Electronic health record data in cardiovascular research

Arjan Sammani | 2022

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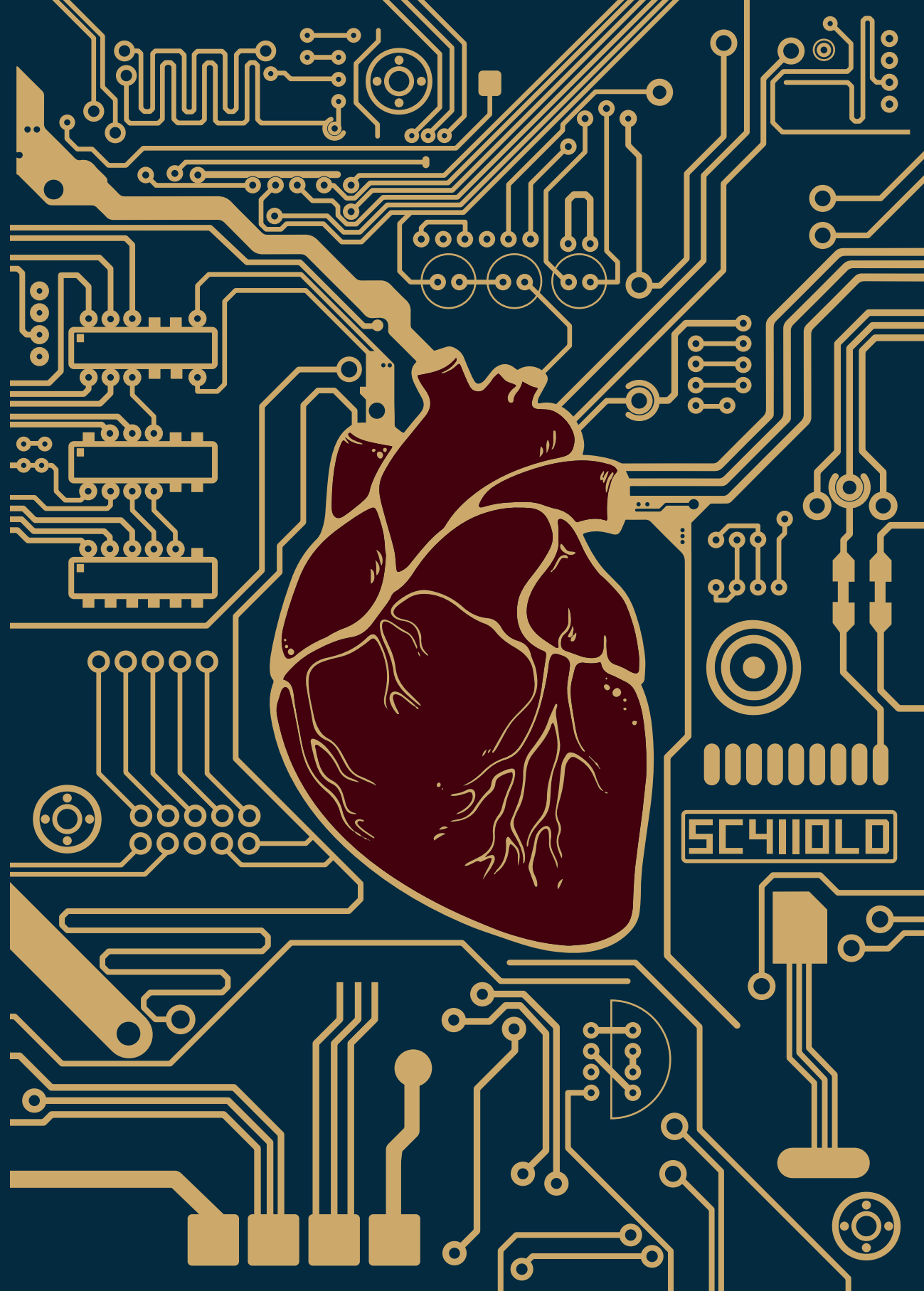
Sammani


SCHILD

Electronic Health Record Data in Cardiovascular Research

Elektronische patiëntendossier data in cardiovasculair onderzoek

(met een samenvatting in het Nederlands)

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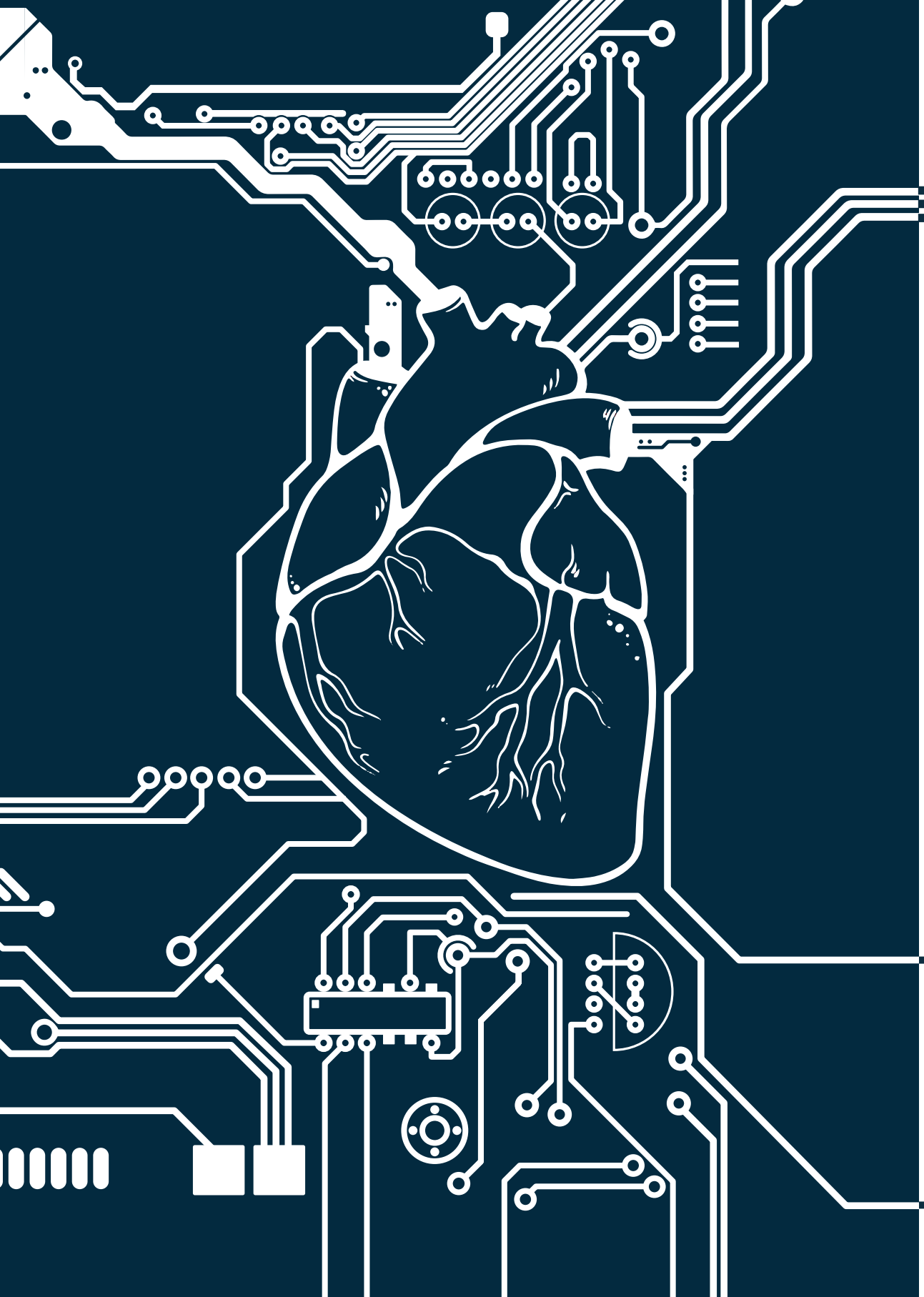

CHAPTER 1

General introduction and thesis outline

Adapted from: Sammani A, Baas AF, Asselbergs FW, te Riele ASJM. Diagnosis and Risk Prediction of Dilated Cardiomyopathy in the Era of Big Data and Genomics.

Journal of Clinical Medicine. 2021; 10(5):921.

INTRODUCTION

Electronic health records (EHR) have adjusted the nature of clinical medicine and research, allowing continuous capture of clinical data and improving research infrastructures. EHRs contain data that can progress our understanding of disease aetiology, classification, and prognosis. From the EHRs, data can be entered manually into registries by experts, or raw EHR data can automatically be exported into big data platforms. Then, novel methods such as machine and deep learning can model complex interactions by identifying new phenotypes, predicting prognosis or help create big data research infrastructures by extracting data from medical text. This thesis focusses on the use of data from clinical registries to investigate the epidemiology and prognosis of dilated cardiomyopathy (DCM) and proceeds with exciting methods to create and use big data from EHRs.

Historic overview of DCM

DCM constitutes an anatomic description of abnormal left ventricular (LV) morphology and function in the absence of common pathophysiologic conditions (i.e., coronary artery disease or abnormal loading conditions). As such, it may be a final common pathway to many disease entities where outcome is strongly influenced by aetiology.[1] One of the first DCM descriptions may be found in a case series by William Evans in 1948, describing "familial cardiomegaly" after excluding valvular, hypertensive, and congenital heart disease as causes of cardiac enlargement.[2] An autopsy in a subsequent family of two young sisters with "idiopathic cardiomegaly" also revealed dilatation of the LV.[3]

DCM Definitions

In the last decades, both European and American professional societies have proposed classifications of cardiomyopathic disorders (Figure 1). In 2006, the American Heart Association (AHA) published a seminal document describing the genetic basis of cardiomyopathies.[4] Subsequently in 2008, the European Society of Cardiology (ESC) emphasized that morphofunctional phenotype is the basis for cardiomyopathy classification and recognized extra-cardiac manifestations such as skeletal myopathy in cardiomyopathy patients.[4] The MOGE(S) classification was next proposed in 2013, which subclassified each of the cardiomyopathies into genetic forms and emphasized the necessity to further subdivide the DCM phenotype as it may affect prognosis and treatment.[5] While these position documents have greatly influenced our understanding of the phenotypic heterogeneity of DCM, the existing definitions remained limited in case of intermediate phenotypes, such as in carriers of pathogenic genetic variants who may have incomplete disease expression. Similarly, LV systolic dysfunction or dilatation can be very mild or even absent in some acquired diseases, such as myocarditis. For these reasons, the ESC Working Group on Myocardial and Pericardial Disease proposed a revised definition including "hypokinetic non-dilated cardiomyopathy" (HNDC) as a marker of early or preclinical DCM in 2016.[6] As per this framework, DCM (and HNDC) have genetic (±30%) and non-genetic (±70%) causes, of which the latter includes toxic substances (medication (antineoplastic, psychiatric antiretroviral), alcohol, cocaine, amphetamines, ecstasy, iron overload, nutritional deficiency, endocrinologic causes, tachycardiomyopathy, peripartum cardiomyopathy, infection and auto-immune disorders.[1,6,7]

Diagnosis of DCM and differential diagnostic considerations

DCM is diagnosed in the presence of **1)** LV dilatation (indexed LV end-diastolic diameter (LVEDd) >117% for age and sex, or the LV end-diastolic volume (LVEDV) ≥ 2 standard deviations from normal according to normograms); and **2)** LV systolic dysfunction (LVEF <45% and/or LV fractional shortening <25%). Full diagnostic work-up for DCM typically includes a focused history, laboratory evaluation, electrocardiography (ECG), Holter monitoring, echocardiography, cardiovascular magnetic resonance imaging (CMR) (with late gadolinium enhancement (LGE)) and genetic testing. In addition, differential diagnoses should be ruled out (e.g. ischemia detection to exclude coronary artery disease).[1] Given that LV dilatation and dysfunction are the final common pathways in many heart diseases, other cardiomyopathies (arrhythmogenic cardiomyopathy (ACM), hypertrophic cardiomyopathy (HCM), non-compaction cardiomyopathy (NCCM) and restrictive cardiomyopathy (RCM)) may mimic the DCM phenotype.[8] For instance, end-stage HCM may show overlapping clinical characteristics (LV dilatation and reduced LVEF) and ACM may present with a biventricular or left-dominant phenotype.[9–13] To distinguish DCM from common differential diagnostic considerations, CMR has proven to be very useful in recent years as it provides a good visualisation of not only the LV but also the right ventricular (RV) myocardium.[10] In addition, LGE patterns on CMR may assist in determining the aetiology: while not mutually exclusive, LV midwall LGE may be seen in genetic forms of DCM or myocarditis, whereas subepicardial LGE may be caused by myocarditis, sarcoidosis or chemotherapy.[14]

Genetic testing in DCM

Genetic testing has greatly increased our understanding of the aetiologies of DCM and has led to the identification of individuals at risk of developing disease.[15–17] In recent years, next generation sequencing (NGS) has tremendously accelerated genetic testing in DCM given its low-cost, flexibility, short turnaround time, and genome-wide coverage. NGS gene panels and a whole-genome sequencing can be used to identify pathogenic point variants, small insertions and deletions, or large structural copy number variations.[9,18,19] As a result NGS is now the clinical gold standard for genetic evaluation of DCM.

Most common pathogenic variants in DCM patients are identified in genes encoding sarcomere proteins (e.g., Titin (*TTN*) and Myosin Heavy Chain 7 (*MYH7*)); Z-disk components (e.g., Filamin-C (*FLNC*) and BLC2 Associated Athanogene 3 (*BAG3*)); and in the Lamin A/C (*LMNA)* gene, encoding a structural protein of the nuclear envelope.[15–17] Variant interpretation,

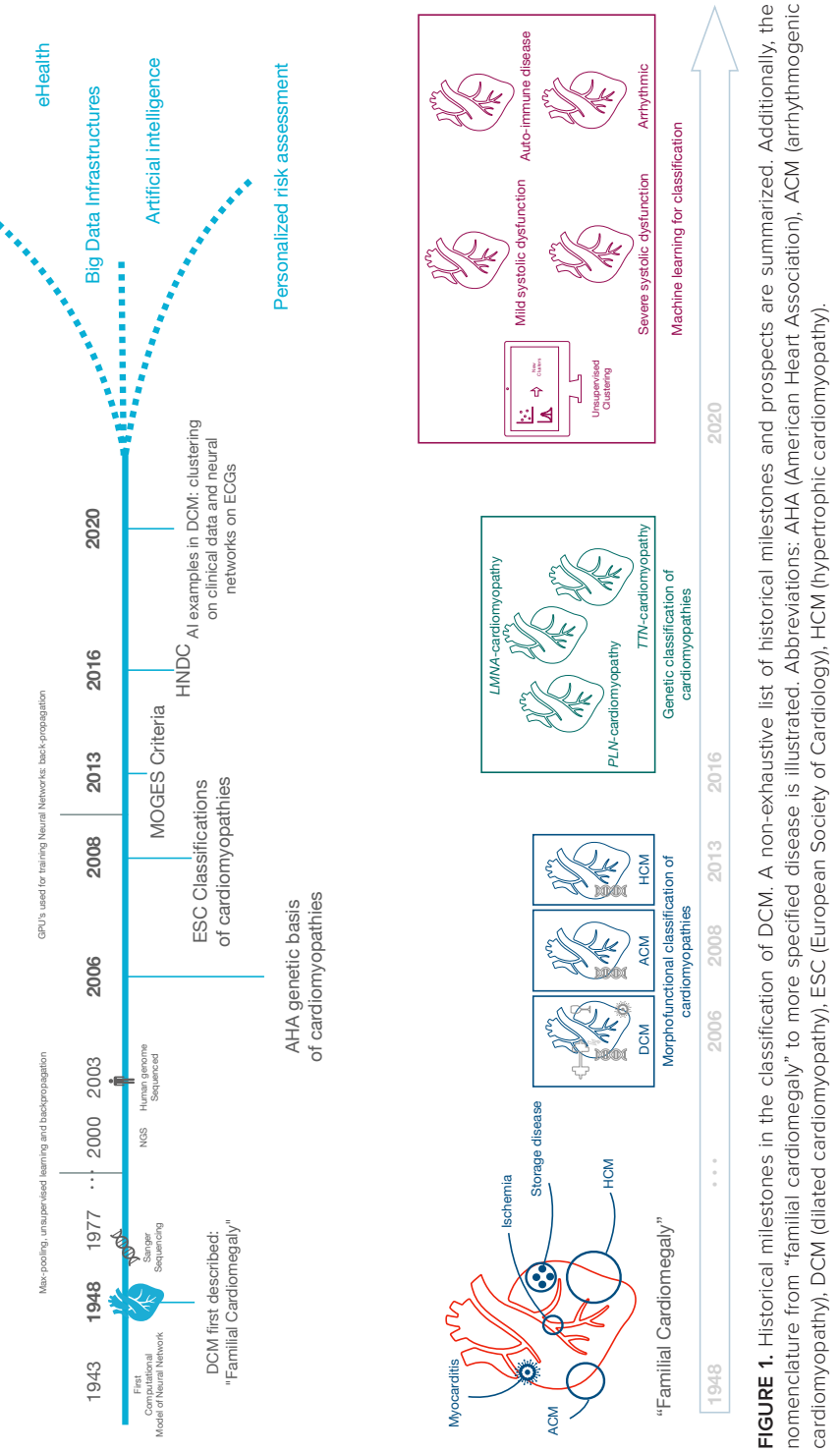

FIGURE 1. Historical milestones in the classification of DCM. A non-exhaustive list of historical milestones and prospects are summarized. Additionally, the nomenclature from "familial cardiomegaly" to more specified disease is illustrated. Abbreviations: AHA (American Heart Association), ACM (arrhythmogenic cardiomyopathy), DCM (dilated cardiomyopathy), ESC (European Society of Cardiology), HCM (hypertrophic cardiomyopathy).

however, requires due diligence, as pathogenic variants may have been overreported in the past and variant reclassification has direct implications on patients and at-risk relatives. To this end, the ClinGen consortium has re-evaluated reported pathogenic variants to generate international consensus on variant interpretation.[20] However, even with first-rate variant curation, genetic variation only explains up to 40% of DCM cases. In patients without a family history of DCM (i.e., sporadic DCM), this yield can decrease to 10%, suggesting a bigger role for non-genetic causes including cardiotoxic medication (anthracycline), alcohol, and inflammation (figure 2).[6,21–24]

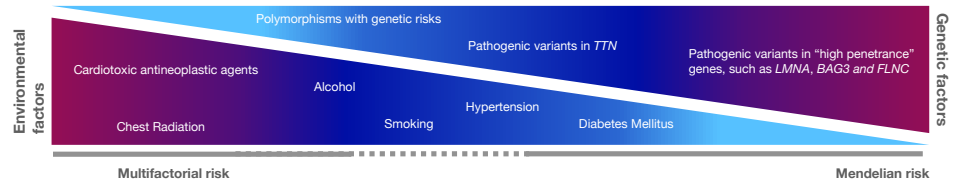

FIGURE 2. Schematic overview of genetic susceptibility and environmental factors affecting dilated cardiomyopathy. This schematic overview illustrates on the right a more mendelian risk profile with pathogenic variants in "high penetrance" genes versus a more multifactorial risk profile on the left. Importantly, the truth may be a combination of both, e.g. *TTN* variants in patients with Dilated Cardiomyopathy with alcohol abuse. Polygenic risks may also affect disease in pathogenic variants in "high penetrance" genes.

In recent years, we have come to appreciate genotype-phenotype associations within the spectrum of DCM.[25] For instance, microvoltages and frequent ventricular extrasystoles on ECG and Holter monitoring are often seen in carriers of *PLN* pathogenic variants, while in *LMNA* variant carriers a low p-wave amplitude and prolongation of the PR interval with narrow QRS complexes are typically observed.[25–27] The combination of distinct phenotypic features together with their genetic aetiology resulted a new nomenclature of these clinical entities, such as: "*PLN*-cardiomyopathy" and "*LMNA*-cardiomyopathy".[28–30]

DCM Prognosis

Historically, DCM had a 1-year mortality of ±30% and 5-year mortality of up to ±50%.[31] Because of therapeutic advancements, however, mortality rates have been decreasing, leading to 5-year mortality rates of 20% nowadays.[32] In general, patients with DCM are at risk of frequent hospitalisation and overt heart failure, for which left ventricular assist devices and orthotopic heart transplantation are the effective last resort treatments[33]. Independent predictors of progressive heart failure include low LVEF, RV dilatation, global segmental wall motion abnormalities, high New York Heart Association (NYHA) class, older age, male sex, the presence of conduction disorders, and LGE on CMR (i.e., fibrosis).[31,34]

Other predictors include reduced exercise capacity, low systolic blood pressure, and low haemoglobin.[35]

Patients with DCM are at risk of life-threatening ventricular arrhythmias (LTVA) and may therefore benefit from implantable cardioverter-defibrillator (ICD) implantation.[36] Current guidelines provide a Class IIA recommendation for ICD implantation in symptomatic (NYHA ≥ II) DCM patients with an LVEF ≤35%, despite ≥3 months of optimal pharmacological therapy.[37] However, not all patients with a low LVEF derive benefit from ICD implantation, and improved selection of these patients is warranted.[38] It seems obvious that those with prior sustained ventricular arrhythmias (i.e., secondary prevention) should receive an ICD, whereas recommendations for primary prevention cases are less straightforward as illustrated by the negative DANISH trial.[39] Improvement of patient selection may be reached with clinical risk prediction models, including exploration of artificial intelligence models.

THESIS OUTLINE

PART ONE Real world data from registries

Registries are an important source of clinical data that can be used in prospective and retrospective research studies to answer pertinent clinical questions. In part one, we use data from various (inter)national and historical registries to investigate the clinical heterogeneity of DCM and to ultimately develop a risk calculator to predict the risk for LTVA In **chapter 2**, we investigate end-stage heart failure in a cohort of patients who underwent heart transplantation. Based on thirty years of experience in the University Medical Centre Utrecht, we describe the population and the gradually changing indications for heart transplantation throughout the years from ischemic to non-ischemic heart failure. In **chapter 3**, we gather data from the *ESC Eurobservational Research Programme for Cardiomyopathy & Myocarditis* registry to investigate clinical and genetic differences between familial and non-familial DCM. This chapter also studies the role of family history in the context of clinical presentation and genetic yield. As patients with DCM have increased risk of life-threatening ventricular arrhythmias, we subsequently performed a systematic review and meta-analysis to find predictors for these events, which are described in **chapter 4**. In **chapter 5,** we used these predictors as well as other clinically relevant parameters to create a "risk calculator" for patients with DCM to predict ventricular arrhythmias. We created several models that may be used: a model using easily accessible clinical data and two additional models where additional phenotype and genotype information may be used, such as LGE on CMR and pathogenic genetic variants.

PART TWO Data infrastructure for clinical applications of artificial intelligence

Big data infrastructures comprising EHRs can now be used with new techniques, such as deep and machine learning. In part two, we design a research data platform, apply text-mining techniques, and ultimately develop a deep learning model for prediction of LTVA. In **chapter 6** we portrayed the design of our UNRAVEL big data analytics research data platform and specify its data infrastructure design and methods. This data platform includes structured (i.e. laboratory results) and unstructured (clinical text) data of patients with (suspected) inherited cardiomyopathies and their relatives. In **chapter 7**, we developed neural networks for automatic multilabel detection of diagnoses codes (international classification of disease, version 10) from discharge letters from this data platform. In **chapter 8**, we investigate methods to identify patients with hypertrophic cardiomyopathy in the EHR using text-mining and machine learning. In **chapter 9**, we developed neural networks to identify patients with DCM at risk of LTVA using ECGs and investigate the ECG characteristics that drive these predictions.

