. Firstly, despite severity not being included in the training of our model, *hART* identified that patients with severe CHD exhibited consistently elevated risks of HF throughout their lifespan, which supports recent studies (14). Our results suggest that future studies can use the model to effectively stratify patients into risk groups, which could inform the allocation of resources towards patients with higher severity. Secondly, our findings provide evidence that the predicted HF trajectory for patients with genetic CHD aligns with previous studies indicating a higher likelihood of surgery, complication, and HF in this specific cohort (37). We observe that once patients with genetic syndrome reach the age of 50, their risk profile starts resembling that of patients without the genetic syndrome. Moreover, by utilizing the attention matrix heat maps, we can identify the diminishing influence of early time steps in patients with genetic syndrome over time. These results highlight the ability of *hART* to understand the significance of birth conditions and their evolving impact on HF throughout individuals' lifespans, which is crucial in managing congenital and chronic diseases. Thirdly, our results support the correlation between the evolving risk of HF and mortality, indicating that the model can accurately capture this relationship despite age of death not being included in the training (38). This motivates the use of HF trajectories to assess the overall lifespan health condition of patients with CHD and to inform clinical decision-making and the timing of specialty referral (6, 12). Finally, our study showcased how *hART* can assess HF risk for individual patients and can capture the importance of the timing of medical events, such as arrhythmic surgeries. Our findings underscore the attention mechanism's ability to contextualize medical events within patient histories.
This study also provides one of the first graphical representation of lifelong HF trajectories, providing a novel tool for clinicians to use the power of deep learning to inform their interventions (9, 15). Comparing patient populations can help clinicians understand the trends and impacts of patient histories on lifespan HF risk. Additionally, the use of HF trajectories at an

individualized level can facilitate the precision delivery of care by identifying turning points and transitions periods based on process of health development, i.e., medical events and genetics, and determinants of health (9, 39, 40). The attention mechanism in *hART* provides an advantage over previously used RNN models (18) by offering interpretability for clinicians, allowing for a clear understanding of the factors, specifically how the timing of medical events contribute to the model's predictions (26). The addition of the informative attention weights can provide valuable information to clinicians about the most important medical events in a patient's life. By visualizing the attention weights at each time point, we can show which data points the model is focusing on and the relative importance of each data point. This can help clinicians identify key medical events, such as the onset of a disease or the start of a treatment and understand their impact on the patient's overall health.

Future research in the field of CHD will focus on analyzing the capabilities of deep learning-informed disease trajectories to better understand the complex nature of lifespan diseases, incorporating a wide range of medical data, and assessing different outcomes (9). While the current model shows promise with its flexibility and generalizability, there are limitations to be addressed. One limitation of modeling patient data in discretized time intervals using attention is that it may not capture the full complexity of the data. In many cases, medical data is recorded at irregular intervals, which can provide deeper insight into the progression of a disease (41). Additionally, discretizing the time intervals may make it more difficult to model the autoregressive nature of the data, where future time points are predicted based on previous ones. Another limitation which we will address in future studies is the inclusion of only 23 selected variables. The flexibility and generalizability of *hART* will facilitate the inclusion of more patient features, and assessment of different outcomes in future studies. In terms of clinical applications, the success of our model will motivate its use to analyze other clinical questions such as, finding the optimum time for intervention for an individual patient, stratifying patients into risk group based on trajectories, and examining the impact of specialist follow-ups on the quality of life of CHD patients (15). For example, one way to find the optimal time for follow-up using predicted disease trajectories is to identify the points in the trajectory where there is a significant change in the risk of the disease or in the patient's overall health. These points may indicate a need for additional medical attention or intervention and can provide guidance on the timing of follow-up visits. Moreover, comparing the predicted trajectories of different patients can provide insight

into common patterns and trends, which can inform the development of general follow-up guidelines. By using predicted disease trajectories in combination with clinical expertise, it is possible to find the optimal time for follow-up and ensure that the right patient receives the right care at the right time (6, 9).

In conclusion, with the increasing complexity of care for patients with chronic illness, the ability to deliver precise individualized care has become essential. In this study, we have developed a deep learning-informed framework to assess the lifespan risk of HF for patients with CHD. Our attention-based model was trained on the largest database of CHD patients and addressed limitations observed in previous studies by accurately captures long and short-range dependencies in patient histories while offering enhanced interpretability for clinicians through the inclusion of HF trajectories and attention matrices. The graphical framework of lifelong HF trajectories provided by this study empower clinicians to effectively identify high-risk individuals, optimize intervention timing, and assess the evolving impact of comorbidities in CHD patients. Overall, this study highlights the value of disease trajectory modeling in improving our understanding of the long-term effects of CHD complications.