In **part three**, I discuss how future studies should progress with diagnosis and risk prediction of DCM using EHR data in cardiovascular research, illustrated by the work presented in this thesis and related literature.

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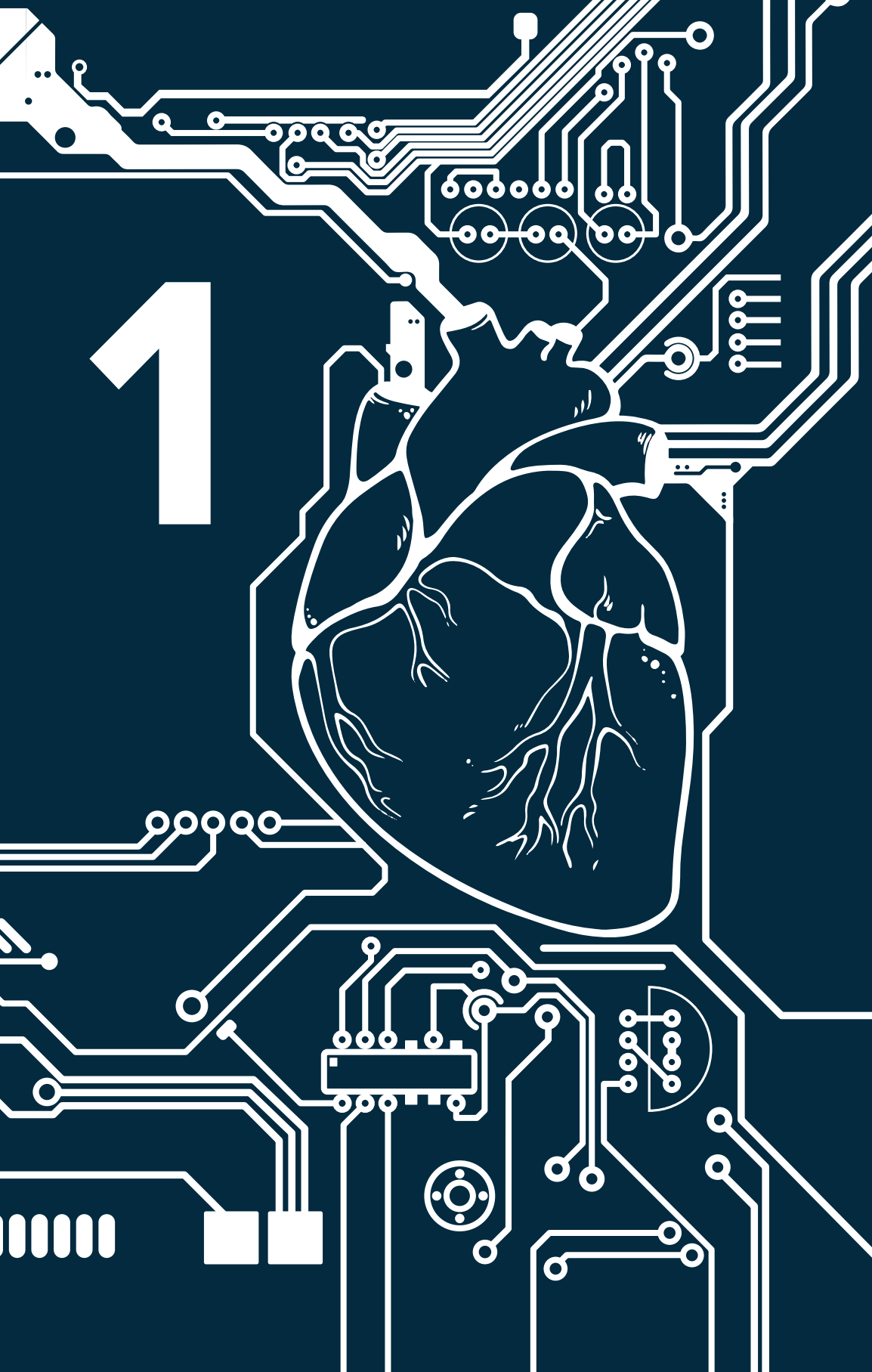

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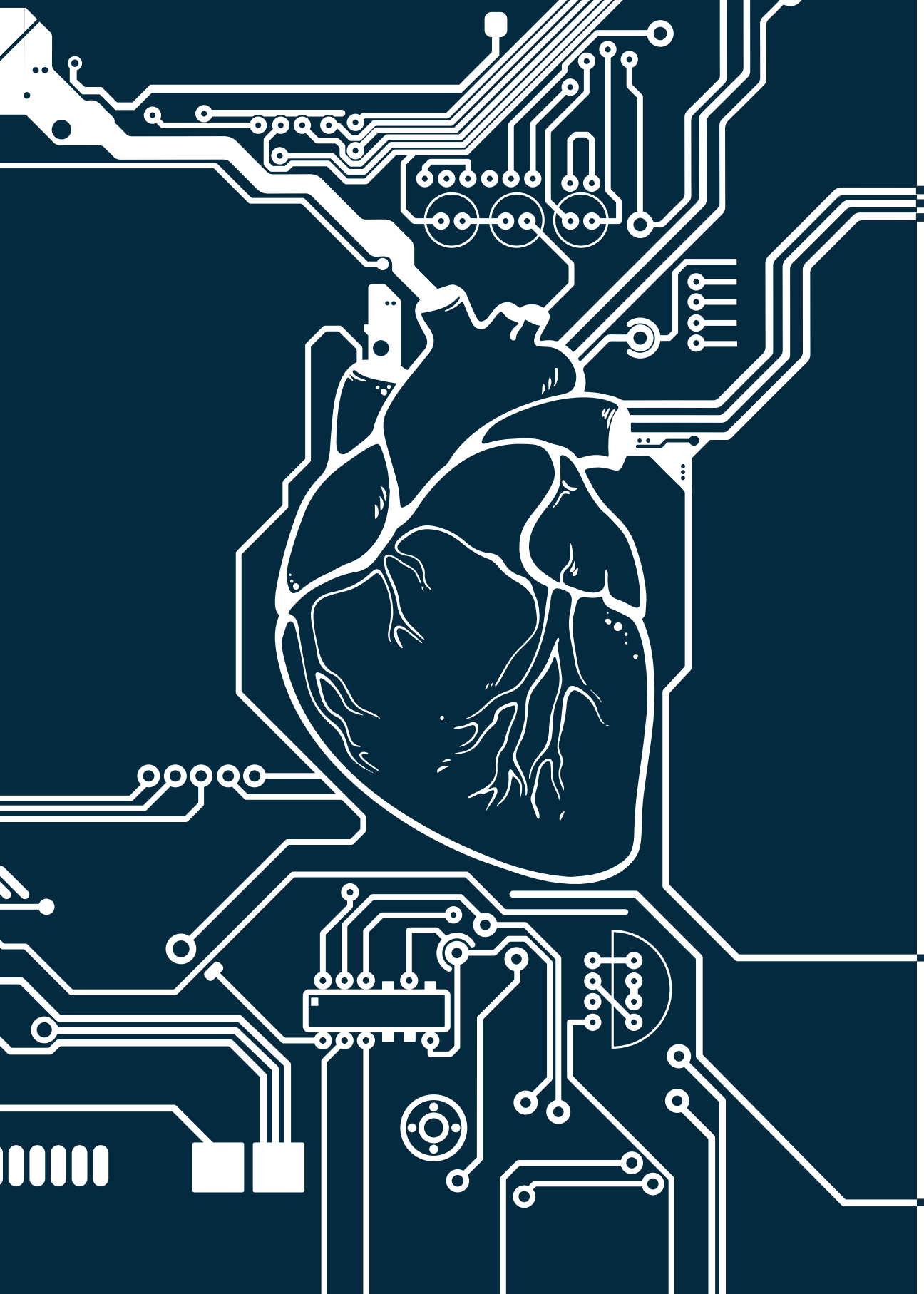
PART I

REAL-WORLD DATA FROM REGISTRIES



CHAPTER 2

Thirty years of heart transplantation at the University Medical Centre Utrecht

A. Sammani*[1], A.M. Wind*[1], J.H. Kirkels*, C. Klöpping*, M.P. Buijsrogge, F.Z. Ramjankhan[‡], F.W. Asselbergs*, N. de Jonge*

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ABSTRACT

Purpose

To analyse patient demographics, indications, survival, and donor characteristics for heart transplantation (HTx) during the past 30 years at the University Medical Centre Utrecht (UMCU).

Methods

Data have been prospectively collected for all patients who underwent HTx at the UMCU from 1985 until 2015. Patients who were included underwent orthotopic HTx at an age >14 years.

Results

In total, 489 hearts have been transplanted since 1985; 120 patients (25%) had left ventricular assist device (LVAD) implantation prior to HTx. A shift from ischaemic heart disease to dilated cardiomyopathy has been seen as the leading indication for HTx since the year 2000. Median age at HTx was 49 years (range 16-68). Median waiting time and donor age have also increased from 40 to 513 days and from 27 to 44 years respectively (range 11-65). Donor cause of death is now primarily stroke, in contrast to head and brain injury in earlier years. Estimated median survival is 15.4 years (95% confidence interval 14.2-16.6) There is better survival throughout these years.

Conclusion

Over the past 30 years, patient and donor demographics and underlying diseases have shifted substantially. Furthermore, the increase in waiting time due to lack of available donor hearts has led to a rise in the use of LVADs as bridge to transplant. Importantly, an improvement in survival rates is found over time which could be explained by better immunosuppressive therapy and improvements in follow-up care.

INTRODUCTION

Orthotopic heart transplantation (HTx) has been an effective treatment for end-stage heart failure for many years and was performed in more than 120,000 patients worldwide up until 2015. [1] Since 1967, when the first HTx was performed by Christiaan Barnard in South Africa, survival rates have increased significantly. [2] In the early days, this was mainly due to improvements in diagnosis and treatment of complications such as acute rejection. [3] These improvements were led by the introduction of the calcineurin inhibitors cyclosporine in 1980, and tacrolimus several years later, and the development of the bioptome, allowing diagnostic endomyocardial biopsies for the histological diagnosis of rejection. A systematic grading scale for the classification of rejection was also very important. [4]

Nowadays, the main limitation of HTx is the lack of donor hearts worldwide. In the Netherlands the first HTx was performed in Rotterdam in 1984 and in Utrecht in 1985, after a long period of decision-making by the government. To date, around 100 patients are on the national waiting list, whereas approximately 45-50 patients are transplanted each year. This lack of donor hearts leads to prolonged waiting times. The limited availability of donor hearts is partly compensated for by left ventricular assist devices (LVADs), which are used to bridge patients with advanced heart failure until a donor heart becomes available. Interestingly, the improved durability of LVADs makes them suitable as a long-term alternative for HTx. [3,5,6]

In this article we describe the demographics, indications, survival, and donor characteristics over the past 30 years in patients who were transplanted at our centre.

METHODS

Study design

This single-centre retrospective analysis included all patients ≥14 years of age who underwent orthotropic HTx at our centre from 1985 until 2015. Data were collected from a database containing prospectively registered heart transplantations performed after 1985, and missing data were collected from patient charts. For comparison over time, patients were grouped into six clusters by year of transplantation: (I) 1985-1989, (II) 1990-1994, (III) 1995-1999, (IV) 2000-2004, (V) 2005-2009 and (VI) 2010-2014.

Screening, definition, and in-house protocol

Patients were considered for HTx according to national guidelines, last updated in 2008. [7] Briefly, indication for HTx is end-stage heart disease not amenable by more conservative measures. Since HTx is an intensive medical treatment, the patient must be willing, capable, and emotionally stable to withstand the uncertainties likely to occur both before and after transplantation. Furthermore, the expected 1-year mortality of the potential patient should exceed the 1-year mortality after HTx, which is 10-15%. An estimation of the prognosis in patients with end-stage heart failure is difficult but can be estimated using, for instance, the Heart Failure Survival Score (HFSS) which consists of a combination of several non-invasive measures such as peak VO2, ejection fraction and intraventricular conduction delay, and the Seattle Heart Failure Model. [8,9]

Contraindications for HTx are defined as high pulmonary vascular resistance (PVR), active systemic infection, active malignancy, inability to comply with complex medical regimen, severe peripheral or cerebrovascular disease and irreversible dysfunction of another organ. [6] Nonetheless, these contraindications are generally not absolute but only temporary and have to be judged in relation to the clinical picture of the patient. As an example, irreversible elevated PVR increases the risk of right-sided failure of the transplanted heart. However, there is no absolute cut-off value, so it has to be seen as an incremental risk factor.

After referral, the first step is optimisation of medical therapy after which patients undergo screening for contraindications. Eligibility of patients is assessed by a dedicated team consisting of at least a cardiologist trained in end-stage heart failure and transplantation, a cardiothoracic surgeon, and specialised nurses. According to the guidelines for HTx, patients are considered either: (1) not eligible for HTx, (2) a future candidate for HTx or (3) listed for HTx. [7]

Patients on the waiting list, as well as the patients who were deemed too good for transplantation at prior evaluation, will be regularly re-evaluated given the dynamic nature of the clinical course (Fig. 1).

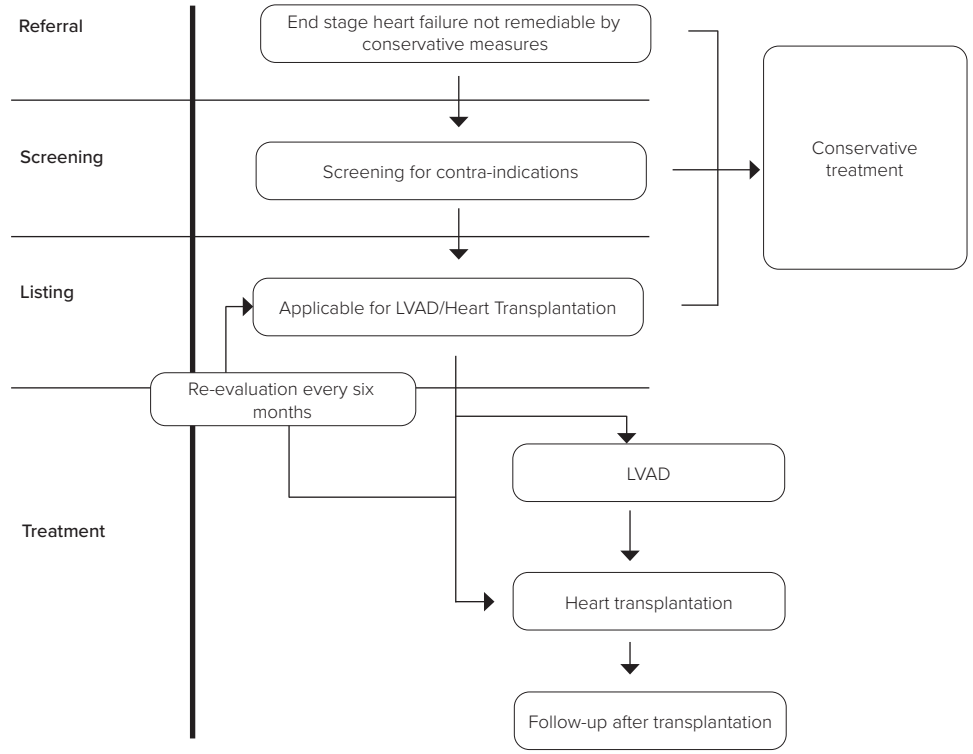

FIGURE 1. From referral to transplantation. LVAD Left Ventricular Assist Device.

Statistical analysis

Re-transplanted patients (n=8) were listed as having one primary indication, and a secondary indication named 'other'. Survival data were gathered using the hospital patient information system. Group comparisons were made using the chi-square test for categorical variables, the one-way ANOVA and post-hoc test for normally distributed continuous variables, and the Kruskal-Wallis or Mann-Whitney U test for non-normally distributed continuous variables when appropriate. Survival rates were calculated using the Kaplan-Meier method and tests for trends were performed using the log-rank test. Conditional survival curves were analysed for patients surviving the first year after HTx. Statistical significance was assumed at $p < 0.05$. Statistical analyses were performed using IBM SPSS version 21 for Windows (SPSS Inc., Chicago, Illinois, USA). Graphs and sub-analysis were performed using GraphPad Prism version 6.02 for Windows.

RESULTS

This analysis includes 489 heart transplants in 481 patients in the UMCU from 1985 until 2015 (Fig. 2, Table 1).

TABLE 1. Characteristics of heart transplantation recipients

Patient characteristics Averages presented as means ±SD or median (IQ) when appropriate	**HTx patients n=489**	**Range or percentage**
Median age at transplantation (IQ)	49 (IQ 39-56)	16-68
< 20 years (n, %)	*10*	*2.0%*
20-40 years (n, %)	*126*	*25.8%*
40-60 years (n, %)	*306*	*62.6%*
> 60 years (n, %)	*47*	*9.6%*
Male n, %	372	76%
Pretransplant diagnosis (n, %)		
Non-ischaemic dilated CMP	220	45%
Ischaemic heart disease	214	43.8%
Hypertrophic CMP	21	4.3%
Restrictive CMP	4	0.8%
Congenital heart disease	8	1.6%
Valvular heart disease	14	(2.9%
Re-transplant	8	1.6%
Pretransplant BMI (±SD)	23.5 (±3.3)	13.7 – 34.9
Pretransplant PVR without intervention (±SD); (n=471)	177 (±88)	16-561
Pretransplant PVR with intervention (±SD); (n=18)	230 (±92)	65-419
Median pretransplant creatinine (n=483)	106 (IQ 89-127)	40-328
LVAD bridging, n (%)	120	25%
Median time with LVAD on waiting list in days (IQ); (n=117)	266 (IQ 147-484)	(9-1384)
Median waiting time for transplantation in days, (IQ), (n=486)	150 (IQ 48-301)	0-1688
1985-1989	*40 (IQ 16-84)*	*0-262*
1990-1994	*107 (IQ 41-162)*	*3-653*
1995-1999	*119 (IQ 43-249)*	*0-559*
2000-2004	*158 (IQ 56-259)*	*1-1509*
2005-2009	*287 (IQ 119-463)*	*1-1235*
2010-2014	*513 (IQ257-806)*	*1-1688*

SD *standard deviation*; IQ *interquartile range*; CMP *cardiomyopathy*; BMI *body mass index*; PVR *pulmonary vascular resistance*; LVAD *left ventricular assist device*

Recipient characteristics

Over time a gradual increase in numbers of transplantations per year can be seen, with a peak in 1996 and declining afterwards (Fig. 2a). Median age at HTx was 49 with an interquartile range (IQ) of 39-56 and has remained constant throughout the years. Over 60% of our patients were between 40-60 years of age at the time of transplant. Our cohort was predominantly male (76%) with no significant change over time. Primary indications for HTx were non-ischaemic dilated cardiomyopathy (DCM) (220 patients, 45%) and ischaemic heart disease (214 patients, 44%), followed by hypertrophic cardiomyopathy (21 patients, 4.3%), acquired valvular disease (14 patients, 2.9%), congenital heart disease (8 patients, 1.6%), restrictive cardiomyopathy (4 patients, 0.8%) and re-transplants (8 patients, 1.6%) (Fig. 2c, Table 1). Comparing indication for HTx, a significant shift can be seen (p = 0.028) in the number of recipients, from ischaemic heart disease to DCM over the course of the groups (Fig. 2b, table 1). Whereas only 40% of recipients were of DCM origin in the first 5 years, this indication now comprises 57% of cases. Ischaemic heart disease, however, decreased from 52% to 30% (Fig. 2b, Table 2). Eight patients have had re-transplantations due to primary graft failure of the first donor heart. BMI increased from 22 to 24 over the years (p = 0.01). Mean PVR did not show changes.

LVAD implantation in our centre began in 1993, first on a small scale. In total 120 patients (25%) received LVAD implantation prior to HTx and given the low numbers in the early years, a significant increase (p<0.0001) in use can be observed later on with a median of 133 in 1990-1994 to a median of 594 days in 2010-2014. The average LVAD support time was a mean of 364±313 days, ranging from 9-1384 days.

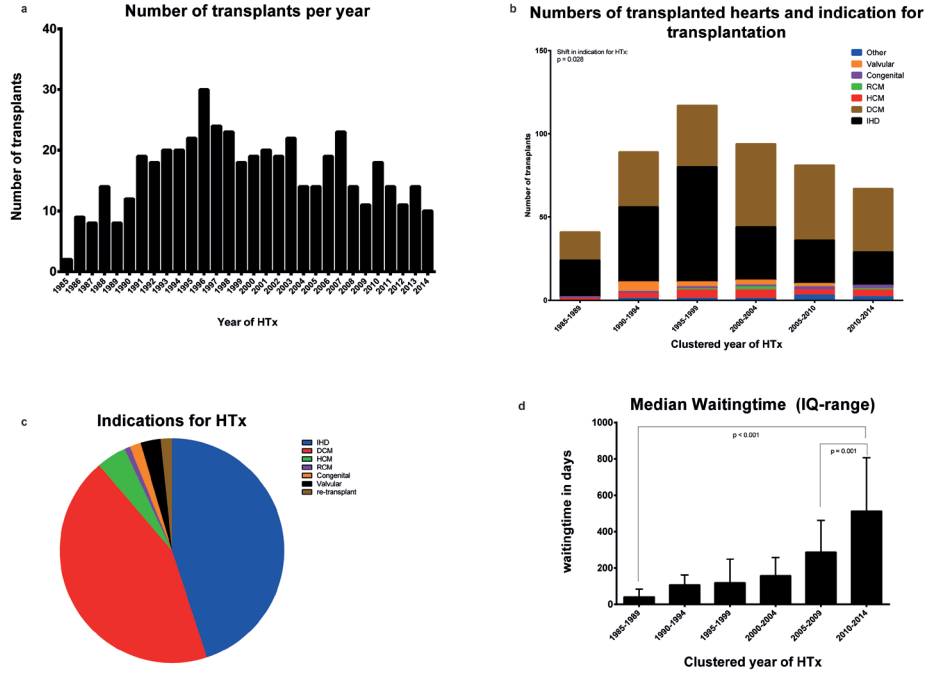

FIGURE 2. Number of transplants, indication for transplantation and median waiting time

Waiting time to transplantation

Overall median waiting time for transplantation was 150 (IQ 48-301) days with a range of 0-1688 days. A significant (p<0.001) increase in waiting time can be seen from a median of 40 days in 1985-1990 to 513 days in 2010-2014. Since the introduction of continuous flow LVADs in 2006, with proven longer durability, the waiting time has increased even further (p = 0.001) (Fig. 2d, Table 1).

Survival

Kaplan-Meier data of total survival and conditional survival (those patients who survived the first year after HTx) are presented in Fig. 3. Median survival was 15.4 years (95% confidence interval 14.2-16.6) for the entire cohort, including 13 patients who have survived for over 25 years after HTx. There is a significant trend towards better survival when comparing the groups over time (Fig. 3).

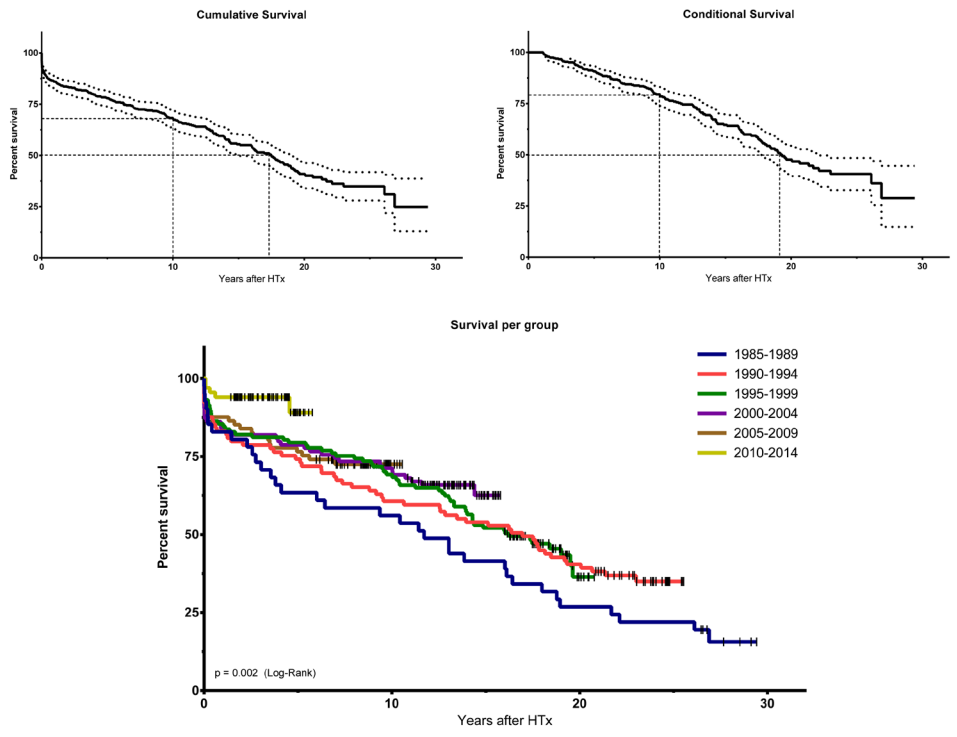

FIGURE 3. Overall survival, conditional survival, and survival in groups

Donor characteristics

Median donor age was 40 [IQ 28-48] years for the whole cohort but has increased significantly (p<0.001) from 27 years to 44 years from 1985 to 2014. The oldest donor was 65 years; 207 (43%) of our donors were female and 280 (57%) were male (Table 3). The cause of death was mainly cerebral stroke (272, 57%) and head and brain injury (163, 34%). The remaining causes were brain tumours (14 = 3%), suicide (11, 2%), gunshot wounds (3, 1%) and 15 (3%) of unregistered cause. A significant (p<0.001) shift in cause of death, however, can be observed. In the early years of HTx the major cause of death was head and brain injury (over 60% of donors), this has come down to 18% in recent years. The opposite holds true for stroke as a cause of death for donors (29 to 65%) (Table 2).

TABLE 2. Significant change in demographics from 1985 to 2015

Change in demographics from 1985-1990 to 2010-2015 *Averages presented as means ±SD or median [IQ] and p-value when appropriate*	**1985-1989**	**2010-2014**	**P-value**
Pretransplant diagnosis	40.5%	56.7%	0.028
Non-ischaemic dilated CMP	52.4%	29.9%	
Ischaemic heart disease	2.4%	6.0%	
Hypertrophic CMP	2.4%	1.5%	
Restrictive CMP	2.4%	3.0%	
Congenital heart disease	-%	-%	
Valvular heart disease	-%	3.0%	
Other			
Pretransplant BMI (±SD)	22(±3.5)	24(±3.7)	0.01
Median waiting time for transplantation in days (IQ) (n=486)	40[16-84]	513[257-806]	<0.001
Donor cause of death (n=484)			
Brain tumour (%)	0%	6%	<0.001
Stroke (%)	30%	65%	
Gunshot wound, (%)	0%	1%	
Suicide (%)	2%	10%	
Head and brain injury (%)	61%	18%	
Unknown (%)	7%	3%	

SD *standard deviation*; IQ *interquartile range*; CMP *cardiomyopathy*; BMI *body mass index*;

TABLE 3. Significant change in demographics from 1985 to 2015

Change in demographics from 1985-1990 to 2010-2015 *Averages presented as means ±SD or median [IQ] when appropriate*	**N**	**Range or percentage**
Donor age in years (n=482)	40 [28-48]	11-65
Male, *n* (%)	280	57%
Donor cause of death (n=477)		
Brain tumour, *n* (%)	14	3%
Stroke, *n* (%)	272	57%
Gunshot wound, *n* (%)	3	1%
Suicide, *n* (%)	11	2%
Head and brain injury, *n* (%)	162	34%
Unknown, *n* (%)	15	3%

SD *standard deviation*; IQ *interquartile range*

DISCUSSION

In this article we describe the demographics, indications, and survival of HTx and donor characteristics over the past 30 years.

Firstly, addressing to demographic trends, we see that over the years DCM has replaced ischaemic heart disease as the main reason for HTx in our cohort. Worldwide this same trend can be observed. [1,7,10–14] One possible explanation might be the better treatment of coronary artery disease, resulting in less patients with end-stage heart failure at an age that still allows HTx. Overall, the other characteristics of the recipients did not change very much over time; as can be expected, it concerns more men than women and the median age at which patients were transplanted was around 50. These figures are comparable with those from other European countries. [12,14]

Donor characteristics, however, did change dramatically from predominantly traumatic events as cause of death in the past to largely cerebrovascular events in more recent years, accompanied by a significant increase in donor age (median age 27 years in 1985, vs 44 years in 2014, with extremes to 65 years.) This change encompasses an entirely different risk profile of donors since hearts of older patients with stroke, by definition, have more vascular comorbidities, affecting not only the eligibility of the donor heart, but also result in an increased risk of coronary allograft vasculopathy after transplantation. [15,16] With respect to donor age, Europe and especially the Netherlands completely diverge from the international data, as the median age of all cardiac donors used worldwide (including European data) is still only 35 years. [1] This has to be explained by the low mortality of traffic accidents in the Netherlands in comparison with other countries. [3] But without using those older donor hearts, almost no heart transplantations would be performed in the Netherlands. Despite the significantly higher donor age, we demonstrate improved survival after HTx. This can be attributed to several factors. Apart from the availability of better immunosuppressive therapy and growing experience with this specific patient category in general, an important aspect is that all our follow-up is performed in-house and not elsewhere as in many other centres. Furthermore, international statistics are negatively biased by many smaller centres performing only a few transplantations per year and lacking this experience. This improved experience is also related to the treatment of complications such as cardiac allograft vasculopathy, renal failure and malignancies. [3,10] Furthermore, because of the lack of donor hearts there is more stringent selection of recipients in comparison with other countries, potentially resulting in a younger transplantation cohort than reported by the International Society for Heart and Lung Transplantation (54 years). [1]

Another remarkable change over time is the use of LVADs as bridge to transplantation. This option was not available at the start of the program in 1985, but nowadays is an inseparable part of it. Due to the extremely long waiting time until transplantation, many patients deteriorate while on the waiting list. A large number of these patients can now be treated by mechanical circulatory support, using an LVAD as bridge to transplantation, which potentially causes deleterious displacement effects for the waiting time. The dilemma now conceived is an even longer waiting time as more patients survive until transplantation without an accompanying increase in donor hearts. But without the use of LVADs, many patients with acute heart failure would not have made it to transplantation or even to the waiting list at all. Clearly, implantation of an LVAD also implies perioperative risk but this outweighs the mortality of progressive acute heart failure by far. [17] Furthermore, it has to be realised that due to the improvements in technology and design the durability of LVADs has increased substantially, allowing the longer waiting time until transplantation, with a remarkable good quality of life and exercise tolerance. [18,19]

Conclusion

Over the past 30 years, substantial differences can be noted in HTx. Patient demographics show a shift from ischaemic heart disease to DCM. The donor situation has completely changed from younger trauma victims to older patients dying from a cerebrovascular accident with a higher chance of pre-existing cardiovascular abnormalities. Due to the longer waiting time, an increasing number of patients have to be bridged to transplantation by a LVAD.

Despite these potentially adverse aspects, there is an improvement in survival rates which could be explained by better immunosuppressive therapy and improvements in follow-up care.

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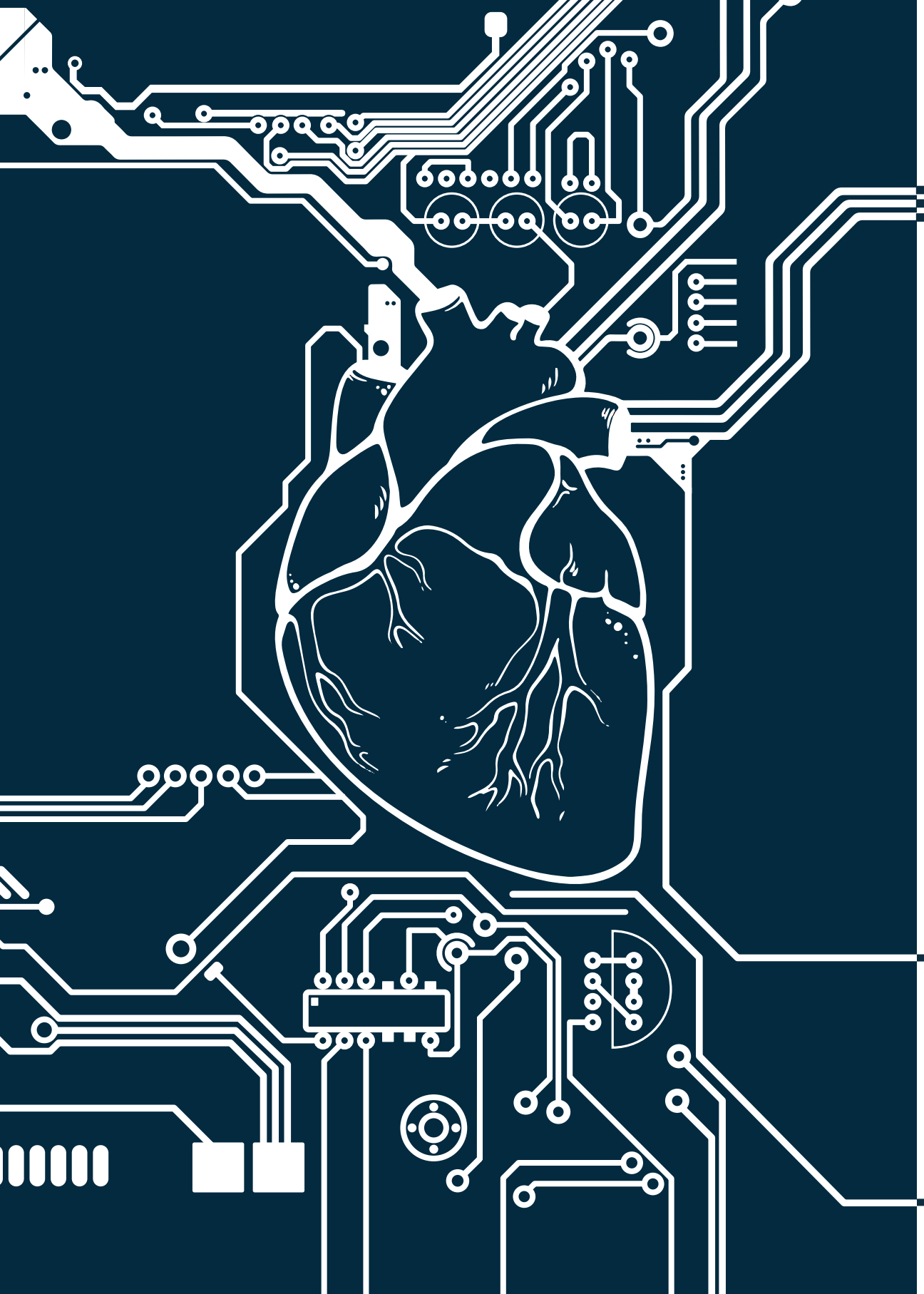

CHAPTER 3

Differences between familial and sporadic dilated cardiomyopathy: ESC EORP Cardiomyopathy & Myocarditis registry

Folkert. W. Asselbergs, MD PhD, Arjan Sammani, MD, Perry Elliott, MD, PhD, Juan R. Gimeno, MD, PhD, Luigi Tavazzi, MD, PhD, Michael Tendera, MD, PhD, Juan Pablo Kaski, MD, Aldo P. Maggioni, MD, PhD, Pawel P. Rubis, MD, Ruxandra Jurcut, MD, PhD, Heliö Tiina, MD, PhD, Leonardo Calò, MD, Gianfranco Sinagra, MD, PhD, Marija Zdravkovic, MD, PhD, Iacopo Olivotto, MD, PhD, Aušra Kavoliuniene, MD, PhD, Cécile Laroche, MD, Alida L.P. Caforio, MD, PhD, Philippe Charron, MD, PhD on behalf of the Cardiomyopathy & Myocarditis registry investigators group.

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ABSTRACT

Aims

Dilated cardiomyopathy (DCM) is a complex disease where genetics interplay with extrinsic factors. This study aimed to compare the phenotype, management and outcome of familial DCM (FDCM) and non-familial (sporadic) DCM (SDCM) across Europe.

Methods & Results

Patients with DCM that were enrolled in the prospective ESC EORP Cardiomyopathy & Myocarditis Registry were included. Baseline characteristics, genetic testing, genetic yield and outcome, were analysed comparing FDCM and SDCM.

1260 adult patients were studied (238 FDCM, 707 SDCM, 315 not disclosed). Patients with FDCM were younger (p<0.01), had less severe disease phenotype at presentation (p<0.02), more favourable baseline cardiovascular risk profiles (p ≤ 0.007) and less medication use (p≤0.042). Outcome at one year was similar and predicted by NYHA class (HR 0.45; 95%CI[0.25-0.81]) and LVEF per % decrease (HR 1.05; 95%CI[1.02 - 1.08]. Throughout Europe, patients with FDCM received more genetic testing (47% vs 8%, p<0.01) and had higher genetic yield (55% vs 22%, p<0.01).

Conclusion

We observed that FDCM and SDCM have significant differences at baseline, but similar short-term prognosis. Whether modification of associated cardiovascular risk factors provide opportunities for treatment remains to be investigated. Our results also show a prevalent role of genetics in FDCM and a non-marginal yield in SDCM although genetic testing is largely neglected in SDCM. Limited genetic testing and heterogeneity in panels provides a scaffold for improvement of guideline adherence.

INTRODUCTION

Dilated cardiomyopathy (DCM), defined as left ventricular dilation and systolic left ventricular (LV) impairment unexplained by coronary artery disease or abnormal loading conditions, is a leading cause of heart failure and heart transplantation with an estimated prevalence of ~36 cases per 100,000 in Europe.[1]

Prior studies on clinical characteristics of patients with non-familial (sporadic) forms of DCM (SDCM) and familial DCM (FDCM) have reported that FDCM presents at earlier age, but presented conflicting evidence regarding phenotype severity. Some studies found more favourable clinical profiles in FDCM compared to SDCM whereas others report similar baseline phenotypes without any distinctive features[2–5] Due to genotype-phenotype associations, such as frequent ventricular arrhythmias in LMNA and PLN mutation carriers, heterogeneity in prognosis however may be expected between FDCM and SDCM.[6] Others postulated that FDCM present as SDCM and that proper active family screening is needed to distinguish true SDCM from undetected FDCM. This screening has been shown to effectively identify DCM and improve prognosis.[3]

Many studies have shown that DCM can be inherited as a genetic trait[1,7–11] and that structural or functional LV abnormalities are present in 20% of asymptomatic relatives of patients with DCM.[12,13] Genetic mutations are reported in more than a third of index patients with FDCM and in 8-25% of SDCM.[8,14] The most common disease causing variants are found in genes coding for sarcomere proteins such as TTN, MYH7 and FLNC, and the nuclear envelope gene LMNA.[15–17] Evidence also suggests that genetic predisposition in DCM may interact with extrinsic disease triggers such as toxin exposure (ethanol, chemotherapy, cocaine), viral infection and pregnancy.[1,18,19] Nonetheless, toxin exposure may also be the sole putative trigger of DCM, for instance in alcoholic cardiomyopathy.[18]

The ESC EORP Cardiomyopathy & Myocarditis Registry is a prospective observational multinational survey of consecutive patients with cardiomyopathies.[20] To investigate the complexity in clinical characteristics and genetic yield, the current analysis of this registry aims to: (i) study clinical cardiovascular differences in adult FDCM and SDCM; (ii) report the frequency of genetic testing across Europe and (iii) report differences in genetic yield between familial and sporadic DCM.

METHODS

The general policy as well as baseline results of the new EURObservational Research Programme (EORP) cardiomyopathy registry of the ESC have been previously published. In short, the EORP cardiomyopathy registry is a multicentre registry where participating centres were asked to enter baseline, follow-up and genetic data of about 40 consecutive patients with cardiomyopathy per centre.[20] Patients were included from December 1st 2012 until December 30th 2016.

Inclusion/exclusion criteria

Adult patients with DCM defined by ESC consensus criteria were studied. Specifically: (1) left ventricular ejection fraction <45% (>2 SD) and/or fractional shortening <25% (>2 SD), as ascertained by echocardiography, radionuclide scanning or cardiac magnetic resonance imaging; and (2) left ventricular end-diastolic diameter >117% of the predicted value corrected for age and body surface area (Henry's formula), which corresponds to 2 SD of the predicted normal limit +5%. Patients with heart failure attributable to coronary artery disease and clinically suspected or biopsy-proven myocarditis were excluded.[20,21]

Definitions

Familial dilated cardiomyopathy (FDCM) was defined by the presence of two or more affected individuals in a single family or the presence of an index patient with DCM and a first degree relative with documented unexplained sudden cardiac death at <35 years of age. Patients that did not meet these criteria were deemed sporadic DCM (SDCM). Patients with missing data concerning familial status (n=315) were compared to both FDCM and SDCM for clinical differences to account for bias. Primary outcome was defined as a composite of cardiovascular death, implantation of a ventricular assist device or heart transplantation. Secondary end-point was hospitalization for urgent cardiac reason. Genetic testing and variant classification was planned and performed according to clinician's judgement. Genetic variants and their classifications were reported by individual researchers representing their centres. Since lab techniques and genetic coordinates were not recorded, centralized variant classification was not possible. The definitions of included variables have been listed in prior EORP publications and are included in the supplementary file S1.[20,27]

Statistical Analysis

Univariable analysis was applied to both continuous and categorical variables. Continuous variables were reported as mean ± standard deviation and/or as median and interquartile range (IQR) when appropriate. Among-group comparisons were made using a non-parametric test (Kruskal–Wallis). Categorical variables were reported as counts and percentages. Among-group comparisons were made using a χ^2 test or a Fisher's exact test if any expected cell count was less than 5. Plots of Kaplan-Meier curves for primary outcome were performed. Cox proportional hazards model was used for survival estimates reporting hazard ratios (HR's) and 95% confidence intervals (95%CI's) in univariable and multivariable analysis. As the goal was to report covariates and their association to outcome rather than a clinical risk calculator, both multivariable results as well as variable selection ($p<0.05$) were reported. To compare to external datasets, comparison of proportions was calculated using the "N-1" Chi-squared test. A two-sided *P*-value of <0.05 was considered as statistically significant. For sensitivity analyses, probands of FDCM were compared to SDCM. Analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

The cohort comprised 1260 patients, of whom 238 had FDCM, 707 SDCM and 315 were unclassified (unknown). Patients with unknown status were compared to FDCM and SDCM. The analysis revealed the "unknown" group to be similar to SDCM. These results as well as head to head group-comparisons are available in the supplementary file S2.

The characteristics and treatment of patients with FDCM and SDCM are reported in Table 1. Compared to SDCM, patients with FDCM were younger (44 years [IQR 31-52]) vs 51 years[IQR 41-58], p<0.001), had lower NYHA class (p<0.001) and BNP and NT-proBNP levels (p<0.028), less frequent left bundle branch block (9% vs 22%, p<0.001), smaller left ventricular end diastolic diameter (p<0.001) and higher left ventricular ejection fraction (LVEF) (37% vs 31%, p<0.001). Sixty percent of FDCM patients were index cases compared to 99% of SDCM patients (p < 0.001). Patients with SDCM had a higher burden of cardiovascular risk factors (hypertension, dyslipidaemia, diabetes, smoking, alcohol intake and high BMI than FDCM (all p≤0.007). A larger proportion of patients with SDCM received β-blockers, diuretics, mineralocorticoid receptor antagonists and other anti-arrhythmic agents (p ≤ 0.042) compared to FDCM. A sensitivity analysis comparing solely FDCM index patients with SDCM showed that all characteristics except BMI remained significantly different between the groups (Supplementary file S2, Table 1.1.A).

TABLE 1. Baseline table of patient characteristics, pharmacotherapy and outcome

		All (N=1260)	FDCM (n=238)	SDCM (n=707)	*p-value**
Age at diagnosis (years), median (IQR)		49 (40-58)	44 (31-52)	51 (41-58)	*<0.01*
Male		935 (74%)	165 (69%)	536 (76%)	*<0.05*
NYHA class	**I**	198 (19%)	65 (35%)	84 (14%)	*<0.01*
	II	448 (43%)	79 (42%)	261 (44%)	
	III	316 (30%)	37 (20%)	187 (31%)	
	IV	87 (8%)	6 (3%)	65 (11%)	
Family history of SCD		132 (12%)	65 (29%)	28 (4%)	*<0.01*
	Cardiovascular risk factors				
Hypertension		479 (38%)	54 (23%)	288 (41%)	*<0.01*
Dyslipidaemia		472 (38%)	62 (26%)	274 (39%)	*<0.01*
Diabetes Mellitus		211 (17%)	25 (11%)	127 (18%)	*<0.01*
Alcohol use ≥ 1 units/day		174 (16%)	20 (10%)	124 (20%)	*<0.01*
Smoking (current and former)		507 (42%)	71 (31%)	323 (47%)	*<0.01*
Renal impairment		172 (14%)	24 (10%)	94 (13%)	*0.20*
	Cardiovascular history				
History of Atrial Fibrillation		356 (28%)	63 (27%)	202 (29%)	*0.53*
History of Stroke		87 (7%)	12 (5%)	47 (7%)	*0.38*
History of resuscitation		61 (5%)	15 (6%)	32 (5%)	*0.28*
	ECG parameters				
Atrioventricular block	1st	108 (9%)	20 (9%)	57 (8%)	*0.02*
	2nd	6 (1%)	3 (1%)	2 (0%)	
	3rd	14 (1%)	6 (3%)	4 (1%)	

TABLE 1. Continued

		All (N=1260)	FDCM (n=238)	SDCM (n=707)	*p-value**
	ECG parameters				
QRS Duration (ms), median, IQR		105 (92-130)	100 (90-112)	104 (90-130)	*0.02*
LBBB		219 (21%)	18 (9%)	133 (22%)	*<0.01*
RBBB		41 (4%)	6 (3%)	24 (4%)	*0.53*
	Echocardiography parameters				
LVEF (%), median (IQR)		31 (25-40)	37 (29-45)	31 (24-40)	*<0.01*
LVEDD (mm), median (IQR)		64 (58-70)	60 (54-67)	64 (59-70)	*<0.01*
Diastolic Dysfunction (grades)	Normal	209 (25%)	63 (38%)	97 (20%)	
	I (impaired relaxation)	299 (37%)	57 (35%)	169 (35%)	*<0.01*
	II (pseudonormal)	152 (19%)	28 (17%)	108 (22%)	
	III/IV (restrictive)	156 (19%)	16 (9%)	109 (22%)	
	Laboratory parameters				
Haemoglobin (g/dL), median (IQR)		14 (13-15)	14 (13-15)	14 (13-15)	*0.23*
BNP (pg/mL), median (IQR)		297 (72-717)	108 (36-555)	404 (106-718)	*0.03*
NT-proBNP (pg/mL), median (IQR)		1102 (312-3341)	589 (156-1663)	1276 (452-3527)	*<0.01*
	Cardiac Magnetic Resonance Imaging				
Performed		259 (21%)	66 (28%)	148 (21%)	*0.04*
Abnormal		237 (19%)	57 (24%)	136 (19%)	*0.04*
Late gadolinium enhancement		153 (64%)	41 (65%)	92 (67%)	*0.83*
	Medication				
β -blockers		1130 (90%)	203 (85%)	644 (91%)	*0.01*
Diuretics		895 (72%)	123 (54%)	540 (77%)	*<0.01*
ACE-inhibitors or ATII-receptor blockers		1121 (89%)	208 (88%)	634 (89%)	*0.329*
Mineralocorticoid receptor antagonists		795 (63%)	119 (50%)	470 (67%)	*<0.01*
Other antiarrhythmics		361 (29%)	56 (24%)	215 (30%)	*0.04*

Data are presented as number and percentages of valid. Patients with missing family status were not included in the subgroup SDCM in this table since their status was unknown. They have been included in the supplementary file S2 table 1 both a separate group and combined with SDCM. Continuous data are presented as medians. NYHA: New York Heart Association. SCD: Sudden Cardiac Death. BMI: Body Mass Index. LBBB: Left Bundle Branch Block. RBBB: Right Bundle Branch Block. LVEF: Left Ventricular Ejection Fraction. LVEDD: Left Ventricular End Diastolic Diameter. Median presented with first and third interquartiles (IQR). Mean presented with ±Standard Deviation (SD). *FDCM vs SDCM

Follow-up data were available in 1105 (88%) cases (median follow-up duration: 372 days; interquartile range (IQR) 363-428). There were no differences observed in primary and secondary outcomes, or all-cause mortality when comparing FDCM (n=209) to SDCM (n=611) (supplementary table 3Bis). Age at first primary event was also similar for FDCM and SDCM (Figure 1).