FIGURES AND TABLES

Table 1: Comparison of selected demographic and clinical characteristics between different CHD patient profiles. The percentage of patients within specific patient profiles who have experienced heart failure (HF) and undergone surgery, as well as the prevalence of certain medical and demographic characteristics. Additionally, the table provides the average age at which medical events occurred within each patient profile. The table is intended to provide insights into the distribution of medical events and patient characteristics within the studied patient profiles, and to facilitate further analysis of patient subgroups.

	HF (%)	HF Age	Surgery (%)	Surgery Age	Female (%)	Severe CHD (%)	Genetic Syndrome (%)
All Patients (**n** = 137493)	11.74	62.97	7.30	23.09	50.17	7.10	8.32
Male (**n** = 68514)	12.41 *	61.26*	7.86*	23.82		6.86	8.68*
Female (**n** = 68979)	11.07 *	64.88*	6.74*	22.24		7.35	7.95*
SevereCHD (**n** = 9764)	14.04*	23.22*	39.54*	8.16*	51.89		21.01*
Non SevereCHD (**n** = 127729)	11.56*	66.66*	4.84*	32.41*	50.04		7.35*
Genetic Syndrome (**n** = 11433)	10.85	35.02*	15.68*	7.24*	47.96*	17.94*	
No Genetic Syndrome (**n** = 126060)	11.82	65.30*	6.54*	26.53*	50.37*	6.12*	
Age of Death (<40 years old) (**n** = 2598)	19.25*	12.27*	19.71*	5.01*	45.30	33.56*	28.87*
Age of Death (>40 and <70 years old) (**n = 4031**)	43.81*	56.85*	9.90*	54.04*	42.12	6.70*	7.24*
Age of Death (>70 years old) (**n** = 11541)	56.44*	76.84*	5.09*	70.56*	51.10	1.44*	3.51*

* Statistically significant at P<0.05.

Supplementary Table 1: Selected Variables

Demographic: Sex (2), Age, Genetic Syndrome (2)

Medical Events: Myocardial Infarction (MI), Stroke, Infective Endocarditis (IE), Arrhythmia (ARR), Ventricular Arrhythmia (VARR), Sepsis, Acute kidney disease (AKD), Heart Failure (HF), Hypertension, Pulmonary Hypertension (PH), Diabetes, Chronic Kidney Disease (CKD), Chronic Liver Disease (CLD), Chronic Obstructive Pulmonary Disorder (COPD), Obstructive Sleep Apnea (OSA), Congenital surgery (Congsx), Arrhythmic surgery (ARRsx), Percutaneous Coronary Intervention (PCI)

Figure 1: *hART* method overview. (a) A conceptual illustration of the input longitudinal record of a CHD patient. (b) A retrospective patient HF risk trajectory output by *hART*. (c) Attention-based architecture of *hART*. Time steps at t-1 and t are passed through hART to output the predicted values of the future 6-month HF risk, represented as y_t and y_{t+1}. Each input time step is passed through two attention blocks connected by a fully connected layer, then a final dense layer that allows the model to output a single value per input. The model also has a skip connection around the second attention block. (d) Masked multi-headed self-attention mechanism of the attention block to prevent the model from peeking into the future.

Figure 1: Heart Failure Trajectory Framework (Central Figure)

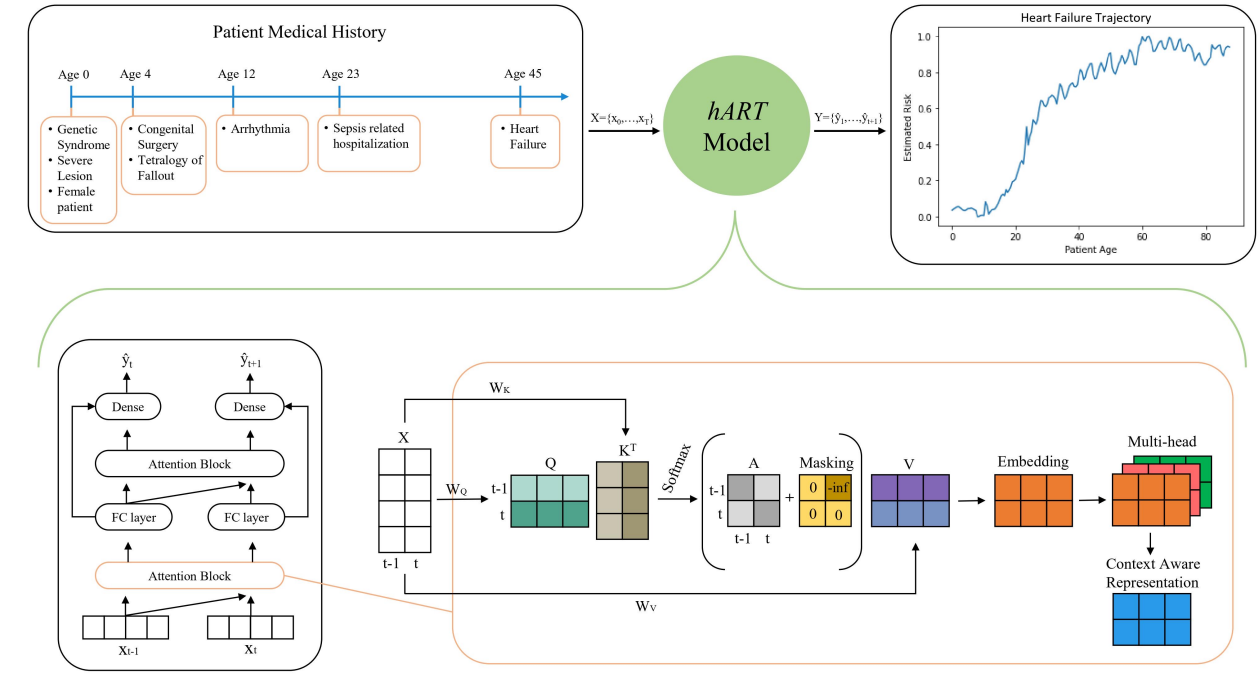


Figure 2. Performance results of *hART* (attention) and the baseline models. A) PRC b) ROC

Figure 2: Model Performance

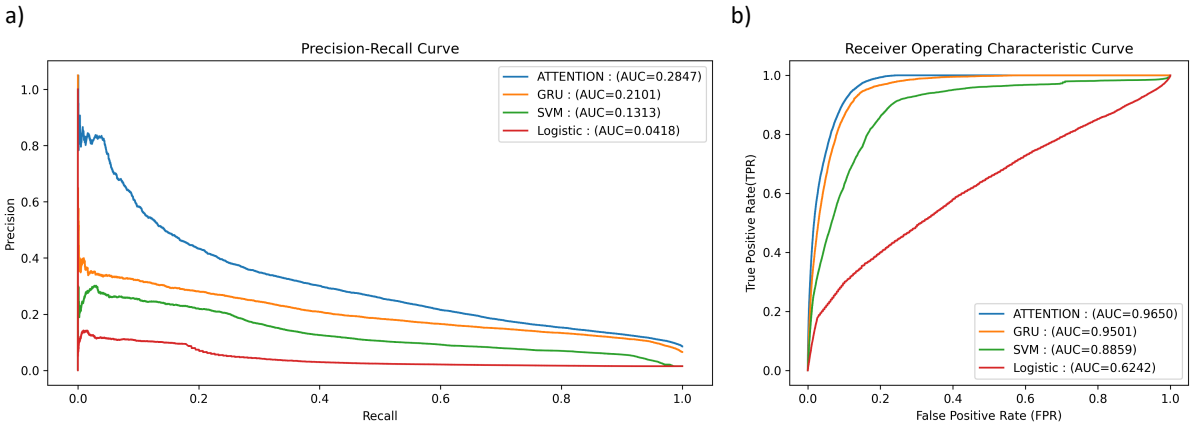


Figure 3: Patient Population Trajectories. The top row depicts a comparison of the predicted HF trajectory between the population with and without a specified characteristic (a. severe CHD lesion; b. genetic syndrome). The trajectories are shown as the mean trajectory and the confidence interval of all patients from each population. The middle row depicts the average of attention weight matrix computed over the exposure population, with darker blue representing the time step which contributes more to the HF risk prediction at the given time step (y-axis row). The bottom row depicts the actual distribution of heart failure occurrence based on the patient population of CHD.