In multivariable analysis, BMI per unit decrease (HR 1.11; 95% CI[1.02-1.22]) and LVEF per % decrease (HR 1.08; 95%CI[1.03-1.11]) were associated with primary and secondary outcome. After stepwise selection NYHA class I/II versus III/IV (HR 0.45; 95%CI[0.25-0.81]) and LVEF per % decrease (HR 1.05; 95%CI[1.02 - 1.08] were predictive. There were no significant associations for all-cause mortality. Results of all analyses are available in the Supplementary file S2, table 10.

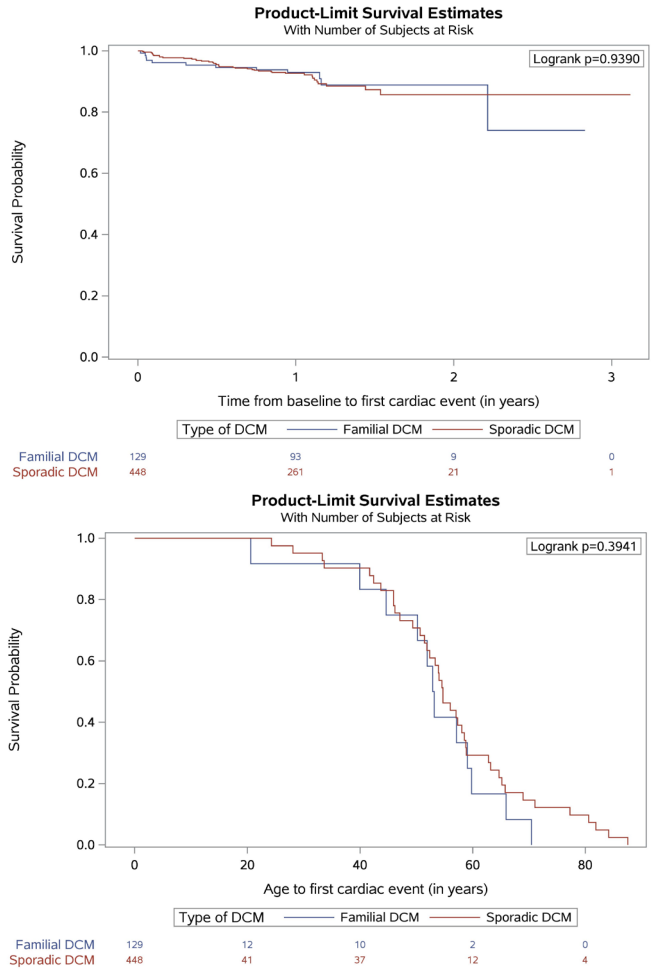

FIGURE 1. Survival probability curves for primary outcome plotted over both time and age comparing SDCM to FDCM.

TABLE 2. Multivariable analysis for primary outcome.

Variable	Pval Hazard Ratio	Hazard Ratio (95% CI)
Age at diagnosis per year increase	0.040 (S)	0.973 (0.949;0.999)
LBBB	0.635 (NS)	0.804 (0.327;1.977)
NYHA class I or II vs. III or IV	0.061 (NS)	0.483 (0.226;1.035)
Alcohol intake 1 unit per day or more	0.618 (NS)	1.224 (0.553;2.705)
Body Mass Index (kg/m^2) per unit increase	0.012 (S)	0.896 (0.823;0.977)
Diabetes mellitus	0.029 (S)	2.815 (1.111;7.131)
Hypertension	0.859 (NS)	1.070 (0.509;2.251)
Smoking current of former	0.921 (NS)	0.964 (0.472;1.970)
LVEF per % decrease	<0.001 (S)	1.073 (1.031;1.117)

Primary end-point was defined as a composite of cardiovascular death, implantation of a ventricular assist device or heart transplantation.
Cox proportional hazards model is presented (hazard ratio's and 95% confidence intervals). NS: not significant. S: Significant. NYHA: New York Heart Association. LBBB: Left Bundle Branch Block. LV: Left Ventricular Ejection Fraction.

Genetic testing

In total, 214 out of 1260 (17%) cases were genetically tested (58 out of 707 (8%) SDCM and 114 out of 238 (48%) of FDCM). In 110 cases, the information on genetic testing was missing. Genetic testing was less frequently performed in Eastern Europe and North Africa (respectively 4 and 0%), whereas North, South and West Europe performed genetic testing in 21-27% of their population (Table 3).

In 63 out of 114 (55%) tested cases of FDCM, at least one disease causing variant was reported compared to 13 out of 58 (22%) in SDCM. These variants were most prevalent in sarcomere (n=42) and nuclear genes (n=27), with most variants being discovered in LMNA (16% yield in FDCM, 3% yield in SDCM) and MYH7 (14% yield in FDCM, 0% in SDCM) (Supplementary file S2, Table 7).

TABLE 3. Regional differences for genetic testing in DCM

	All (N=1260)	FDCM (N=238)	SDCM (N=707)	P-value*
North Europe (n=179)	37 (21%)	19 (56%)	11 (16%)	*<0.001*
South Europe (n=425)	116 (27%)	74 (59%)	23 (14%)	*<0.001*
West Europe (n=206)	48 (23%)	15 (56%)	24 (16%)	*<0.001*
East Europe (n=302)	13 (4%)	6 (18%)	0 (0%)	*<0.001*
North Africa (n=38)	0 (0%)	0 (0%)	0 (0%)	*NC*
Total (1150)	214 (17%)	114 (48%)	58 (8%)	*<0.001*

In 110 cases, genetic testing was unknown. NC: not calculable. *FDCM vs SDCM

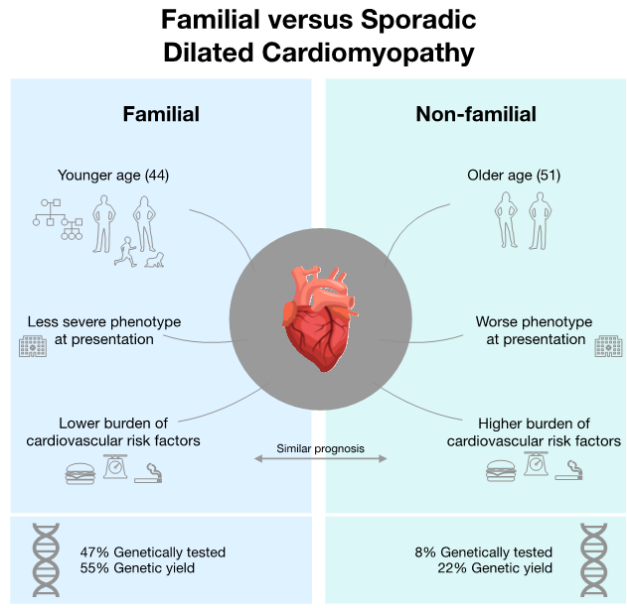

FIGURE 2. Summary of the main findings of this study

DISCUSSION

The three main findings of this study are: (i) patients with FDCM present at younger age with a less severe phenotype and lower burden of cardiovascular risk factors but similar short term prognosis to SDCM; (ii) patients with FDCM are genetically tested more frequently and with higher diagnostic yield than SDCM and; (iii) there are important differences in the use of genetic testing across European centres enrolled in the ESC cardiomyopathy registry. For a central illustration, these findings are summarized in Figure 2.

Disease burden

Overall, DCM patients included in this cohort had similar demographic and clinical characteristics compared to DCM populations described in the literature.[2,4,5,12,22] However, in contrast to some studies, we found that patients with FDCM were diagnosed at a younger age and have a less severe phenotype than patients with SDCM but have similar cardiovascular prognosis.[2,5] This was also seen in the prescribed medication, where we observed that patients with FDCM received less β-blockers, diuretics and mineralocorticoid receptor antagonists. These findings may reflect of cascade family screening in patients with suspected FDCM. However, when comparing FDCM index patients to SDCM patients, the clinical differences remained significant. Because family screening has shown to effectively identify DCM patients at earlier stages of disease, potentially benefiting prognosis, genetic counselling remains an important pillar of care in patients with DCM and their relatives.[3] Prognosis of DCM has been improving for the end-point of cardiovascular death of heart transplantation/assist device implantation, arguably because of better cardiovascular care and the early identification and classification of disease.[23] Our observations however are more in line with earlier reports and less favourable outcome, which may be caused because of a selection bias towards more expert/tertiary centres.[22]

A relevant finding of this study was that patients with SDCM had a higher burden of cardiovascular risk factors, such as hypertension, hypercholesterolaemia and smoking. Because it is well known that these risk factors are more prevalent with increasing age and our patients with SDCM were significantly older than FDCM this result might be expected.[24] However, the age difference between SDCM and FDCM does not fully account for the observed increase in risk factors. When comparing our patients with SDCM to external cohorts from the same age group, we still observe a significantly increased burden of cardiovascular factors ($p<0.01$) in our patients with SDCM.[24,25] In addition, the presence of common cardiovascular risk factors is also associated with worse outcome in SDCM. Smoking, for instance, independently increased sudden cardiac death in SDCM[26] and diabetes confers a two- to five-fold added risk for heart failure development, even after adjustment for other traditional risk factors such as coronary heart disease.[27] Alcohol is also known to be the both sole cause of cardiomyopathy and may negatively affect cardiac function in mutation carriers. In a recent report including 716 DCM cases, excessive alcohol consumption resulted in an absolute LVEF reduction of ±9% in patients with a truncating TTN variant.[18] These results support the hypothesis that cardiovascular risk factors and external toxic substances interplay with genetic frailty, (auto)immunity or endocrinological disorders in the DCM phenotype.[1] Whether modification of cardiovascular risk factors provide opportunities for treatment remains to be investigated.

Differences in prognosis between FDCM and SDCM remain controversial with most follow-up studies of DCM not dividing populations in familial and non-familial categories.[3,28,29] Conflicting results of prior studies may be due to the absence of reliable clinical or morphological parameters to differentiate between FDCM and SDCM.[1,3,28,29] Genotype-phenotype associations affecting prognosis in DCM have been reported: mutations in LMNA and RBM20 predispose for more/younger heart transplantations.[6] Mutations in FLNC, LMNA and PLN have been associated with sustained ventricular arrhythmias in DCM.[30] Nonetheless, our analysis did not yield a significant difference in outcome between FDCM and SDCM.

Genetic mutations in DCM

Mutations in over 40 genes are causally related to DCM and explain up to 61% of cases in FDCM and up to 25% in SDCM.[1,8,14,16,31] Our data confirm the higher yield in FDCM.[8] At present, genetic screening is advised in patients with family history of DCM or a personal history of atypical features such as conduction/rhythm-disturbances[7,8,11,31] and yet, less than 50% of all cases in the registry were tested. Moreover, the fact that heterogeneous screening strategies were used may have impacted on the yield of testing.[20] For instance, mutations in Titin (TTN) have been implicated in up to 22% of SDCM, but this gene was only tested in 19% of our patients with SDCM.[32,33] The selective nature of genetic testing may explain the high prevalence of mutations in genes coding for sarcomere genes and LMNA.

Genetic testing in Europe

We observed differences in genetic testing between European centres. Genetic testing was most prevalent in Northern, Southern and Western Europe (around 20% of the cohort) and least common in Eastern Europe and North Africa. Importantly, Southern Europe included a majority (54%) of the patients with FDCM in this cohort, which could have led to sampling bias.[34,35] These shortcomings should by accounted for in terms of external validity of this study. Furthermore, the regional differences in our study as well as differences described by prior EORP studies provide opportunities to improve guideline adherence in Europe.[20,35,36] Even though guideline adherence is highest in secondary and tertiary centres and higher for cardiologists than other specialities, care may be fragmented in highly complex diseases such as inherited cardiomyopathies.[37] This fragmentation can cause unwanted protocol deviations which may deteriorate quality of care. Several strategies have been suggested

to improve guideline adherence. These strategies include common care pathways, ongoing education and focus groups.[37] In terms of genetic testing, actively looking for familial manifestations of disease in patients and relative, and acquiring a detailed family history is quintessential and may improve genetic yield dramatically.

Study Limitations

In contrast to controlled clinical studies, our data are likely to be heterogeneous given the nature of the study design. As the structure of the registry requested to introduce patients from expert/tertiary centres, this may have caused a selection bias. Second limitation is that not all genes were tested in all patients and centralized variant classification was not repeated in this study. Given that genetic testing was unknown in 110 patients, this might constitute another limitation. Even though myocarditis is formally an exclusion criterion, inflammation-caused/mediated reasons for DCM are very difficult to diagnose. Therefore, we cannot exclude with certainty that a proportion of non-familial DCM might be suspected for inflammatory diseases. As the EORP study was not designed for inter-regional comparisons and these analyses were not planned, such comparisons may be arbitrary and unrepresentative. Furthermore, sub analyses using ethnicity/race to provide insight into heterogeneity of populations are limited by poor accuracies of ethnicity/race in electronic health records. Importantly, even though we performed sensitivity analyses with and without patients with unknown classification, this still might have led to biased results. Lastly, the fact that no difference in outcome was detected in our DCM populations may be due to sample size and requires confirmation in larger studies.

Conclusion

FDCM and SDCM have significant differences at baseline. Patients with FDCM appear to present at earlier stage of disease. Patients with SDCM in this registry have less favourable clinical profile. Whether modification of associated cardiovascular risk factors provide opportunities for treatment remains to be investigated. Genetic testing confirms a prevalent role of genetics in FDCM but is largely neglected in SDCM. Although SDCM may probably be multifactorial, genetic influences need further understanding. Limited genetic testing provides a scaffold for improvement of guideline adherence.

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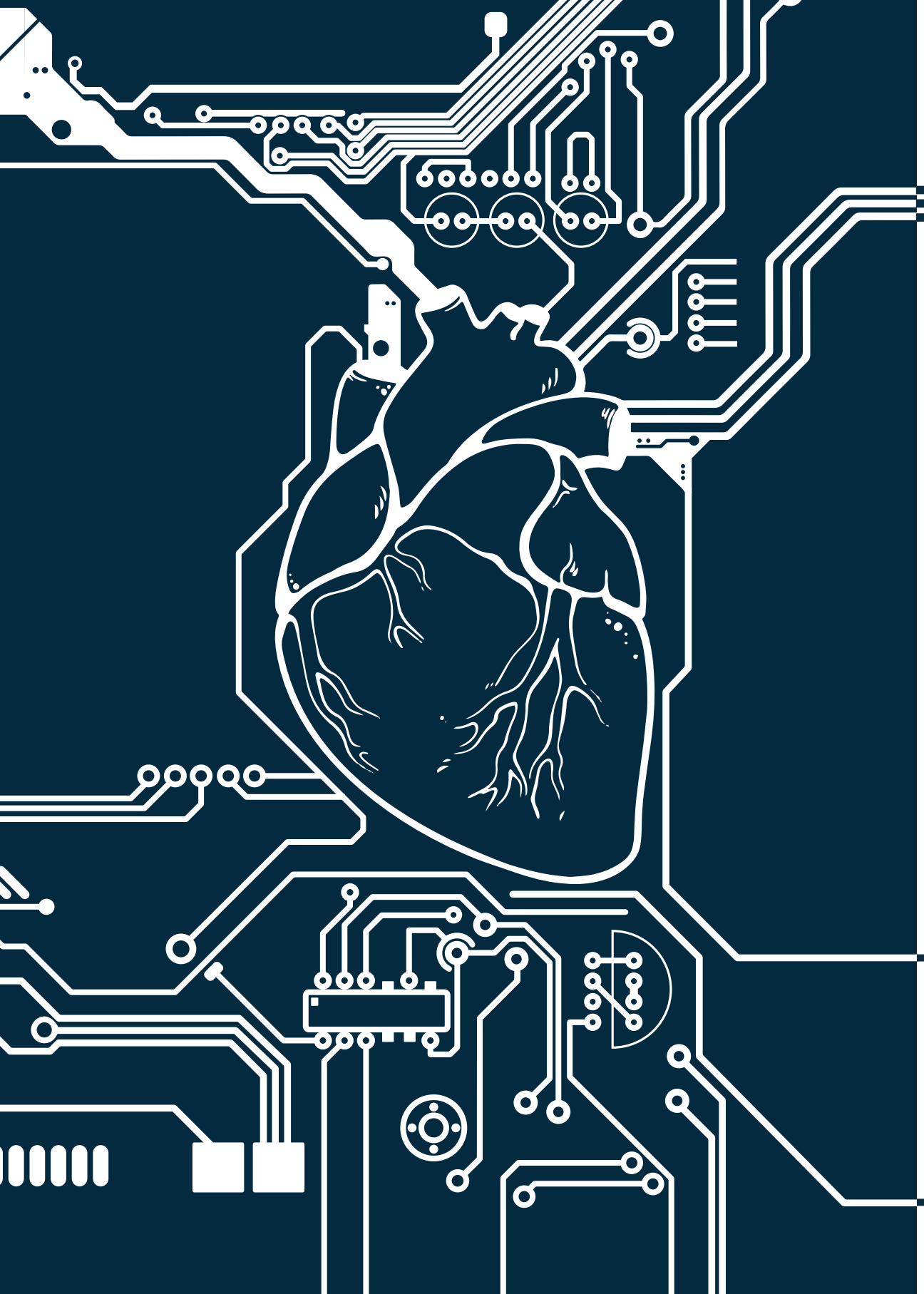

CHAPTER 4

Predicting sustained ventricular arrhythmias in Dilated Cardiomyopathy: A Meta-Analysis and Systematic Review

Arjan Sammani MD, Elham Kayvanpour MD, Laurens P. Bosman MD,
Farbod Sedaghat-Hamedani MD, Tanja Proctor MSc, Weng-Tein Gi MD, MSclH,
Alicia Broezel, Katrin Jensen MD, Prof Hugo A. Katus MD, Anneline SJM. te Riele MD PhD,
Prof Benjamin Meder MD, Prof Folkert W. Asselbergs MD PhD

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ABSTRACT

Aims

Patients with non-ischemic dilated cardiomyopathy (DCM) are at increased risk of sudden cardiac death (SCD). Identification of patients that may benefit from implantable cardioverter-defibrillator (ICD) implantation, remains challenging. In this study we aimed to determine predictors of sustained ventricular arrhythmias in patients with DCM.

Methods

We searched MEDLINE/EMBASE for studies describing predictors of sustained ventricular arrhythmias in patients DCM. Quality and bias were assessed using the QUIPS tool, articles with high risk of bias in ≥2 areas were excluded. Unadjusted hazard ratios (HR) of uniformly defined predictors were pooled, while all other predictors were evaluated in systematic review.

Results

We included 55 studies (11451 patients and 3.7±2.3 years follow-up). Crude annual event rate was 4.5%. Younger age (HR 0.82), hypertension (HR 1.95), prior sustained ventricular arrhythmia (HR 4.15), left ventricular ejection fraction (LVEF) on ultrasound (HR 1.45), left ventricular (LV) dilatation (HR 1.10), and presence of late gadolinium enhancement (LGE) (HR 5.55) were associated with arrhythmic outcome in pooled analyses. Prior non-sustained ventricular arrhythmia and several genotypes (mutations in Phospholamban (PLN), Lamin A/C (LMNA), and Filamin-C (FLNC)) were associated with arrhythmic outcome in non-pooled analyses. Quality of evidence was moderate and heterogeneity among studies was moderate to high.

Conclusions

In DCM patients the annual event rate of sustained ventricular arrhythmias is approximately 4.5%. This risk is considerably higher in younger patients with hypertension, prior (non-) sustained ventricular arrhythmia, decreased LVEF, LV dilatation, LGE, and genetic mutations (PLN, LMNA, FLNC). These results may help determine appropriate candidates for ICD implantation.

INTRODUCTION

Non-ischemic dilated cardiomyopathy (DCM) is characterized by systolic dysfunction and dilatation of the left ventricle (LV) in the absence of coronary artery disease or abnormal loading conditions.(1) Patients with DCM are at increased risk of sudden cardiac death (SCD) and may benefit from an implantable cardioverter-defibrillator (ICD).(2, 3) Prior studies have shown that ICD implantation substantially reduces mortality in patients with heart failure, and consequently LV ejection fraction (LVEF) continues to be the main criterion to select patients for prophylactic ICD implantation.(1, 2, 4) However, these prior data were primarily obtained in patients with ischemic heart disease as illustrated by the DANISH trial.(4) Even though an updated meta-analysis on ICD trials still showed ICD implantation is effective, it shows these recommendations cannot be rightfully extrapolated to those with non-ischemic DCM.(4, 5)

Over the past years, many studies described risk factors for ventricular arrhythmias in non-ischemic DCM. These studies uniformly reported previous sustained ventricular arrhythmias and late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) as important predictors of arrhythmic events.(6) Of note, the prognostic value of many other investigated clinical risk factors remains unclear. In addition, most results were obtained in observational cohorts with relatively small patient numbers and high variation in reported associations. Prior reviews summarizing the available evidence dealt with this issue by combining both arrhythmic and heart failure outcomes, which however limits their ability to draw definite conclusions about SCD prevention.(7, 8)

In light of these shortcomings, we performed a meta-analysis and systematically reviewed the studies that assessed predictors of sustained ventricular arrhythmias in DCM. We evaluated quality of evidence and summarized the reported associations using pooled analysis where appropriate. The obtained results may be of value for making management recommendations for this growing group of at-risk DCM subjects.