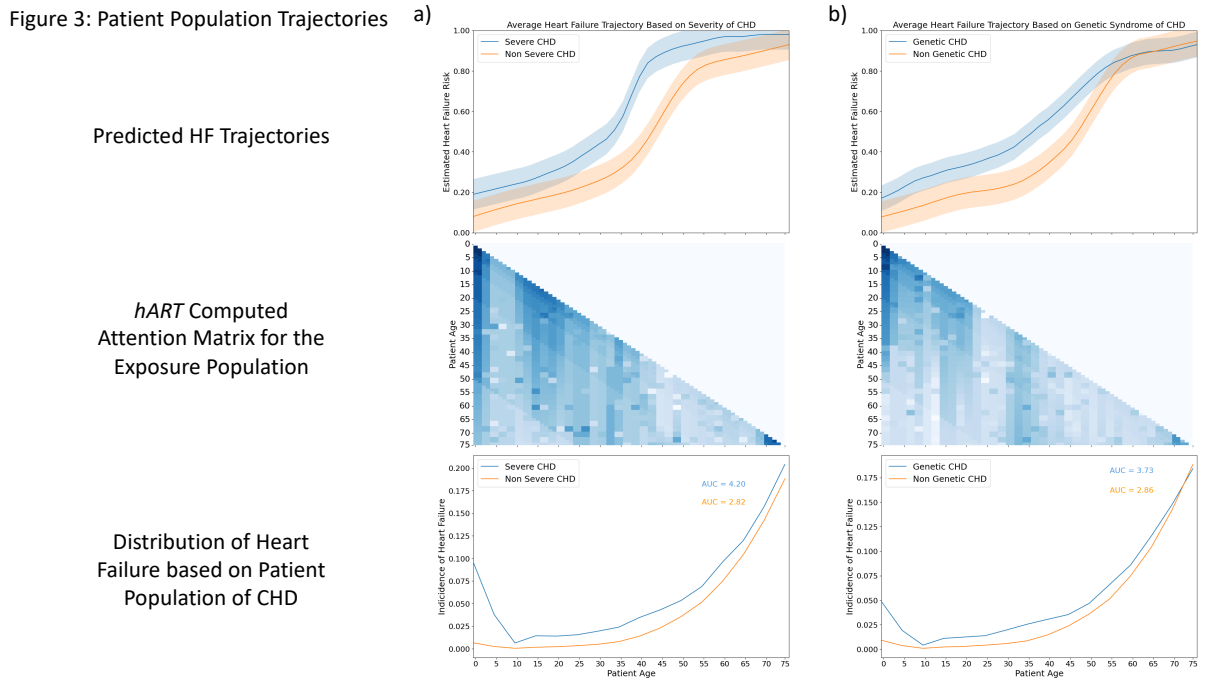


Figure 4: Trajectories based on Age of Death. Figure 4a depicts the trajectories in terms of overall health for populations divided based on the age at death. Overall health was calculated by scaling the reciprocal of predicted HF risk by the reciprocal of the risk of HF at age of death. The trajectories reflect the depreciation of overall health related to heart failure. Figure 4b illustrated the attention weights associated to the population of patients who died before the age of 40.