METHODS

We performed a systematic search of MEDLINE and Embase in February 2018 for clinical studies on risk factors for sustained ventricular arrhythmias in patients with DCM which was updated on January 2020. In short, ischemia detection was mandatory for diagnosis of DCM in adult patients and since our outcome of interest is sustained ventricular arrhythmia, articles with only a composite outcome of heart failure without sub analysis of arrhythmic outcome were excluded (e.g. DANISH trial). A detailed description of our search strategy, inclusion, and exclusion criteria, as well as data extraction table can be found in the Supplementary Material. This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.(9)

Study eligibility

Any original study involving an adult population with DCM as defined by the European Society of Cardiology(10) that investigated an association of more than one risk factor with a predefined arrhythmic outcome was considered eligible for inclusion. Bibliographies of relevant reviews were checked for additional references. Only studies that specifically reported outcome associations for ventricular arrhythmias were included, hence those studies with composite endpoints that included non-arrhythmic events were not considered eligible for inclusion.

Primary outcome

Our primary outcome of interest was sustained ventricular arrhythmias, which was defined as spontaneous sustained ventricular tachycardia (VT), ventricular fibrillation (VF), (resuscitated) SCD, or appropriate ICD intervention for a ventricular arrhythmia. Non-sustained VT was excluded as an outcome. Since the majority of studies exclusively reported risk estimates for combined arrhythmic outcome, we were obliged to consider all arrhythmic outcomes as equal.

Quality assessment

Individual study quality and risk of bias were assessed using the Quality in Prognostic Studies tool (QUIPS).(11) Study quality was assessed independently by two investigators (A.S. and E.K.); in case of disagreement, a third investigator (F.S.) also assessed study quality to reach consensus.

Statistical analysis

Our analyses were divided into two components: (1) a systematic review, and (2) a meta-analysis of studies that were amenable for pooled analyses. First, we extracted all study characteristics, risk ratios (RRs), odds ratios (ORs), hazard ratios (HRs), confidence intervals (CIs) and p-values per risk factor. If HRs and CIs were not reported, authors were contacted to obtain these data. The obtained associations on RRs, ORs and p-values were systematically reported in a table format and summarized in the text. Second, we performed a meta-analysis of all studies that reported HRs, provided that the risk factor in question had uniform definitions across studies. We excluded studies only reporting ORs from the meta-analysis, as ORs can only be reliably pooled when follow-up time is equal. Furthermore, since adjustment of HRs was performed differently in studies, only crude (i.e. unadjusted) HRs were included in the meta-analysis.

Using the meta package in R (version 3.5.1 R Core Team (2018)), random-effects meta-analysis for the HRs were conducted.(12) Statistical heterogeneity between studies was assessed using the χ^2 test for homogeneity, expressed by I^2 index. P-values were interpreted in a descriptive manner using a significance value of <0.05.

Subgroup analyses were performed to assess the influence of ICD implantation. For sensitivity analyses, fixed-effect meta-analyses were performed and the difference to the results of the random-effects analysis were discussed.

RESULTS

Search results

Figure 1 shows our search results and selection process. In short, our literature search yielded 1996 unique citations that were carefully screened based on title and abstract. Of these, 1793 citations were excluded as they did not report risk factors for arrhythmic outcomes in the appropriate population. The remaining 203 candidate publications received a thorough full-text assessment, resulting in a total of 51 studies that met the inclusion criteria. After updating the search in 2020, this yielded an additional four papers totalling 55 included studies. Of the included studies, 29 reported HRs uniformly and were thus included in the meta-analysis.

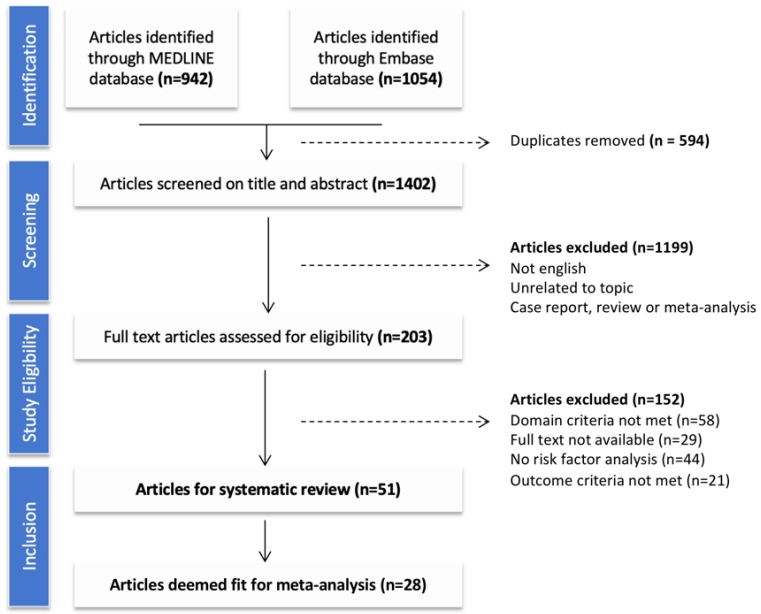


FIGURE 1. Flowchart of search results and selection process

Study characteristics

Study characteristics are provided in Supplementary Table 1. The 55 included studies were published between 1992 and 2019 and comprised a total number of 11451 DCM patients of whom 76% were male and had mean age of 54±7.9 years. Mean follow-up time was 3.7±2.3 years with a crude annual event rate of 4.5% (95%CI [4.30-4.76]). The 28 meta-analysed studies included a total number of 6287 DCM patients with 73% male and a mean age of 55.0±4.3 years. Mean follow-up time of the meta-analysed studies was 3.9±2.6 years with a crude annual event rate of 4.29% (95%CI [4.02-4.57]).

Quality assessment

Using the QUIPS tool, the risk of bias was evaluated in six areas in observational prognostic research: (1) study participation, (2) study attrition, (3) prognostic facture measurement, (4) outcome measurement, (5) study confounding, and (6) statistical analysis and reporting. Results are shown in Figure 2. The highest risk of bias was introduced by study attrition, limited adjustment for confounders, and limitations in statistical analysis. Details can be found in the Supplementary Material.

Risk factors for life-threatening arrhythmias

The main risk factor associations are reported by category below. All extracted data are available in the Supplementary Material. The pooled HRs from our meta-analyses are summarized in Figure 3; the corresponding forest plots can be found in the Supplementary Material.

History and Demographics

Age was investigated as a predictor in nine studies, of which seven were pooled in the meta-analysis. This resulted in a small yet significant protective effect of age per 10 years increase (pooled HR 0.82; 95%CI [0.74-0.1.00]) with moderate heterogeneity (I^2=51%). The remaining three studies that were not meta-analysed reported the same direction of effect, although this did not reach statistical significance .[S31, S47, S40]

Male sex was investigated as a predictor in 16 studies, of which eight were pooled in the meta-analysis. The pooled results revealed a non-significant higher risk of arrhythmias in males (pooled HR 1.51; 95%CI [0.96-2.37]) with moderate heterogeneity (I^2=57%). In two of the remaining eight studies that were not meta-analysed, male sex was associated with an increased risk in arrhythmia .[S51, S43]

NYHA class was investigated as a predictor in ten studies. Meta-analysis of five of these studies showed an increased arrhythmic risk for NYHA classes III/IV compared to classes I/II, but this did not reach statistical significance (pooled HR 1.37; 95%CI [0.77-2.46]). The heterogeneity was significant (I^2=65%). Likewise, four additional studies that were not meta-analysed did not show a significant association between NYHA class and arrhythmic risk in the long-term.[S41, S43, S42, S44, S55]

Hypertension was investigated as a predictor in four studies, of which two were meta-analysed.[S13, S23] Both of these studies reported a significant association of hypertension with life-threatening ventricular arrhythmias, leading to a pooled HR of 1.95 (95%CI [1.26-3.00]). The two remaining studies that were not pooled did not show any significantly increased risk.[S51, S7]

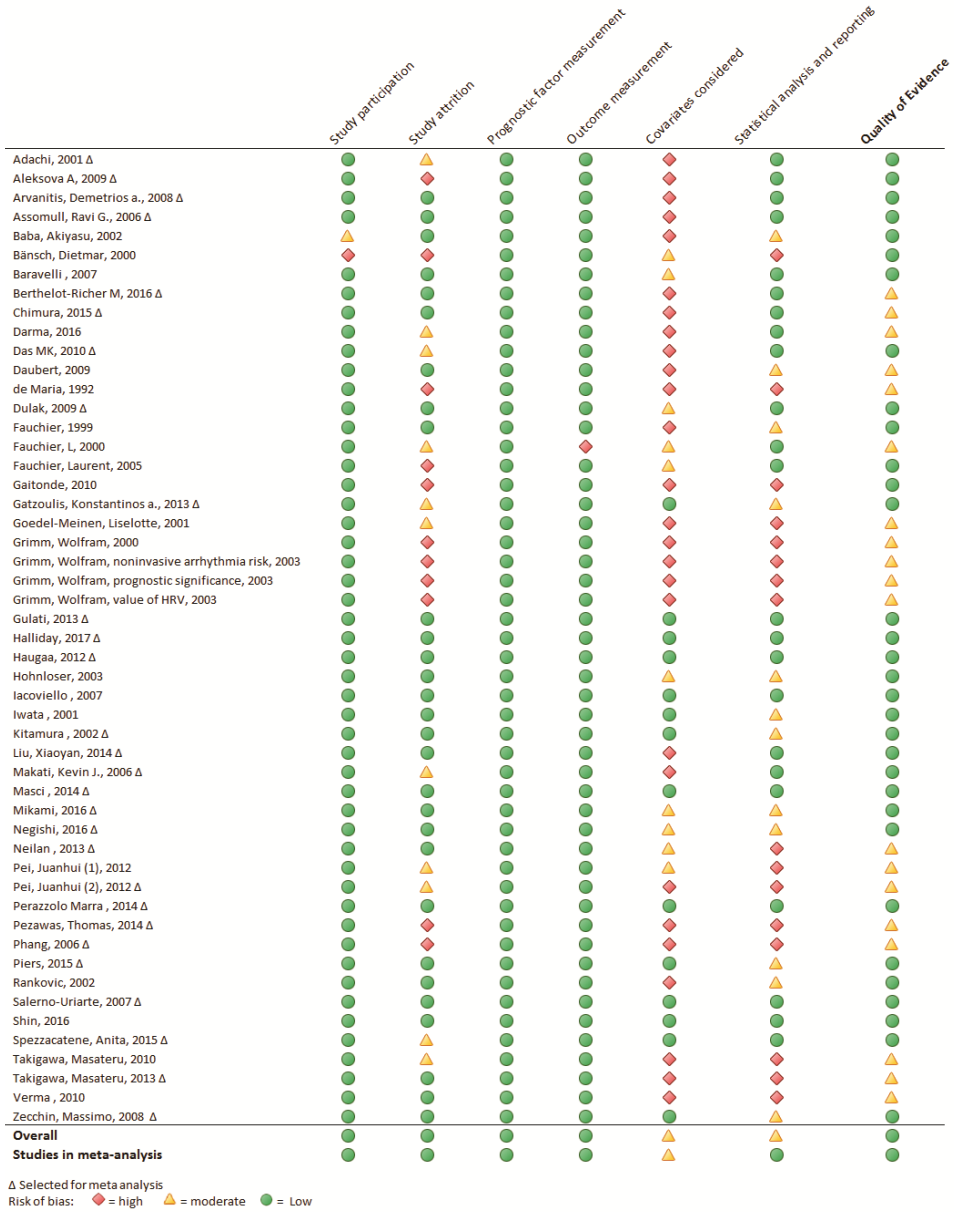
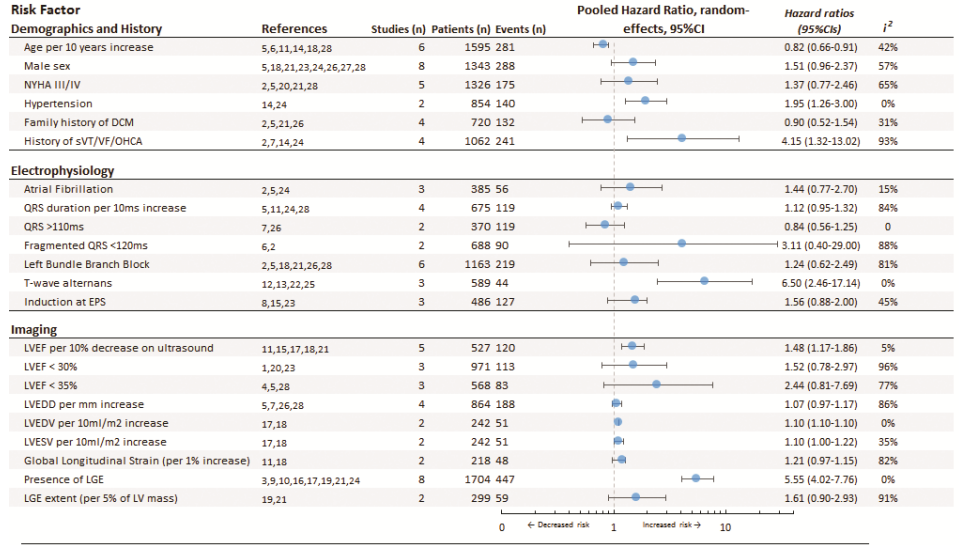


FIGURE 2. Quality assessment using Quality in Prognostic Studies tool of 51 articles included in the systematic review and meta-analysis.



Risk Factor Demographics and History	References	Studies (n)	Patients (n)	Events (n)	Pooled Hazard Ratio, random-effects, 95%CI	Hazard ratios (95%CIs)	I^2
Age per 10 years increase	5,6,11,14,18,28	6	1595	281		0.82 (0.66-0.91)	42%
Male sex	5,18,21,23,24,26,27,28	8	1343	288		1.51 (0.96-2.37)	57%
NYHA III/IV	2,5,20,21,28	5	1326	175		1.37 (0.77-2.46)	65%
Hypertension	14,24	2	854	140		1.95 (1.26-3.00)	0%
Family history of DCM	2,5,21,26	4	720	132		0.90 (0.52-1.54)	31%
History of sVT/VF/OHCA	2,7,14,24	4	1062	241		4.15 (1.32-13.02)	93%
Electrophysiology							
Atrial Fibrillation	2,5,24	3	385	56		1.44 (0.77-2.70)	15%
QRS duration per 10ms increase	5,11,24,28	4	675	119		1.12 (0.95-1.32)	84%
QRS >110ms	7,26	2	370	119		0.84 (0.56-1.25)	0
Fragmented QRS <120ms	6,2	2	688	90		3.11 (0.40-29.00)	88%
Left Bundle Branch Block	2,5,18,21,26,28	6	1163	219		1.24 (0.62-2.49)	81%
T-wave alternans	12,13,22,25	3	589	44		6.50 (2.46-17.14)	0%
Induction at EPS	8,15,23	3	486	127		1.56 (0.88-2.00)	45%
Imaging							
LVEF per 10% decrease on ultrasound	11,15,17,18,21	5	527	120		1.48 (1.17-1.86)	5%
LVEF < 30%	1,20,23	3	971	113		1.52 (0.78-2.97)	96%
LVEF < 35%	4,5,28	3	568	83		2.44 (0.81-7.69)	77%
LVEDD per mm increase	5,7,26,28	4	864	188		1.07 (0.97-1.17)	86%
LVEDV per 10ml/m2 increase	17,18	2	242	51		1.10 (1.10-1.10)	0%
LVESV per 10ml/m2 increase	17,18	2	242	51		1.10 (1.00-1.22)	35%
Global Longitudinal Strain (per 1% increase)	11,18	2	218	48		1.21 (0.97-1.15)	82%
Presence of LGE	3,9,10,16,17,19,21,24	8	1704	447		5.55 (4.02-7.76)	0%
LGE extent (per 5% of LV mass)	19,21	2	299	59		1.61 (0.90-2.93)	91%

FIGURE 3. Summary of meta-analysis. Pooled hazard ratios with 95% CIs are plotted. Results are grouped in "Demographics and History", "Electrophysiology" and "Imaging". For references and individual study data, see supplementary materials.

Abbreviations: CI: confidence interval | NYHA: New York Heart Association | VT: ventricular tachycardia | sVT: sustained ventricular tachycardial OHCA: out-of-hospital cardiac arrest | EPS: electrophysiological study | LVEF: Left Ventricular Ejection Fraction | LVEDD: Left Ventricular End Diastolic Diameter | LVEDV: Left Ventricular End Diastolic Volume | LVESV: Left Ventricular End Systolic Volume | LGE: Late Gadolinium Enhancement.

Family history of DCM was investigated as a predictor in four studies, which were all pooled in the meta-analysis. Pooled results did not direct towards an increased risk of arrhythmia (HR 0.90; 95%CI [0.52-1.54]) with moderate heterogeneity (I^2=31%).

History of sustained ventricular arrhythmia was investigated as a predictor in ten studies, of which four were pooled in the meta-analysis. All these studies revealed an association between history of sustained ventricular arrhythmia and recurrent future arrhythmias, resulting in a strong pooled HR of 4.15 (95%CI [1.32-13.02]), however significant heterogeneity was observed (I^2=93%). Of the six remaining studies, three showed a significantly higher arrhythmic risk ($p \leq 0.03$), whereas the other studies did not reach statistical significance. [S9, S22, S29, S37, S47, S49]

Syncope was investigated as a predictor in two studies, which were not meta-analysed due to missing HRs. None of these studies show any significant associations between syncope and arrhythmic outcome.[S44, S14]

Genetics

Mutations in genes coding for Lamin A/C (LMNA) Phospholamban (PLN), RNA binding motif protein 20 (RBM20), Myosin Binding Protein C (MYBPC3), Myosin Heavy Chain (MYH7),

Cardiac Troponin T (TNNT2), and cardiac troponin I (TNNI3) were studied in a previously published meta-analysis.(13) Mutations in LMNA and PLN significantly led to more ventricular arrhythmias (p <0.05). Truncating mutations in Filamin C (FLNC) were investigated in three studies which reported frequent premature sudden death and ventricular arrhythmias (82%) in the study participants.(14, 15)

Additionally, Ser96Ala polymorphisms in Histidine-Rich Calcium binding protein were investigated by one study, and were strongly associated with life threatening ventricular arrhythmias (HR 9.62; 95%CI [2.18 – 42.39]).[S2]

Electrophysiology

Atrial fibrillation was investigated as a predictor in seven studies, of which three were pooled in the meta-analysis. While all these studies reported an increased risk of ventricular arrhythmias in DCM patients with atrial fibrillation, none of them reached statistical significance, resulting in a non-significant pooled HR of 1.44 (95%CI [0.77 – 2.70]). Of the four remaining studies that were not pooled, only one reported a significant association between atrial fibrillation and ventricular arrhythmias.[S41, S47, S51, S34]

QRS duration per 10ms increase was investigated as a predictor in five studies of which four were meta-analysed. Three studies directed towards an increased risk, but only two reached statistical significance leading to a non-significant pooled HR of 1.12 (95%CI [0.95-1.32]) with significant heterogeneity (I^2=84%). One additional study showed no long-term increased risk with an HR of 1.00 (95%CI [0.98-1.02).[S55]

QRS duration >110ms was investigated as a predictor in two studies which were both meta-analysed. The pooled HRs however did not reach statistical significance and direction of effect contrasted QRS duration per 10ms increase (pooled HR 0.84; 95%CI [0.56-1.25]).[S7, S25]

Fragmented QRS (fQRS) was defined as any QRS morphology <120ms with additional R waves or notching of the R or S waves in at least two contiguous leads. fQRS was investigated as a predictor in two studies, which were both meta-analysed leading to a non-significant association with arrhythmic events (pooled HR 4.11; 95%CI [0.40 – 42.41]). [S19, S5]

Left Bundle Branch Block (LBBB) on 12-lead ECG was investigated as a predictor in seven studies, which were all pooled in the meta-analysis. This resulted in a non-significant association between LBBB and ventricular arrhythmias (pooled HR 1.05; 95%CI [0.532 – 2.09]), although significant heterogeneity was observed (I^2=81%).

Nonsustained VT (nsVT) was defined as ≥3 ventricular beats at ≥100 beats per minute either in patient's history or observed on 24hour-Holter monitoring. nsVT was investigated as a risk factor in 14 studies which were not pooled due to missing HRs. In the majority of these studies (n=9), nsVT directed towards a significantly increased arrhythmic risk (p≤0.05).[S29, S36, S37, S38, S41, S42, S46, S12, S51]

Heart Rate Variability Standard Deviations of all NN intervals (HRV SDNN) was defined as the standard deviation of intervals between normal sinus beats on Holter monitoring. While six studies investigated HRV as a predictor, none were pooled in the meta-analysis due to the use of different cut-off values and definitions. Three of six studies showed a significant association between HRV and arrhythmic risk, while the other three studies reported no significant association.[S21, S36, S37, S42, S44, S46]

T-wave alternans (TWA) was defined as a change in T-wave morphology that occurs in each alternant beat and measured during exercise test by spectral analysis. TWA was investigated as a predictor in six studies, of which three were pooled in the meta-analysis. This resulted in a significant association with ventricular arrhythmias (pooled HR 6.5; 95%CI [2.46 – 17.14]). The remaining three studies confirmed this association by reporting a significantly increased arrhythmic risk in the presence of TWA. [S33, S42, S45]

Signal-averaged ECG was investigated as a predictor in three studies, which were not pooled given the inconsistent methods of measurement and variable definitions of late potentials. None of the studies showed significant association with arrhythmic events.[S29.S41,S42]

Imaging

LV ejection fraction

LVEF per 10% decrease was investigated as a predictor in 13 studies using both echocardiography and cardiac magnetic resonance imaging (cMRI), of which eight were meta-analysed. This showed a non-significant association with ventricular arrhythmias (pooled HR 1.30; 95%CI [0.98-1.71]) with moderate heterogeneity (I^2=58%). When pooling LVEF that was measured solely on echocardiography, this led to a significant association with ventricular arrhythmias (pooled HR 1.45; 95%CI [1.19-1.78]) with little heterogeneity (I^2=0%). Additionally, seven other studies investigated LVEF per 5 or 10% decrease of which four reported a statistically significant effect directed towards increased arrhythmic risk. [S43, S42, S46, S55]

LVEF <30% was investigated as a predictor in six studies of which three were meta-analysed. The heterogeneity was large (I^2=96%), leading to a non-significant pooled HR of 1.52 (95%CI [0.78 – 2.97]). In contrast, the three remaining studies all described a statistically significant increased arrhythmic risk. [S41, S44, S47]

LVEF < 35% was investigated as a predictor in three studies, which were all meta-analysed leading to a pooled HR of 2.4 (95%CI [0.81 – 7.69]). [S4, S5, S28]

LV volumes

Left Ventricular End Diastolic Diameter (LVEDD) per mm increase on echocardiography was investigated as a predictor in four studies which were all meta-analysed. While all studies were directed towards an increased arrhythmic risk with increasing LVEDD, only one reached statistical significance resulting in a non-significant pooled HR (HR 1.07; 95%CI [0.97 – 1.17]) with significant heterogeneity (I^2=86%).

Left Ventricular End Diastolic Volume (LVEDV) and Left Ventricular End Systolic Volume (LVESV) per 10ml/m^2 increase on cMRI were assessed as a predictor in two studies which were pooled in the meta-analysis. Both parameters led to a small but significantly increased arrhythmic risk (pooled HR 1.10 (95%CI [1.10 – 1.11]) for LVEDV per 10ml/m^2, and pooled HR 1.10 (95%CI [1.00 – 1.22]) for LVESV per 10ml/m^2).

Late Gadolinium Enhancement (LGE)

The presence of LGE was investigated as a predictor in eight studies which were all pooled in the meta-analysis. This revealed a strong association between presence of LGE and ventricular arrhythmias (pooled HR 5.55; 95%CI [4.02 – 7.67]). Since definitions of localisation patterns of LGE were not uniform, the association of its specific patterns with arrhythmic events could not be further evaluated.

LGE per 5% increase in absolute LV mass was investigated in two studies which were both meta-analysed. Pooled results showed a non-significant increased risk for ventricular arrhythmias (HR 1.61; 95%CI [0.90 –2.93]), however with significant heterogeneity (I^2=91%). The combined presence of LGE and QRS duration >120ms was investigated in one study and was associated with an increased arrhythmic risk (HR 9.53, 95%CI [2.84 – 31.98]).[S52]

Other imaging parameters

Global Longitudinal Strain (GLS) was defined by the average maximum systolic shortening in a 16-segment LV model. GLS per 1% increase was assessed as a predictor in two studies, which were both meta-analysed leading to a non-significant pooled HR of 1.21 (95%CI [0.97 – 1.51]] with high heterogeneity (I^2=82%).

Other imaging parameters on echocardiography and right heart catheterisation were not associated with arrhythmic risk. One study investigated myocardial tissue damage in Single Photon Emission Computed Tomography (SPECT) using a semi-quantified myocardial severity index and reported a mild, yet significantly increased arrhythmic risk for higher severity indices (HR 1.01; 95%CI [1.00 – 1.02]).[S26]Subjective description of segmental wall motion abnormalities on echocardiography was associated with an increased arrhythmic risk (HR 4.1; 95%CI [1.90 – 9.00]). [S39]

Miscellaneous

Several blood biomarkers such as atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), estimated glomerular filtration rate (GFR), norepinephrine, and potassium did not significantly affect arrhythmic risk.[S47, S31, S13, S22, S4] One study reported that plasma creatinine per µmol/litre increase was associated with increased arrhythmic risk (HR 1.01; 95%CI [1.00 – 1.02]).[S13] Another study reported every one standard deviation increase of Growth Differentiation Factor 15 (GDF-15) in blood was associated with increased arrhythmic risk (HR 2.1; 95%CI [1.1-4.3])[S52]

Sensitivity Analyses

Since 18 out of 29 studies included ICD recipients, all analyses were repeated by excluding studies with ICD carriers. As shown in the Supplementary Materials, this revealed that pooled effects remained similar for all meta-analysed risk factors. In addition, changing our meta-analysis strategy from random-effects model to fixed effects model did not reveal any considerable differences in pooled risk estimates.

Risk factors associated with increased risk of life threatening arrhythmic events

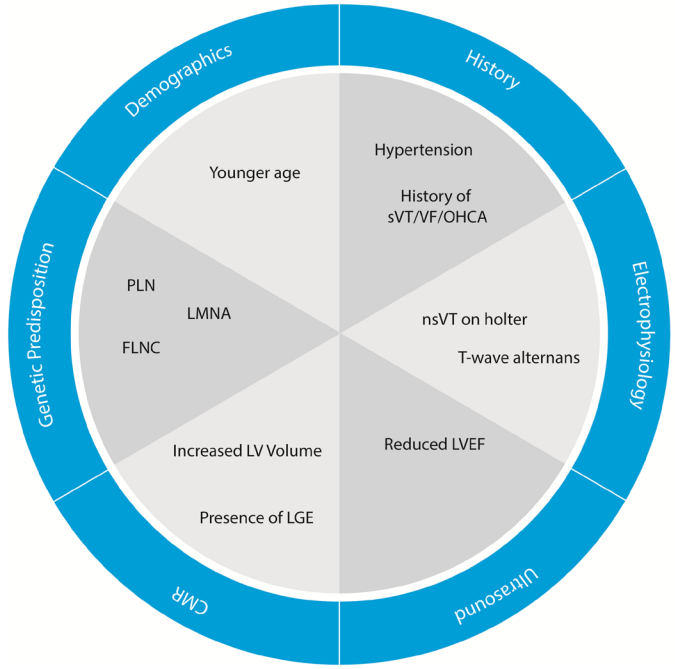


FIGURE 4. Predictors of sustained ventricular arrhythmias in non-ischemic DCM.

DISCUSSION

This study aimed to systematically review predictors of sustained ventricular arrhythmias in non-ischemic DCM, examine the quality of evidence, and establish potential risk factors of adverse clinical outcome. We found an annual risk of 4.5% of sustained ventricular arrhythmias, which underlines the importance of ICD implantation in this cohort. Of note, arrhythmic risk is considerably higher in younger patients with hypertension, prior (non) sustained ventricular arrhythmia, decreased LVEF in ultrasound, LV dilatation, the presence of LGE, and genetic mutations (PLN, LMNA, FLNC). While these findings may help select appropriate candidates for ICD implantation, they must be interpreted in light of 1) the quality of evidence; 2) clinical utility of promising risk factors; and 3) future directives.

Quality of Evidence

An important limitation of prior studies is the lack of statistical power and limited adjustment for confounders. Because the number of events per variable in our included studies was often less than ten (a number generally recommended in regression analysis), statistical models had limited power for adequate confounder adjustment.(11, 16) This resulted in variable risk of bias in overall studies which may in part explain the inconsistency of reported results. Furthermore, some included reports are up to 20 years old. During this period, medical treatment for heart failure has changed substantially and event rates have changed too. In addition, diagnostic methods have evolved over the years, which may have led to more frequent diagnosis of DCM.

To compensate for power limitations, we attempted to pool results from studies that report HRs into a quantitative meta-analysis. Our decision to only meta-analyse studies that report HRs resulted in a lower risk of bias given their use of recommended statistical methods. However, since pooling is only appropriate in the setting of uniform definitions, the number of studies included in our meta-analysis was unfortunately limited. Given these constraints in individual study quality, historical changes in heart failure workup and our inability to pool all available results, we deem overall quality of evidence to be moderate, which should be taken into consideration when assessing the results of our study.

Promising risk factors

For a prognostic model to be useful in daily clinical practice, its predictors must be reproducible and easy to obtain. In this light, the utility of parameters limited in standardisation such as TWA and HRV remains limited, whereas conventional measurements have consistently performed better in recently published risk prediction models for hypertrophic (HCM) and arrhythmogenic cardiomyopathy (ACM).(17, 18) Based on our findings, promising risk factors include younger age, hypertension, prior (non)sustained ventricular arrhythmia, decreased LVEF, LV dilatation, LGE, and presence of genetic mutations in PLN, LMNA, and FLNC (Figure 4).

History and demographics

Younger age was associated with ventricular arrhythmias, which is in line with literature on other cardiomyopathies and primary arrhythmia syndromes. This finding may reflect faster conduction in younger heart and lower thresholds for arrhythmia due to changes in Ca^{2+} handling. (19) Given the competing risks of heart failure and arrhythmic outcome, the exact influence and mechanism of young age remains up to investigation.

Male sex was not significantly predictive of arrhythmias although the results do indicate an association. This is similar to HCM but distinctly different from ACM, in which male sex was a strong predictor of arrhythmias.(17, 20). There is a growing body of literature suggesting sex differences in cardiovascular diseases and a lower incidence of sudden cardiac death in women. Suggested mechanisms may be related to hormonal effects on Ca^{2+} handling, shorter QT interval in adult males and differences in underlying pathology such as coronary artery disease. [18] However, studies on direct effects of sex differences have not been conclusive and its exact involvement in ventricular arrhythmia remains unclear.(21, 22)

In our pooled data, hypertension was significantly associated with outcome. This effect may be caused by cardiac remodelling with persistent systemic hypertension as experimental clinical studies have provided evidence for myocardial fibrosis and changes in LV function. (23) Whether this constitutes an opportunity for arrhythmia prevention by antihypertensive medication (i.e. risk factor modulation) remains up for investigation.

Genetics

The evidence for an association between genotype and outcomes has been recently reported in a meta-analysis.[13] Ventricular arrhythmias in PLN, LMNA and FLNC in DCM patients are markedly higher.(13, 14) Phospholamban is known for an overlap syndrome between DCM and ACM.(24) It regulates the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2a) pump and interplays with Na^{+}/Ca^{2+} exchanger (SLC8A1 or NCX1), which is important for maintaining calcium homeostasis in cardiomyocytes.(25) Calcium dysregulation can elicit early/delayed after depolarisations thereby increasing arrhythmogenicity.(26) Lamin A/C is a nuclear envelope protein and has been association with arrhythmias in many studies.(13) Mutations in Lamins A and C may lead to nuclear abnormalities. Because these proteins also interact with the cytoskeleton and extracellular matrix, they can affect the structural myocardial stability, which explains the detrimental effect in the heart.(27) Filamin C is essential for cardiomyocyte structuring, anchoring membrane proteins to the cytoskeleton and binding several proteins in the Z-disk of the sarcomere. Mutations in Filamin C may lead to an overlapping DCM and ACM phenotype with LV dysfunction and frequent ventricular arrhythmias.(14) These association of genotype with outcome suggest a potential for individualized treatment strategies.

Electrophysiology

In our meta-analysed data, prior (non-)sustained ventricular arrhythmias were strongly associated with future arrhythmias. It seems obvious that those with prior sustained ventricular arrhythmias (i.e. the secondary prevention population) should receive an ICD, which is incorporated as a recommendation in many guidelines.(3) However, recommendations for the primary prevention population are less straightforward. Our results suggest that also prior non-sustained VT is associated with subsequent sustained ventricular arrhythmias which is in line with the AMIOVIRT and DEFINITE trials that solely included patients with prior non-sustained VTs or frequent extrasystoles therefore increasing the arrhythmic burden.(28, 29) In addition, it is important to keep in mind that VTs and VF may reflect a different underlying substrate. Recently, a large study in ACM showed that prior VT did not predict subsequent VF events, which appeared to be more stochastic.(30)

Although currently implantation of an ICD is recommended for primary prevention in patients with DCM and LV ejection fraction < 35% and NYHA class II-III who have expected survival of at least 1 year, catheter ablation (CA) of ventricular tachycardia (VT) might be a potential therapeutic approach in the future as stand-alone therapy or as first step before implanting ICD.(31) Tung et al. showed that CA of monomorphic VTs in patients with structural heart disease (ischemic or non-ischemic cardiomyopathy) resulted in 70% freedom from VT recurrence, and that freedom from VT recurrence was associated with improved transplant-free survival, independent of heart failure severity.(32) In a more recent study Santoro et al. showed that whereas VT recurrence without clustering had no prognostic implication in patients with non-ischemic DCM, incidence of VT clustering (VTc) was an independent predictor of mortality. This group might be the better candidate for ICD implantation.(33)

TWA was strongly associated with outcome which may reflect autonomic dysfunction. Even though it holds potential in identifying high risk patients, its clinical role has not been fully defined therefore limiting its utility in daily clinical practice.(34)

Imaging

Non-ischemic DCM is defined diagnostically as either increased LV dilatation or decreased LV function (LVEF<45%) and our pooled results showed that both LV dilatation and decreased LV function confer prognostic information.(35) Even though this was expected, the effect size was relatively small. To date, six trials have investigated the survival benefit of ICD therapy for primary prevention that included patients with DCM. All had an LVEF ≤35%, with an average of 24% in a recently updated meta-analysis therefore limiting its value in patients with an LVEF higher than 35%.(5, 35) Identification of patients with high arrhythmic risk with preserved or slightly reduced LVEF therefore remains uncertain. Reduced LVEF is related to extent of fibrosis, a substrate for zig-zag pathways and re-entrant arrhythmias and its relation to arrhythmia seems logical.(36) CMR has the ability to perform tissue characterization by LGE reflecting presence of localised (segmental) fibrosis.(6) Logically, the presence of LGE is strongly associated with arrhythmia throughout different studies.(8, 37) The role of newer parameters that quantify diffuse fibrosis (e.g. T1 mapping) remains to be investigated.

Prognostic model for ICD implantation in DCM

The results obtained from this meta-analysis may help for further model building to improve risk assessment in DCM. Since patients with DCM can experience both heart failure related outcomes (heart transplantation, assist device, heart failure related death) as well as arrhythmic endpoints (VT, VF, SCD) they are considered to be competing: one event hinders the occurrence of another event of interest. (28) Quite logically, when a patient dies from heart failure, this hinders the occurrence of a possible VT and at any time before experiencing either one of them, patients are simultaneously at risk of both events. Nonetheless, included articles solely reported HR's which can overestimate the probabilities of both event of interest as well as the competing events. To adequately capture real clinical risks, future modelling should focus more on competing risks using methods such as the cumulative incidence competing risk or subdistribution hazards. (38) Future clinical decision support tools for ICD implantation in non-ischemic DCM should incorporate a multitude of relevant variables as well as perform competing event analyses to better reflect real clinical practice.

Conclusion

The annual risk of life-threatening ventricular arrhythmia in DCM is approximately 4.5% and is considerably higher in patients at younger age, patients with hypertension, prior (non) sustained VT, decreased LVEF, LV dilatation, presence of LGE and pro-arrhythmic genetic mutations (PLN, LMNA, FLNC). These results may help for further prognostic model building to improve personalized risk assessment in non-ischemic DCM.

Perspectives

Clinical competency in heart failure patient care and preventive medicine:

SCD risk assessment in non-ischemic DCM can be improved using multiple tests rather than solely relying on LVEF which is in line with the neutral results from the DANISH trial.(4)

Translational outlook

The examples set by the HCM/ACM risk calculators should be followed to enable personalized risk assessment.(17, 20) Such a model should be built by including the promising risk factors of our study but also several other suggested risk factors including sex.

Acknowledgements

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Disclosures

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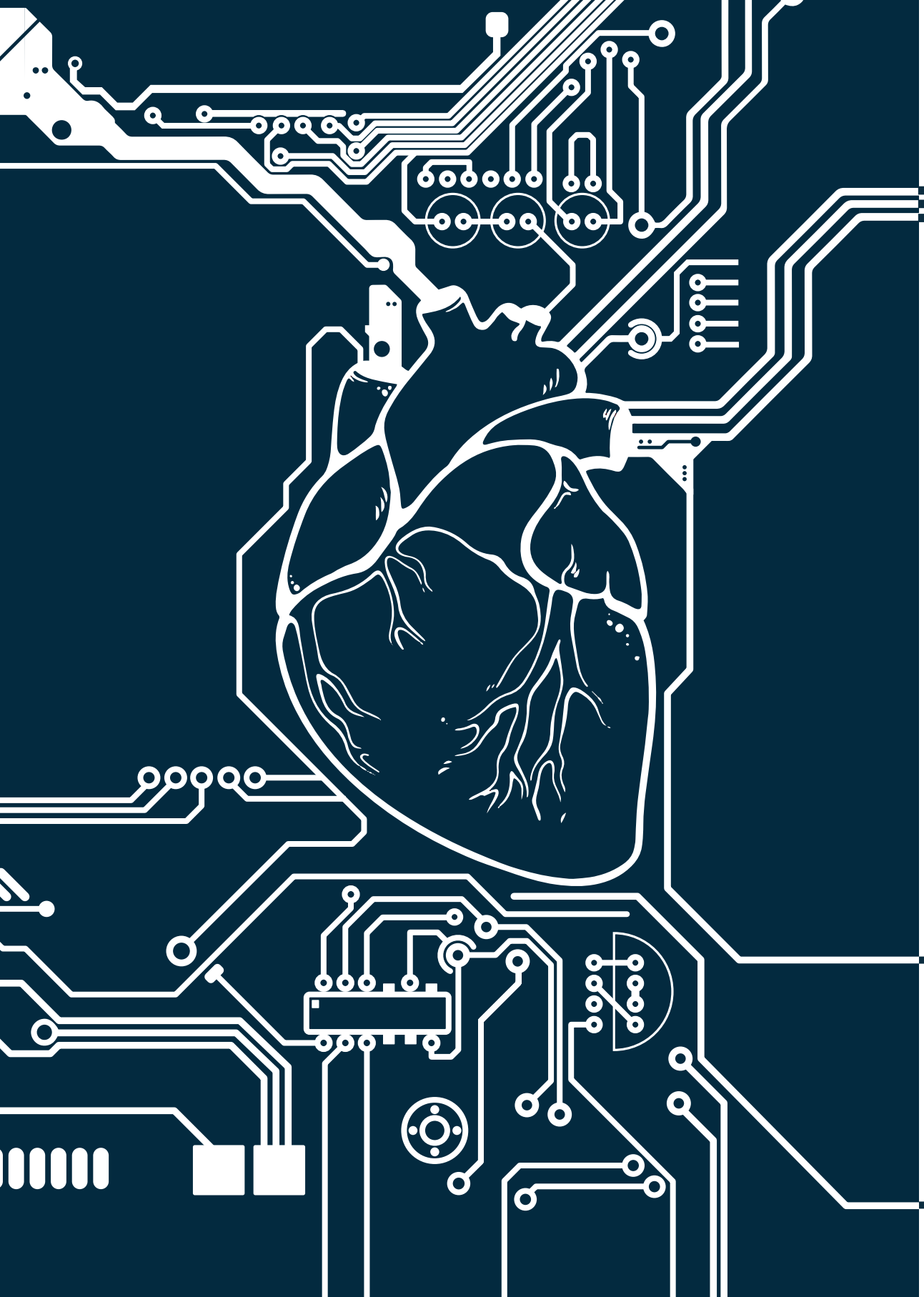

CHAPTER 5

A Novel Risk Model for Predicting Potentially Life-threatening Arrhythmias in Non-ischemic Dilated Cardiomyopathy (DCM-SVA risk)

Elham Kayvanpour, MD*; Arjan Sammani, MD*; Farbod Sedaghat-Hamedani, MD; David H. Lehmann; Alicia Broezel; Jan Koelemenoglu, Przemysław Chmielewski; Angelique Curjol, PhD; Pierre Socie, MD; Tobias Miersch; Jan Haas, PhD; Weng-Tein Gi, MD; Pascale Richard, PhD; Rafał Płoski; Grażyna Truszkowska; Annette F. Baas, MD PhD; Bogna Foss-Nieradko; Ewa Michalak; Małgorzata Stępień-Wojno; Joanna Zakrzewska-Koperska; Mateusz Śpiewak; Tomasz Zieliński; Eric Villard, PhD; Anneline SJM. te Riele, MD PhD; Hugo A. Katus MD PhD; Norbert Frey, MD; Zofia T Bilińska, MD PhD; Philippe Charron, MD PhD; Folkert W. Asselbergs, MD PhD; Benjamin Meder, MD

E. Kayvanpour and A. Sammani contributed equally as first authors

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ABSTRACT

Background

Non-ischemic dilated cardiomyopathy (DCM) can be complicated by sustained ventricular arrhythmias (SVA) and sudden cardiac death (SCD). By now, left-ventricular ejection fraction (LV-EF) is the main guideline criterion for primary prophylactic ICD implantation, potentially leading either to overtreatment or failed detection of patients at risk without severely impaired LV-EF. The aim of the European multi-center study DETECTIN-HF was to establish a clinical risk calculator for individualized risk stratification of DCM patients.

Methods

1,393 patients (68% male, mean age 50.7±14.3y) from four European countries were included. The outcome was occurrence of first potentially life-threatening ventricular arrhythmia. The model was developed using Cox proportional hazards, and internally validated using cross validation. The model included seven independent and easily accessible clinical parameters sex, history of non-sustained ventricular tachycardia, history of syncope, family history of cardiomyopathy, QRS duration, LV-EF, and history of atrial fibrillation. The model was also expanded to account for presence of LGE as the eight8h parameter for cases with available cMRI and scar information.

Results

During a mean follow-up period of 57.0 months, 193 (13.8%) patients experienced an arrhythmic event. The calibration slope of the developed model was 00.97 (95% CI 0.90-1.03) and the C-index was 0.72 (95% CI 0.71-0.73). Compared to current guidelines, the model was able to protect the same number of patients (5-year risk ≥8.5%) with 15% fewer ICD implantations.

Conclusions

This DCM-SVA risk model could improve decision making in primary prevention of SCD in non-ischemic DCM using easily accessible clinical information and will likely reduce overtreatment.

INTRODUCTION

Besides progressive heart failure, non-ischemic dilated cardiomyopathy (DCM) patients are at increased risk for developing sustained ventricular arrhythmias (SVAs) and sudden cardiac death (SCD) and may benefit from primary preventive implantable cardioverter-defibrillator (ICD) implantation (1,2). While left ventricular ejection fraction (LV-EF) has been prospectively validated in ICD implantation guidelines (3,4), the clinical value of other risk factors and cut-off free estimates has not been shown convincingly. The importance of new approaches is, however, imminent: The contemporary Danish-Trial failed to show survival benefit in DCM patients after primary preventive ICD implantation, which questioned the usefulness of LV-EF as sole risk marker in non-ischemic etiologies (5). In sub-group analysis, it became evident that the concurrent mortality risk from heart failure and the stage of the disease is important. In a recent position statement by the European Society of Cardiology, the continuum of DCM phenotypes is appreciated by introducing the concept of dynamic disease expression, highlighting that arrhythmogenic stages can precede ventricular dysfunction and dilatation (6). Nearly one third of DCM patients, for example, develop ventricular arrhythmias without having severely reduced LV-EF (<35%) and hence are not fulfilling guideline criteria for primary prevention (7).

Several clinical and molecular factors for risk prediction in DCM have already been suggested (8-10). Furthermore, a systematic review and meta-analysis of 55 studies was conducted within the European Network DETECTIN-HF in search for independent and robust risk factors (1). For hypertrophic cardiomyopathy (HCM), the European Society of Cardiology (ESC) introduced successfully a cut-off-free, multivariable risk model for predicting life-threatening arrhythmias (11) and 6 years after its introduction several studies have validated its clinical applicability (12,13). However, in case of DCM there is lack of a suitable risk calculator that allows easy integration of the individual factors and that is validated in a sufficiently large cohort. Hence, in daily practice, LV-EF remains the main determinant in decision making for ICD implantation in these patients.

To aggregate commonly available clinical risk factors and aggregate their individual weight to predict ventricular arrhythmia, we aimed to develop a risk calculator for clinical decision making. We restricted the model to broadly available clinical parameters. Our multi-stage model is, however, able to integrate further information such as presence of CMR-derived late gadolinium enhancement (LGE) if available.

MATERIALS AND METHODS

Study design

The demographic and clinical data used for this study was retrieved from local registries (retrospective). For follow-up, patients were investigated at the recruiting center during their routine clinical visit or were contacted by phone during this study. The study was handled in accordance with the Declaration of Helsinki. The ethics committee and institutional review boards of all four centers approved the inclusion and study of biomaterials and collected clinical data and all patients had given informed written consent. After data harmonization and cleaning, a model based on previously identified and selected variables was developed using the Cox proportional hazards model. An internal validation was performed using cross validation.