Figure 4: Trajectories based on Age of Death

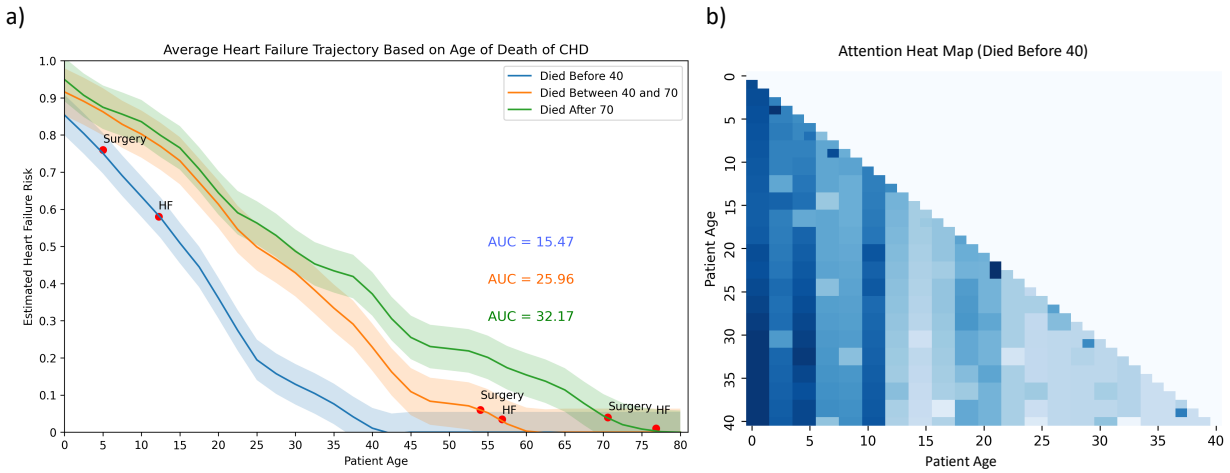


Figure 5: Example of Individualized Trajectories. The top row depicts a comparison of the predicted HF trajectory for the selected individual patient and the baseline. The middle row depicts the individual patient's medical history, with a dark line representing the occurrence of a specified medical event at the given time. The bottom row illustrates the attention weight matrix computed by *hART* for the individual patient. The red boxed illustrate the timing of arrhythmic surgery, highlighting the enduring impact of this event at age 33 (Patient A) compared to the transient effect when it occurred at age 3 (Patient B). The baseline trajectory is the mean trajectory and the confidence interval of all patients from the sub-population which Patient A and B belong (i.e., non-severe CHD lesion, Non-genetic Female Patients with CHD).

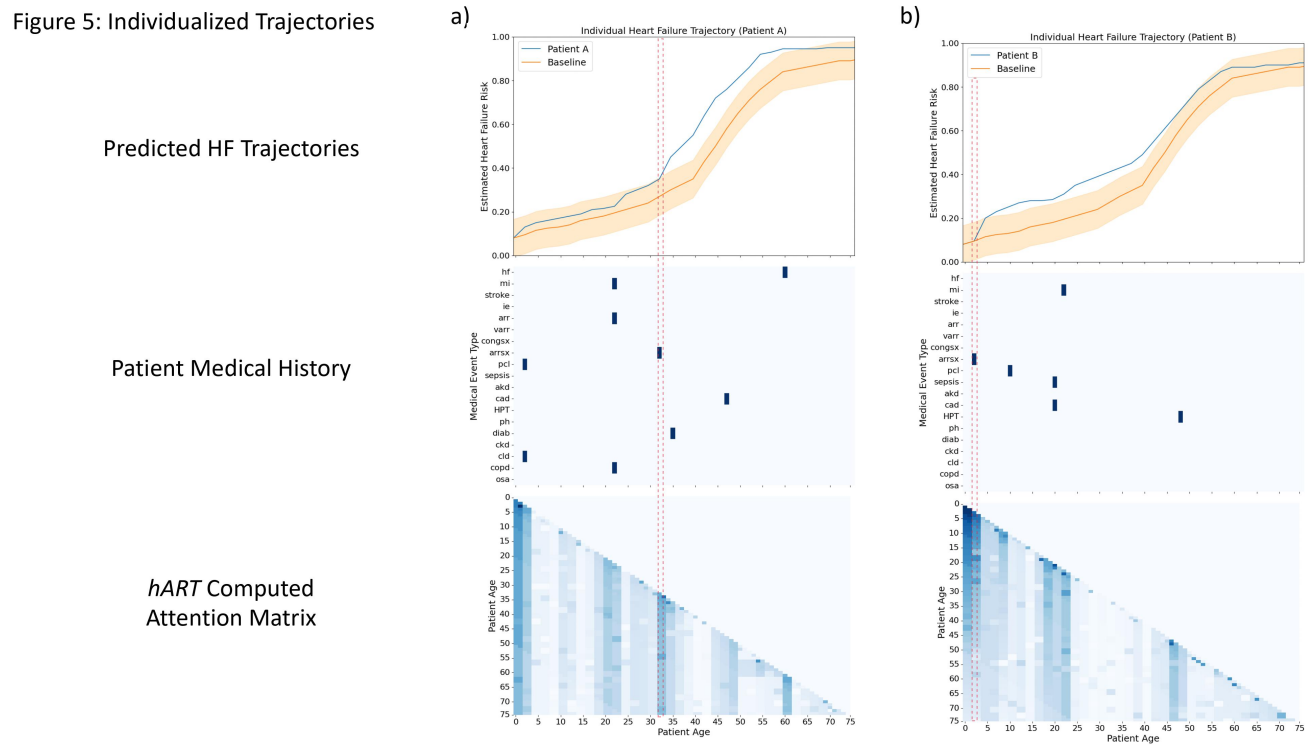
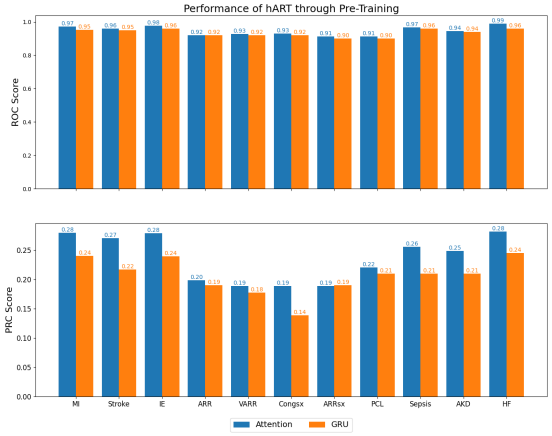