Study population and participating centers

The study cohort originated from specialized cardiomyopathy centers across Europe: (i) Institute for Cardiomyopathies (ICH), Heidelberg, Germany (iia) Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht, the Netherlands (UNRAVEL) (iib) Netherlands Heart Institute, Utrecht, the Netherlands (iii) Unit for Screening Studies in Inherited Cardiovascular Diseases, National Institute of Cardiology, Warsaw, Poland (OBP-NIKARD) and (iv) Referral Center for hereditary heart disease, Pitié Salpêtrière Hospital & Sorbonne University, Paris, France (CEREFCOEUR). Patients were all evaluated and followed-up if they (i) were diagnosed with definite non-ischemic DCM and (ii) had not experienced haemodynamically significant sustained ventricular arrhythmia or aborted SCD before the first visit. All recruiting centers defined non-ischemic DCM according to the guidelines which applied to the time of recruitment. These cohorts include patients with left ventricular or biventricular systolic dysfunction and dilatation that are not explained by abnormal loading conditions or coronary artery disease as well as patients with hypokinetic non-dilated cardiomyopathy with left ventricular or biventricular global systolic dysfunction without dilatation (defined as LVEF<45%), not explained by abnormal loading conditions or coronary artery disease (6). Patients with assured diagnosis of cardiac sarcoidosis, acute or fulminant myocarditis, as well as assured chronic myocarditis were excluded. Only patients ≥18 and <80 years at first visit were included in the model generation. Since we aim to introduce a model that is applicable at first clinical visit, we took the age at first visit as inclusion age. All patients with childhood cardiomyopathy, defined as disease onset in the first 10 years of life, were excluded from the analysis.

Study outcomes

The study outcome was sustained ventricular arrhythmia (SVA) following first visit and included a composite of occurrence of SCD, aborted cardiac arrest (SCA), hemodynamically relevant ventricular tachycardia (VT), which had to be defibrillated internally or externally, and potentially life-threatening arrhythmia, terminated by adequate anti-tachycardia pacing (ATP). The endpoint for a patient was reached in case of the first event. ICD implantation during follow-up, heart transplantation (HTX), implantation of ventricular assist devices (VAD), and all-cause mortality were also reported.

Selection of predictors and sample size

Clinical variables were pre-selected based on the results of a systematic literature review and meta-analysis (1,8-10,14-21), clinical expertise, as well as their availability in clinical practice. The following 10 variables were selected: gender, age at first visit, history for syncope, non-sustained ventricular tachycardia (nsVTs) in patients' history or in Holter performed within 14 days after first visit, family history for cardiomyopathy (CMP), family history for SCD, native QRS duration (QRS duration without pacing), LV-EF and LVEDD in echocardiography, as well as history of atrial fibrillation (AF). Although significantly different between patients with and without events, left atrial (LA) size was not included in the model since LA enlargement predisposes to AF and correlated to this in our cohort. An additional model was built by adding LGE presence as a marker for myocardial scar.

To ensure model's accuracy and precision, a minimum number of 10 events per variable (EPV) are recommended (22). In our study cohort 194 first events were observed, which would allow estimation of 19 variables.

Data collection and statistical analysis

Patients were followed-up prospectively every 6-12 months or earlier if clinical symptoms worsened. Patients' medical records were extracted from the hospital information systems and study databases and critically reviewed by two experienced cardiologists/residents from each center (E.K and F.S from Germany, A.S and F.A from the Netherlands, P.C and Z.B from Poland, and P.C. and P.S from France). Data are available upon request and approval by the data access committee of the Detectin-HF consortium for external analyses. More information about data proposal requests may be found on www.Detectin-HF.eu.

All analyses were performed in Python 3.7. Statistical tests utilized the Scipy 1.4.1 package. Categorical variables were checked for significance with χ^2-tests and continuous variables with t-tests. For developing the Cox regression model Lifelines 0.24.5 was used. The follow-up duration was calculated from the date of first visit to the date of last visit at center or date of reaching an endpoint. In case of missing data points, Multiple Imputation by Chained Equations (MICE) was used for imputation. Patients with more than two missing variables were excluded from model development. The scikit-learn 0.22.1 implementation of MICE was used for the data imputation. The imputation model included all pre-selected predictors and the outcome variable. Overall, 30 datasets were imputed for different random states of the imputer. The imputed datasets were combined according to Rubin's rules (23).

Model development and validation

Multivariable Cox regression was used for the model development. To eliminate problems associated with predictor selection, a significance level of 0.15 was defined. The final risk model was then built with the help of backward elimination. In order to make efficient use of the data, we used the entire cohort to build the risk model.

10-fold cross validation was used to internally validate the model. Furthermore, the cross validation was looped for ten times with different data splits to increase the accuracy of the performance estimation. The degree of agreement between the observed and predicted 5-year risk for SVA was estimated by the average calibration slope, with a value close to 1 showing good overall agreement (24). A calibration plot was also created to graphically evaluate the agreement between predicted and observed outcome. C index and D statistic were used as indicators of how well the model discriminates between high and low risk patients, with a value of 0.5 for C-index indicating no discrimination and 1 for perfect discrimination and increasing values for D-statistic meaning better discriminatory ability of the model.

Model

The following equation calculates the risk of SVA at 5 years for each individual:

$$P(\text{VA at time t}) = 1 - S0(t)^{\exp(LP)}$$

S0(t): the average survival probability at time t, LP: prognostic index which is the sum of the products of the predictors and their associated coefficients for each given patient.

Secondary model development and further validation

For further validation, patients of 3 centers were used for model development and the ones from the remaining center were used for validation. This was performed 4 times so that each center was used once for validation. C index, D-statistic and calibration slope were calculated for each model to evaluate the homogeneity between centers.

For sensitivity analysis penalized Cox regression was used. Four different models were trained to estimate the center effect. Models were built with and without the information about the center. Furthermore, these two scenarios were evaluated on the subset of patients with complete information and additionally the imputed dataset. To eliminate overestimation of risk by including ATPs as event, a further sensitivity analysis was performed excluding ATP events. Additionally, a sensitivity analysis was performed to investigate the model performance in patients without CRT.

To assess any potential superiority of our developed risk model, we compared its performance with current stratification strategies. According to most recent ESC guidelines, ICD implantation is indicated for LV-EF ≤35% + NYHA II/III or for asymptomatic patients with LV-EF ≤30% (25).

RESULTS

Baseline clinical characteristics of study population

Our study population included 1,393 patients with non-ischemic dilated cardiomyopathy. Table 1 lists baseline clinical, electrocardiographic and echocardiographic characteristics of the study cohort. Sixty-eight percent of the patients were male with a mean age of 50.7±14.3 years at first visit. An unexplained syncope before first visit was reported in 6.6% of the patients. 25.2% had positive family history for CMP, and 6.7% had positive family history for SCD. 27.4% were asymptomatic (NYHA I) at time of first visit, 66.9% reported obvious dyspnoea on exertion (NYHA II or III) and 5.7% were symptomatic at rest (NYHA IV). 27.4% had history of atrial fibrillation and the mean native QRS duration was 116±29ms. Mean left ventricular ejection fraction measured using echocardiography was 31±12%. Altogether around two-thirds had an LV-EF ≤35%. Mean left ventricular end-diastolic diameter (LVEDD) was 61.4±10.1mm. Mean atrial size was increased with 43.5±8.1mm, measured in parasternal long axis view (PLAX). Definitions of the pre-selected variables and their codings are summarized in Table 2. Altogether, 1,051 patients had complete data for the 10 pre-selected model parameters and 1,114 for the final model with 7 parameters. None of these 7 parameters correlated significantly with each other (Online Figure 1).

The ICDs were programmed in each center based on its standard clinical practice routine including one VF zone and one or two VT zones with ATP that could be followed by 1 or 2 ICD shocks.

Outcomes (SVA/SVA equivalent events during follow-up)

The minimum follow-up time was one month. During a mean follow-up period of 57.0 months [IQR 25.0; 93.0 months], 193 (13.8%) patients reached the endpoint of first SVA/equivalent. Figure 1 shows Kaplan Meier survival plots of the study population. The study outcome consisted of 7 (0.5%) SCD, 27 (1.9%) aborted cardiac arrest, 96 (6.8%) hemodynamically relevant ventricular tachycardias that had to be defibrillated internally or externally, and 63 (4.5%) potentially life-threatening arrhythmia, which were terminated by adequate ATPs. The mean cycle length of VT at ATP response was available in 35 cases (320±28ms) and the mean cycle length at ICD shock in 32 cases (274±81ms). At last follow-up, 169 (12.1%) patients had died, 61 (4.6%) had undergone HTX, 35 (2.6%) had received VADs, and 583 (44.9%) had received ICD/CRT-D. 244 (17.5%) patients received at some point a CRT-P/CRT-D. Clinical characteristic of patients with and without the endpoint SVA are shown in Table 1.

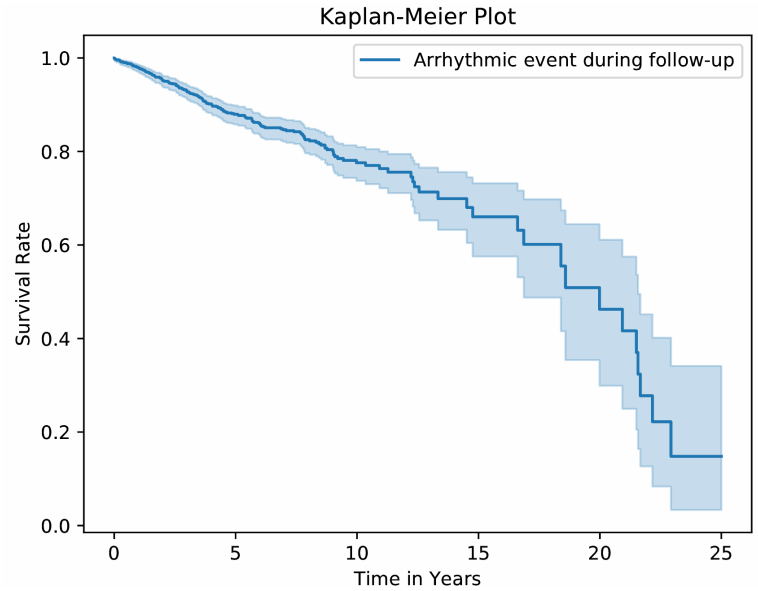

FIGURE 1. Cumulative event-free survival of the entire cohort (SVA). Shaded area shows 95% confidence intervals.

TABLE 1. Clinical characteristics of patients with and without the endpoint SCD

Variable	Overall	Patients with event	Patients with no event	P-Value
Demographics				
Number of patients, n	1393	193	1200	
Male sex, n (%)	950 (68.2%)	144 (74.6%)	806 (67.2%)	0.04*
Mean age at first visit, years ± SD	50.7 ± 14.3	51.0 ± 14.2	50.6 ± 14.3	0.7
Mean age at diagnosis, years ± SD	48.7 ± 14.7	47.4 ± 15.2	49.0 ± 14.6	0.2
Non-sustained VT before first visit, n (%)	225 (20.6%)	58 (46.8%)	167 (17.2%)	<0.0001*
History of unexplained syncope, n (%)	92 (6.6%)	21 (10.9%)	71 (5.9%)	0.01
Family history for CMP, n (%)	275 (25.2%)	35 (28.2%)	240 (24.8%)	0.4
Family history for SCD, n (%)	93 (6.7%)	15 (7.8%)	78 (6.5%)	0.5
NYHA class, n (%)				0.02*
I	376 (27.4%)	37 (19.5%)	339 (28.6%)	0.04*
II	573 (41.7%)	82 (43.2%)	491 (41.5%)	
III	346 (25.2%)	56 (29.5%)	290 (24.5%)	
IV	79 (5.7%)	15 (7.9%)	64 (5.4%)	
Medication at first visit				
ACE inhibitor/AT1 antagonist	1051 (96.2%)	121 (97.6%)	930 (96.0%)	0.4
Aldosteron antagonist	534 (48.9%)	76 (61.3%)	458 (47.3%)	0.003*
Other diuretics	561 (51.3%)	75 (60.5%)	486 (50.2%)	0.03*
Beta blocker	986 (90.2%)	117 (94.4%)	869 (89.7%)	0.09*
Medication at follow-up				
ACE inhibitor/AT1 antagonist	766 (82.1%)	95 (81.9%)	671 (82.1%)	0.9
Aldosteron antagonist	484 (51.9%)	85 (73.3%)	399 (48.8%)	<0.0001*
Other diuretics	452 (48.4%)	85 (73.3%)	367 (44.9%)	<0.0001*
Beta blocker	808 (86.6%)	108 (93.1%)	700 (85.7%)	0.03*
ECG				
History of atrial fibrillation, n (%)	380 (27.4%)	72 (37.7%)	308 (25.8%)	0.0006*
Native QRS duration, mean ± SD	116.2 ± 29.2	122.5 ± 31.3	115.3 ± 28.7	0.003*

TABLE 1. Continued

Variable	Overall	Patients with event	Patients with no event	P-Value
Holter	685	83	602	
nsVT on 24h holter, n (%)	244 (35.9%)	56 (68.3%)	188 (31.4%)	<0.0001*
Echocardiography				
LV-EF ≤ 35%, n (%)	792 (64.8%)	140 (82.4%)	652 (62.0%)	<0.0001*
LV-EF, mean ± SD (%)	31.1 ± 12.3	25.5 ± 10.6	32.0 ± 12.3	<0.0001*
LVEDD, mean (mm)	61.4 ± 10.1	65.7 ± 10.9	60.8 ± 9.8	<0.0001*
Left atrium size, mean (mm)	43.5 ± 8.1	45.8 ± 8.8	43.1 ± 7.9	0.0003*

Model development and validation

Table 3 shows the exploratory univariable analyses with estimates of the hazard ratios and their corresponding confidence intervals. Only sex, history of nsVT and syncope, family history of cardiomyopathy, QRS duration (ms), as well as LV-EF (%) and history of AT were significantly associated with outcome at the preselected significance level and were included in the multivariable analyses to build the final model. The risk of SVA in 5 years for an individual with DCM was finally calculated using following equation: P(VA at 5 years) = 1- $0.9044804^{exp(LP)}$, where LP = Sex * 0.25 + History for nsVT * 0.84 + History for Syncope * 0.57 + Family history for CMP * 0.47 + QRS * 0.007 + LV-EF * -0.04 + History of AT * 0.38.

Cross validation revealed a calibration slope of 0.97 (95% CI 0.90-1.03). The good overall agreement between the predicted and observed 5-year risk is shown in Figure 2. The C-index of the model was 0.72 (95% CI 0.71-0.73). The D-statistic was 1.27 (95% CI 1.19-1.34). This suggests that the hazard of SVA as predicted by the model is 3.6 times higher in the high-risk group compared with the hazard in the low risk group. Table 4 shows the categorical Net Reclassification Improvement (NRI).

Secondary model development with further validation and sensitivity analyses

The overall further validation C-index was 0.65 (95% CI 0.49-0.81) with a calibration slope of 0.79 (95% CI -0.24-1.83) (Online Tables 1A-1D). For sensitivity analyses, we estimated the hazard ratios from the model by adjusting for study center effect. Those were similar to the initial model without attributing the individual center (Online Table 2). The C-index for this model was 0.72 (95% CI 0.71-0.73). We repeated this process for patients with complete data, without and with the data label center. This also resulted in only small changes to the coefficients with a C-index of 0.72 (95% CI 0.71-0.73) and C-index of 0.72 (95% CI 0.70-0.73) respectively (Online Table 3). A further sensitivity analysis was performed excluding patients with ATPs as event. This included 63 fewer patients. The coefficients did not significantly change and the model showed a C-index of 0.71 (95% CI 0.69-0.72), calibration slope of 0.95 (95% CI 0.87-1.03), and D-statistic of 1.27 (95% CI 1.17-1.37) (Online Table 4). We also performed an additional sensitivity analysis to investigate our model performance in patients without CRT. This included 1,149 patients with 134 events. The C-index of the resulting model was 0.72 (95% CI 0.70-0.73) with calibration slope of 0.97 (95% CI 0.88-1.06) and D-Statistic of 1.29 (95% CI 1.17-1.40). This shows that our model performs very well in DCM patients, regardless of whether they carry a CRT or not (Online Table 5).

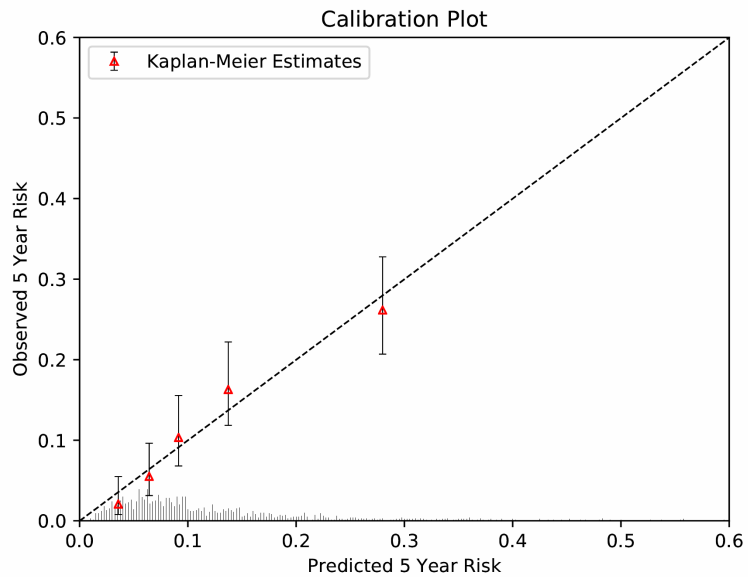

FIGURE 2. Agreement between observed (y axis) and predicted (x axis) 5-year risk for the compound outcome measure. Kaplan–Meier estimates with 95% CI intervals for quintiles of predicted risk are shown by triangles. Number of patients with a predicted risk is shown as spike histogram on x axis.

TABLE 2. Definitions of the pre-selected variables and their codings

Predictor variable	Definition	Coding
Sex (male)	Patients' reported sex	Binary (male/female)
Age	Age at evaluation	Continuous, years
History for nsVT	3 or more consecutive ventricular beats with a rate of >100 beats per minute with the duration of less than 30 seconds without haemodynamic compromise	Binary (yes/no)
History for syncope	Transient loss of consciousness, unexplained or probably cardiac	Binary (yes/no)
Family history for CMP	At least one 1st and/or 2nd degree family member <65 years of age with proven DCM, HCM or ACM	Binary (yes/no)
Family history for SCD	At least one 1st degree family member with proven SCD or aborted SCD <50 years of age	Binary (yes/no)
QRS duration	Duration in ms	Continuous, ms
LV-EF	Determined by echocardiography	Continuous, %
LVEDD	Determined by echocardiography	Continuous, mm
History of AT	Proven atrial fibrillation in history on ECG, or on ECG during regular checkup	Binary (yes/no)

TABLE 3. Univariable Cox regression model

Predictor variable	Univariable model		Multivariable model	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Sex (male)	1.24 (0.88-1.75)	0.22	1.28 (0.92-1.78)	0.14
Age	1.00 (0.99-1.01)	0.88	Not included in the final model	
History for nsVT	2.33 (1.71-3.18)	<0.005	2.31 (1.70-3.14)	<0.005
History for syncope	1.85(1.16-2.93)	0.01	1.78 (1.12-2.81)	0.01
Family history for CMP	1.53 (1.08-2.17)	0.02	1.59 (1.13-2.24)	0.01
Family history for SCD	1.24 (0.72-2.14)	0.45	Not included in the final model	
QRS duration	1.01 (1.00-1.01)	0.03	1.01 (1.00-1.01)	0.01
LV-EF	0.96 (0.95-0.98)	<0.005	0.96 (0.94-0.97)	<0.005
LVEDD	1.01 (0.99-1.03)	0.27	Not included in the final model	
History of AT	1.46 (1.07-2.00)	0.02	1.47 (1.09-1.99)	0.01

TABLE 4 Categorical Net Reclassification Improvement (NRI)

1 Event / 5 Non-event		2 Guideline				3 Total, split		4 Total	
		6 Abnormal		7 Normal					
8 DCM-SVA / 9 Risk Calculator	10 Abnormal	11	95	12	116	13	211	14	268
		15	10	16	47	17	57		
	18 Normal	19	11	20	279	21	290	22	524
		23	11	24	223	25	234		
26 Total, split		27	106	28	395	29	501		
		30	21	31	270	32	291		
33 Total		34	127	35	665			36	792

37 Bold indicates subjects correctly classified by both tests. White indicates subjects incorrectly classified by both tests. Green indicates subjects correctly reclassified by test 2. Red indicates subjects incorrectly reclassified by test 2. NRIe: net proportion of events assigned a higher risk or risk category; NRIne: net proportion of nonevents assigned a lower risk or risk category

38 NRIe = (116 - 11) / 127 = 0.827, NRIne = (11 - 47) / 665= -0.054, NRI = NRIe + NRIne = 0.773

Comparison with conventional risk factors

To underline the performance of the suggested model, Figure 3 shows the impact of potential 5-year SVA risk thresholds for ICD implantation in our 7-parameter model vs. current stratification strategies (ICD implantation in DCM patients with LV-EF ≤35% + NYHA II/III or in asymptomatic patients with LV-EF ≤30%) (25). This analysis could be performed in 792 patients of our cohort, in whom 5-year follow-up information was available. 127 patients had an event. By applying the guideline criteria, 501 out of 792 patients (63.3%) would have been treated with an ICD and 106 patients with events would have been protected. To avoid under-treatment and provide the same level of protection, the developed model would indicate 426 device implantations (53.8%), thereby reducing the total number of ICD implants by 15% [(501–426)/501] (P=0.0001). When implanting the same number of patients with ICDs as current guidelines (n=501) but use the new model for selection of patients, 113 patients with end-point SVA would have been protected. These analyses were repeated in patients with available 3-year follow-up and showed similar significant results (Online Text). Online Figure 2 shows number of events missed when applying our model vs. conventional risk factors. Choosing a threshold of 8.5% predicted 5-year risk would result in equal number of missed events using each method, while implanting 75 fewer ICDs when using our model.

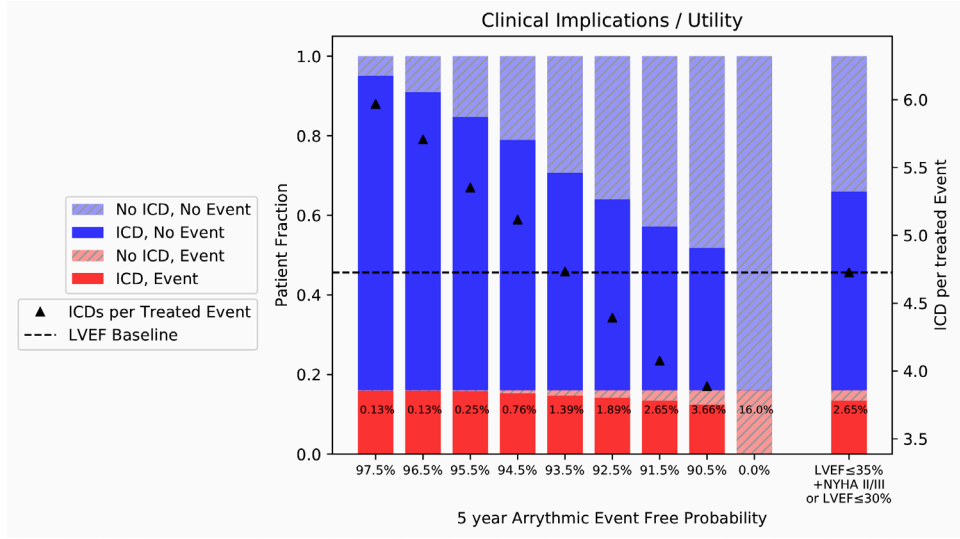

FIGURE 3. Outcome depending on model-based ICD implantation thresholds. Bars show implications of ICD implantation in 0-97.5% of patients (based on the calculated risk), as well as in patients with LV-EF ≤35% + NYHA II/III or asymptomatic patients with LV-EF ≤30% (current ESC guideline). The black triangles represent number needed to treat (NNT, right y axis). The dotted line shows the reference NNT. Left y axis shows patient fraction. The percentages refer to the light red section (no ICD, event).