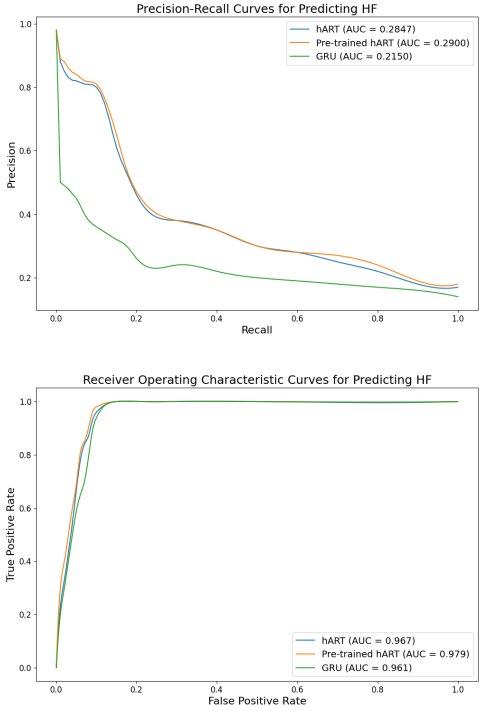
Figure 6: GPT Performance. Figure 6a shows a comparison of the AUROC and AUPRC for predicting each of the 11 time-varying variables between the attention-based *hART-GPT* model and the GRU-based model. Figure 6b shows the ROC and PRC curves for the HF fine-tuning of *hART-GPT* compared to *hART*.

Figure 6: *hART-GPT* Performance

a)



b)



Abbreviations: Myocardial Infarction (MI), Stroke, Infective Endocarditis (IE), Arrhythmia (ARR), Ventricular Arrhythmia (VARR), Congenital surgery (Congsx), Arrhythmic surgery (ARRsx), Percutaneous Coronary Intervention (PCI), Sepsis, Acute kidney disease (AKD), and HF (Heart Failure)

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CHAPTER 4: THESIS DISCUSSION

Modelling risk in CHD is a topic of high priority due to the increasing number of adults with CHD and the associated long-term risk of comorbidities, such as HF. With CHD being one of the most prevalent birth defects globally, lifespan risk assessment is needed to facilitate the precision of delivery of care for this population. This thesis aimed to investigate the assessment and modelling of HF risk in individuals with CHD. This study centres around enhancing the accuracy of long-term HF risk assessment in patients with CHD.

Significant Findings

In this thesis, we conducted a review of existing methodologies for assessing and modelling HF risk in patients with CHD revealing a notable scarcity of approaches capable of generating interpretable long-term HF trajectories. Common methods identified were traditional statistical approaches, regression-based models, survival models, and deep learning approaches. Our main finding suggests that the increased complexity and variety of patient disease presentation, coupled with the evolving demographics and management strategies for patients with CHD, have driven the adoption of more powerful methods supported by the wealth of data available from EHR databases. However, challenges persisted in modelling the complexity of EHR, handling long dependencies, and generating interpretable trajectories. To overcome these limitations, we drew inspiration from the remarkable achievements of attention-based deep learning models, including BERT and GPT-3, which excel in contextualizing words within sentences. Motivated by this success, we applied a similar approach to the medical domain, aiming to contextualize medical events within a patient's comprehensive medical history.

One of the most significant findings from our study is the superior performance of attention-based modelling in predicting lifelong HF. This approach outperformed regression-based approaches and other deep learning-based methods, demonstrating its effectiveness in modelling longitudinal patient data. Additionally, we successfully assessed the differences in lifespan risk estimates of HF between population profiles. Notably, patients with severe CHD exhibited consistently elevated HF risks throughout their lifespan, highlighting the potential of our model, *hART*, for effective risk stratification. Furthermore, the birth condition of patients with genetic syndromes of CHD only leads to increased risk until the age of 50. Additionally, we

have identified that the lifelong evolving risk of HF predicted from *hART* as an indicator of overall health. Our analysis of individual HF trajectories, combined with attention matrix heat maps, allowed us to evaluate the influence of significant medical events on the lifespan risk of HF. Specifically, we found that the timing of arrhythmic surgery had varying effects on HF risk over time. Finally, the extended attention-based model, *hART-GPT*, demonstrated superior performance compared to the GRU model in predicting all time-varying variables for the next step, notably excelling in forecasting comorbidities associated with HF including stroke, infective endocarditis, sepsis, myocardial infarction, and acute kidney disease. Fine-tuning *hART-GPT* specifically for predicting the occurrence of HF resulted in slightly improved performance compared to *hART*.

Interpretation of Findings

Compared to the existing models examined in our literature review, the *hART* and *hART-GPT* models demonstrate the most promising outcomes, exhibiting superior performance and interpretable estimates. This highlights the potential of attention-based deep learning approaches in being able to model long-term dependencies and complex relationship between medical events present in the medical history of patients with chronic illnesses. These findings support the notion that incorporating deep learning and longitudinal patient data can provide accurate estimations of disease trajectories at both an individual and population-level.

In addition to the increased accuracy demonstrated by attention-based learning, our study highlights the potential for interpretable AI. Transformers have consistently demonstrated superior performance in NLP tasks (57). However, it was only with the advent of interpretable and informative interfaces like *ChatGPT* that these models gained widespread popularity and practical usage. The integration of AI algorithms into clinical practice has long been a challenge, primarily due to concerns regarding acceptability, interpretability, and trust of the model's output (9, 52, 60). In this regard, *hART* and *hART-GPT* represent significant advancements as they empower clinicians with a comprehensive lifespan assessment of HF risk, through disease trajectories. Moreover, these models provide an avenue to glimpse into the "black box" of deep learning-informed risk estimations through the examination of the computed attention matrix.

The concept of lifespan HF trajectories and the ability to assess the impact of specific medical events on long-term HF risk hold significant potential for delivering precise

individualized care, especially in the face of the increasing complexity of care for patients with chronic illnesses like CHD. By understanding the long-term trajectory of HF and identifying critical events that influence its progression, healthcare providers can tailor interventions and treatments to each patient's unique needs(6). This approach enables a proactive and personalized approach to care, optimizing outcomes and enhancing the quality of life for individuals with chronic conditions. Additionally, by incorporating the insights gained from assessing long-term HF trajectories, clinicians can adapt care plans and interventions based on a patient's evolving risk profile, ensuring that the care provided remains aligned with the changing needs of the individual over time (9).

The use of the GPT framework, *hART-GPT*, to model patient data also represents a significant advancement for patient representation learning. By leveraging these sophisticated methodologies, patient representation learning aims to capture the complex and meaningful patterns embedded within the EHR data, enabling a more comprehensive understanding of the patient's health profile (64, 65). Current models for patient representation learning primarily concentrate on predicting individual diseases, often overlooking the intricate interplay and holistic aspects of a patient's overall health (64, 65). At the heart of patient representation learning is pre-training, a fundamental concept in DL, which enables the acquisition of meaningful and generalizable features from large-scale healthcare data. *hART-GPT* exhibited superior pre-training performance over the current benchmark GRU-based approach. The findings from other studies align with the performance of pre-training *hART-GPT*, reinforcing the notion that attention and transformer-based models represent a significant advancement in capturing the intricate temporal dynamics and complexities present in patient data (58, 59, 66). Thus, we believe that the flexible framework of the GPT framework presented in the *hART-GPT* can revolutionize lifespan patient representation learning by offering a powerful tool to model and analyze long-term patient data comprehensively.

With successful pre-training and patient representation learning comes the ability to tackle disease-specific challenges. Fine-tuning involves training the model on task-specific data to adapt its pre-learned knowledge to the specific context and requirements of the task (65). This process allows the model to specialize and refine its predictions for the target application. For example, in the case of *ChatGPT*, the model undergoes extensive pre-training on a vast amount of Internet text to develop a general understanding of human language (56). Then, during fine-

tuning, it is further trained to adapt its knowledge for generating humanlike responses in a chatbot scenario and predict the next word. Similarly, *hART-GPT* is pre-trained to capture the intricate relationships and patterns within an entire patient history, providing a foundation of generalizable knowledge. By fine-tuning this model, we can leverage its capabilities to predict not only heart failure but also diverse comorbidities and tasks, opening up significant possibilities for more comprehensive healthcare applications (66).

Limitation and Future Work

The present research represents an important step towards understanding the complex nature of lifespan disease, specifically in the context of CHD. However, there are several limitations that should be acknowledged, and avenues for future research that can further enhance the applicability and performance of the deep learning-informed disease trajectories.

One limitation of the current study is the selection of only 23 variables for training the model. Although we carefully chose these variables based on their relevance to HF risk prediction, we can potentially achieve further improvement by incorporating additional patient features and investigating alternative outcomes. The flexibility and generalizability of the model allow for the incorporation of more diverse data, which can contribute to a more comprehensive understanding of disease trajectories. Additionally, the application of the model to other comorbidities and chronic diseases would be valuable in assessing its accuracy and generalizability. Currently, we are actively extending the application of *hART-GPT* by training it on a comprehensive dataset of patient data representing the general population (67). This expansion allows for the inclusion of an extensive range of features, textual information, and diseases, enhancing the model's capability to capture a broader spectrum of patient characteristics. By fine-tuning *hART-GPT* specifically for patients with CHD, we aim to incorporate the nuanced differences in risk associated with CHD compared to the general population. This targeted approach enables us to deliver more accurate and personalized risk assessments, addressing the unique challenges and considerations specific to CHD patients.

It is essential to acknowledge that the *hART* model's reliance on a specific format of patient data introduces challenges in its practical application. The model's requirement for specific variables and data format implies that patients must possess comprehensive information related to these variables to ensure accurate predictions of HF risk. This limitation constrains the

usability of the *hART* model to specific EHR systems that capture the necessary variables. As a result, the model's effectiveness may be limited to patient populations whose EHRs adhere to the required data format. To overcome this limitation, we will explore incorporating data from diverse EHR systems and various modalities such as textual patient notes, medical imaging, and additional health records. By expanding the scope of data sources, we can enhance the model's applicability and extend its benefits to a wider range of patients and healthcare settings.

Finally, the successful prediction of disease trajectories by the model offers promising opportunities for various applications. One such application is the identification at-risk individuals needing referral to specialized care, which is a limited resource but has been shown to improve outcomes for patients with CHD (5). Additionally, by utilizing the predicted trajectories, clinicians can pinpoint crucial points in the trajectory where there is a notable shift in disease risk or overall health, thus optimizing the timing for these referrals. This information can guide the timing of follow-up visits and aid in providing timely medical attention or intervention, ensuring that patients receive precise and appropriate care at the most opportune moments (6, 9).

CHAPTER 5: CONCLUSION

In conclusion, this thesis makes significant contributions to addressing the increasing complexity of care for patients with CHD and assessing their long-term risk of HF. In this study, we developed *hART* (heart failure Attentive Risk Trajectory), an attention-based deep-learning model, which incorporates HF trajectories and attention matrices to empower clinicians to identify high-risk individuals, optimize intervention timing, and evaluate the long-term impact of comorbidities. These capabilities have profound implications for precision care delivery, leading to improved patient outcomes and optimized resource allocation for individuals with CHD. The study demonstrates the effectiveness of attention-based deep learning models in capturing both long—and short-range dependencies in patient histories, overcoming limitations observed in previous studies. By providing a deeper understanding into the intricate interplay of clinical variables and their effects on heart failure outcomes, *hART* enables healthcare providers to understand HF risk trajectories at a population level, allowing for the identification of high-risk subgroups and appropriate resource allocation. Moreover, the model facilitates individualized risk predictions, enabling personalized interventions and treatment strategies that enhance clinical decision-making and ultimately improve patient outcomes. Overall, this study highlights the value of deep-learning informed HF trajectory to drive precision delivery and management of care for patients with CHD.

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