Addition of LGE presence as marker for myocardial scar

We aimed to establish a broadly applicable risk score and show its superiority compared to traditional stratification. To address emerging or specialized diagnostic tools and their value to improve risk stratification, we tested our model performance after adding LGE presence as marker for myocardial scar. As DCM is considered as a dynamic disease with time-related structural and clinical evolution, we only included the MRIs which have been performed within 6 months before or after first visit (N=667). By doing so, hazard ratio confidence interval and p-value further improved (HR 1.72, 95% CI 1.08-2.77, P=0.02), suggesting that LGE is a useful additional predictor and should be included in risk stratification once available (C-index=0.73; 95% CI 0.71-0.74 and D-statistic=1.31; 95% CI 1.23-1.39). Online Table 6 shows model performance after adding presence of LGE to the initial model. The comparison of this 8-parameter model, including LGE, to current stratification strategies showed even more superiority than the 7- parameter model (Online Figure 3). This analysis could be performed in 778 patients of our cohort, in whom 5-year follow-up information was available. 124 patients had an event. By applying the guideline criteria, 472 out of 778 patients (60.7%) would have been treated with an ICD and 95 patients with events would have been protected. To avoid under-treatment and provide the same level of protection, the developed model would indicate 370 device implantations (47.5%), thereby reducing the total number of ICD implants by 21.6% [(472–370)/472] (P=2.1e-07). When implanting the same number of patients with ICDs as current guidelines (n=472) but use the new model for

selection of patients, 111 patients with end-point SVA would have been protected instead of 95 (14.4% more protection, P=0.007). This shows that our 8-parameter model including LGE can even predict those DCM patients who are at risk to sudden cardiac death (SCD), but not eligible to ICD implantation according to the current guidelines.

DISCUSSION

The utility of ICDs in DCM patients has been controversially discussed. Whereas the DANISH trial showed no significant improvement in all-cause mortality after primary preventive ICD implantation in DCM patients in comparison to contemporary medical and cardiac resynchronization therapy (5), meta-analyses that were performed since then showed significant mortality reduction of up to 24% after primary prophylactic ICD implantation (2,26). Although the overall mortality was not reduced in DANISH trial, SCD was reduced by approx. 50% in the ICD group (5). It is therefore important to identify those patients at high risk for SVAs.

In the current study, we developed and internally validated a clinical risk calculator for estimating 5-year risk of sustained ventricular arrhythmia in patients with non-ischemic DCM. Altogether 1,393 patients from 4 European countries have been used for model development. High-quality retrospective clinical data and prospective follow-ups were available and the proportion of missing data was satisfactorily low. The clinical model predictors were selected relying on previous studies, systematic reviews, meta-analyses, and expert consensus. The model was designed to include only parameters that are broadly available in clinical routine worldwide. There was no exclusion of patients with comorbidities so that the model is applicable to the majority of adult DCM patients. The final model included 7 predictors including sex, history for nsVT, history for syncope, family history for cardiomyopathy, QRS duration, LV-EF, and history of atrial fibrillation. The C-index of our developed model was 0.72 (95% CI 0.71-0.73), showing a good discrimination between patients with and those without SVA. The calibration analysis also showed a good agreement between predicted and observed SVA risk and sensitivity analyses showed no significant center bias.

By comparing the model performance with current stratification strategies, the improvement in risk stratification becomes evident. Applying our model would have resulted in implanting 15% fewer ICDs, while protecting the same number of patients. Additionally, our cut-off-free model could be particularly helpful for decision making in patients who do not fulfil ICD criteria based on current guidelines, e.g. when having LV-EF of >35% in presence of several other risk factors. Besides the 7 clinical model parameters, imaging biomarkers such as presence of LGE have been found to have prognostic value in cardiomyopathy patients, but are not readily available in many primary or secondary centers (8). Adding LGE as an eighth parameter further improved the model (HR 1.72, 95% CI 1.08-2.77, P=0.02) and could be integrated in the risk calculator.

Carrying pathogenic variants in high-risk genes such as Lamin A/C (LMNA), sodium channel protein type 5 subunit alpha (SCN5A), RNA binding motif protein 20 (RBM20),

phospholamban (PLN), or filamin-C (FLNC) have been repeatedly associated with higher rates of life-threatening arrhythmia (27-32). This information is, however, often not available due to missing consent and since current guidelines do not encourage genotyping in DCM patients. Genetic testing including LMNA, SCN5A, RBM20, and PLN were performed in 702 patients (50.4%) of our cohorts, from which 71 (10.1%) patients had at least one pathogenic or likely pathogenic variant in a high-risk gene. While this relatively low number is insufficient to reach statistical power in a generalized model, it still has considerable impact on individual patients and should not be neglected, but incorporated into each patient's management.

Potential limitations

A recruitment bias cannot be ruled out, since all participating centers are specialized for treating cardiomyopathies. In a comparable study on HCM, the applicability of our approach was underlined and results were validated in several succeeding studies (11). Generalizability, however, will depend on further studies applying our risk model and we are already planning a validation study within the German DZHK TORCH-Plus registry. Including ATP as outcome might have resulted in an overestimation of risk as ATP stimulation depends upon ICD programming. However, most recorded VTs were fast paced and thus likely becoming hemodynamically relevant. These assumptions are also reflected in current expert consensus statements on implantable cardioverter-defibrillator programming (33). Importantly, sensitivity analysis excluding ATPs showed similar performance. Lastly, cardiac resynchronization was shown to positively impact on reverse remodeling of DCM and is able to reduce arrhythmia associated outcomes. Still, our model performs well regardless of whether patients were implanted with CRT-P/D or not.

Conclusions

By carefully developing and validating a novel risk stratification model, we aimed to improve decision making for primary preventive ICD implantation in DCM patients. Further DCM cohorts are needed to externally validate this model and further prospective studies are needed to evaluate its impact on mortality, avoidance of ICD complications and costs-effectiveness.

Acknowledgment

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Disclosures

Dr. Charron reports personal fees for consultancies, outside the present work, for Amicus, Pfizer, Alnylam. All other authors have nothing to declare.

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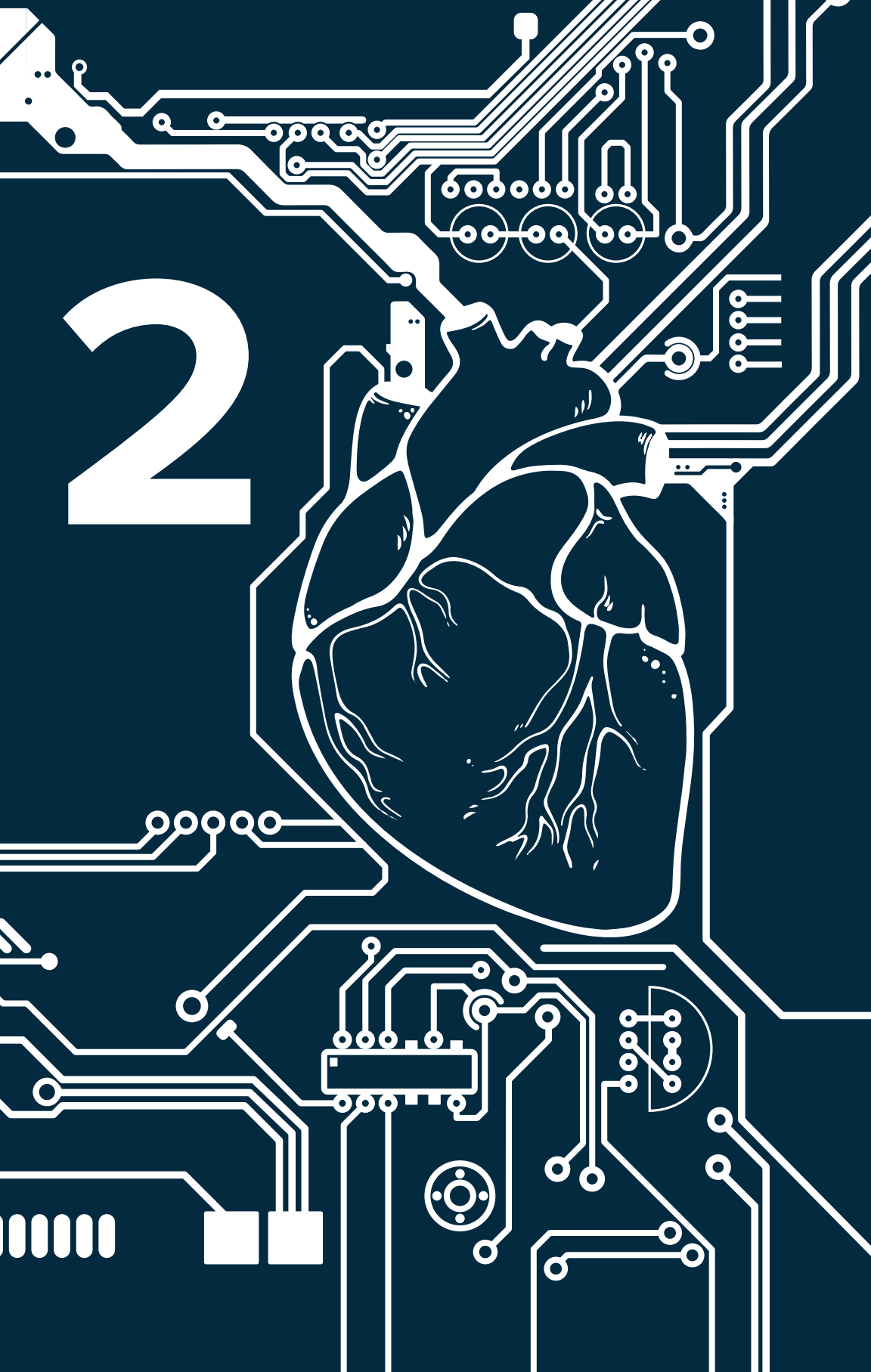

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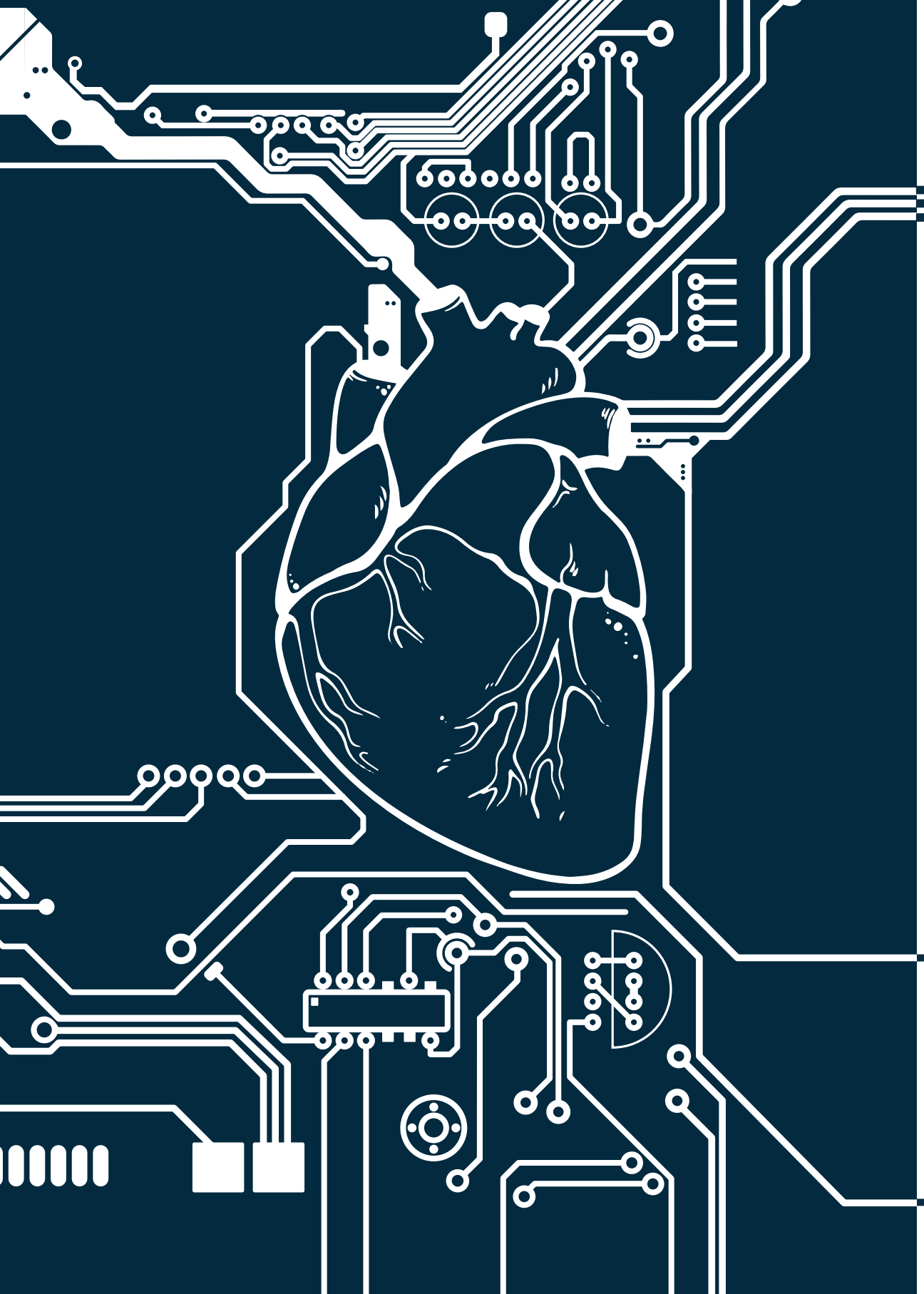
PART II

DATA INFRASTRUCTURE FOR CLINICAL APPLICATIONS OF ARTIFICIAL INTELLIGENCE



CHAPTER 6

UNRAVEL: big data analytics research data platform to improve care of patients with cardiomyopathies using routine electronic health records and standardised biobanking

A. Sammani, M. Jansen, M. Linschoten, A. Bagheri, N. de Jonge, H. Kirkels, L.W. van Laake, A. Vink, J.P van Tintelen, D. Dooijes, A.S.J.M. te Riele, M. Harakalova, A.F. Baas, F.W. Asselbergs

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ABSTRACT

Introduction

Despite major advances in our understanding of genetic cardiomyopathies, they remain the leading cause of premature sudden cardiac death and end-stage heart failure in persons under the age of 60 years. Integrated research databases based on a large number of patients may provide a scaffold for future research. Using routine electronic health records and standardised biobanking, big data analysis on a larger number of patients and investigations are possible. In this article, we describe the UNRAVEL research data platform embedded in routine practice to facilitate research in genetic cardiomyopathies.

Design

Eligible participants with proven or suspected cardiac disease and their relatives are asked for permission to use their data and draw blood for biobanking. Routinely collected clinical data are included in a research database by weekly extraction. A text-mining tool has been developed to enrich UNRAVEL with unstructured data in clinical notes.

Preliminary results

Thus far, 828 individuals with a median age of 57 years have been included, 58% of whom are male. All data are captured in a temporal sequence amounting to a total of 18,565 electrocardiograms, 3619 echocardiograms, data from 20,000 radiological examinations and 650,000 individual laboratory measurements.

Conclusion

Integration of routine electronic health care in a research data platform allows efficient data collection, including all investigations in chronological sequence. Trials embedded in the electronic health record are now possible, providing cost-effective ways to answer clinical questions. We explicitly welcome national and international collaboration and have provided our protocols and other materials on www.unravelrdp.nl.

INTRODUCTION

Cardiomyopathies (CMPs) are internationally defined as heart diseases with structurally and functionally abnormal myocardium not explained by coronary artery disease, hypertension or valvular heart disease [1, 2]. Many CMP patients have a familial history of disease, which typically follows an autosomal dominant inheritance pattern. In the Netherlands, it is estimated that 1 in 200 individuals carry a genetic predisposition for a CMP [3–5]. However, penetrance is incomplete and clinical expression of CMPs is heterogeneous, ranging from overt heart failure and lethal arrhythmias to being asymptomatic [2, 6]. Despite major advances in our understanding of the genetics of these diseases, our knowledge of the pathophysiological substrate of CMPs is limited, and CMPs remain a leading cause of premature sudden cardiac death and end-stage heart failure in persons below the age of 60 years [7].

By integrating electronic health records (EHRs) with research data platforms (RDPs), new insights into disease penetrance, risk assessment and disease pathophysiology can be obtained. In their current format, EHRs comprise both structured and unstructured electronic data that have been gathered, captured and assessed during routine clinical care [8]. Major opportunities lie in the standardisation of unstructured data, such as clinical notes and investigations [8–10]. Integrating these data with other data sources, including outcome registries, imaging, wearables, and research measurements (-omics), has the potential of offering higher-resolution data regarding disease epidemiology, onset and progression.

In this article, we present the design of the UNRAVEL RDP, in which a large dataset of CMP patients is enriched by text mining and linked to biomaterials. The UNRAVEL RDP aims to improve the daily care of CMP patients and their family members by (1) providing a standardised database with routine health care data linked to research-generated data that are easily accessible for big data analytics; (2) facilitating harmonisation of data, clinical care protocols and sharing of algorithms on www.unravelrdp.nl; and (3) providing the basis for approaching patients for in-depth biological research through the generation of induced pluripotent stem cells.

DESIGN

Ethics and registration

The UNRAVEL RDP follows the Code of Conduct and the Use of Data in Health Research and has been approved by the Biobank Board of the Medical Ethics Committee of the University Medical Centre Utrecht (no. 12-387 UNRAVEL Biobank). As a part of UNRAVEL, the use of already existing text files (e.g. clinical notes) is exempt from the Medical Research Involving Human Subjects Act (WMO) as per judgement of the Medical Ethics Committee (Text mining in cardiovascular notes, 18/446, Utrecht, the Netherlands). Eligible patients (see below) are asked to provide written informed consent for use of their clinical data and previously stored material. Consent is required prior to using the clinical (meta) data. In addition, consent is requested to draw blood via venepuncture during routine investigations, to minimise the impact on the patient, and to request information from other medical centres and municipality registries. For additional stem-cell-related research, an informed consent form has been developed and approved by the Medical Ethics Committee. After inclusion, patients are registered as UNRAVEL enrolees in the EHR, and all their clinical data are automatically collected in the RDP (Fig. 1). Data governance is secured by a data management plan. More information on protocols, data governance and informed consent is provided on www.unravelrdp.nl.

Study population

Eligible participants are individuals with proven or suspected genetic cardiac disease, and their relatives. UNRAVEL also includes family members who are not mutation carriers or show no signs of disease; these serve as healthy controls. Participants must be able to provide written informed consent and be at least 18 years of age.

In order to minimise selection bias, patients and relatives from both in- and outpatient clinics are prospectively screened and asked to participate. If a participant is deemed eligible after discharge, the patient is contacted by the managing physician by mail and/or phone to retrospectively request consent. Additionally, previously eligible individuals were retrospectively identified and asked to participate using registered diagnoses in the EHR and a database of all CMP patients who visited the outpatient clinic of a clinical geneticist or had DNA analysis performed at the University Medical Centre (UMC) Utrecht.

Research data platform

Consent is required prior to the extraction of data. Based on in-house clinical protocols, phenotyping of participants includes medical history, family history, physical examination, routine laboratory testing, 12-lead electrocardiography, chest radiography, cardiac ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). These tests are performed at the discretion of the managing physician and have multiple time points in the EHR (Fig 2). In contrast to manually maintained registries, all available data are captured.

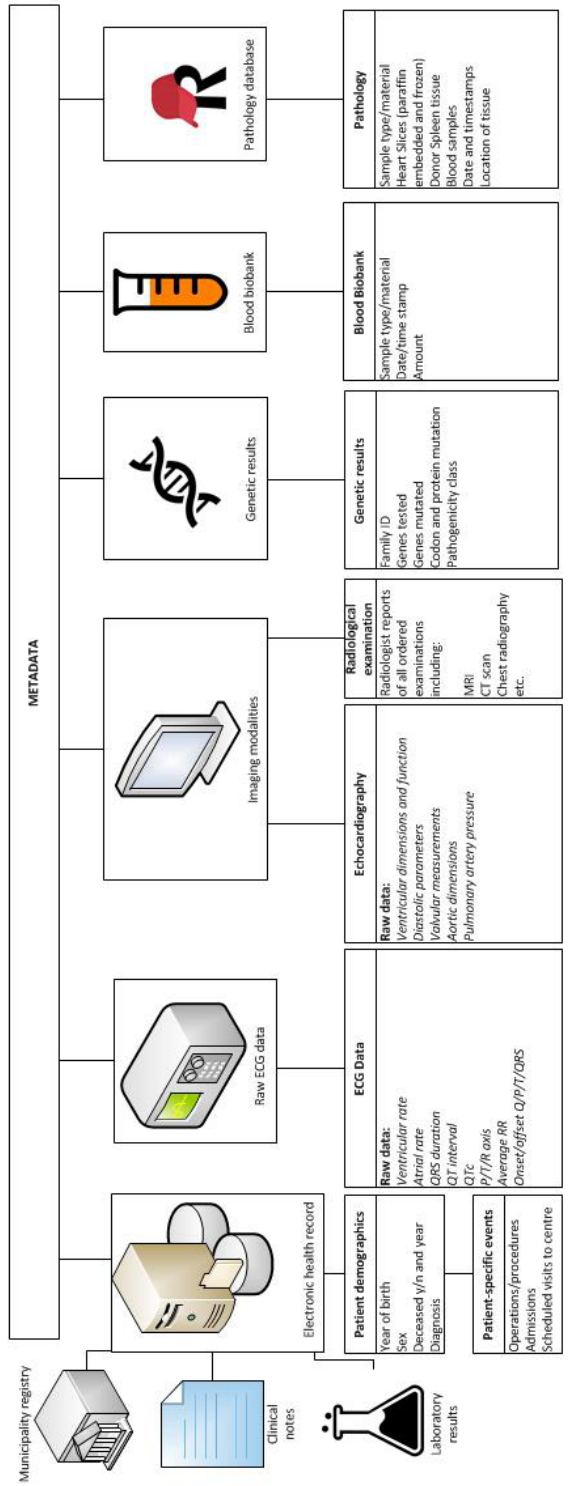

FIGURE 1. Schematic overview of different types of included data. In short, data on investigations and metadata are automatically extracted after informed consent has been provided. Additionally, patient demographics and specific events, such as date of admission, are included. Information from the municipality registry can be requested concerning, for example, death

For example, during a visit to the in-patient clinics several electrocardiograms (ECGs) can be produced per day. Not all data might be entered into manually maintained registries, since this is a meticulous and laborious task.

Raw data is gathered, processed and standardised for all cardiological, electrophysiological, imaging and genetic modalities (Fig. 1). On a weekly basis, these (numeric) data are automatically extracted to the RDP. Metadata is specific information describing the data (such as date of visit, type of ECG or managing physician) which have been gathered for logistical and administrative purposes. These meta-data harbour valuable information and are also stored in the RDP. Data are viewed, combined, linked to external databases and analysed using query-based searches for data extraction using SAS Enterprise Guide (Fig 3).

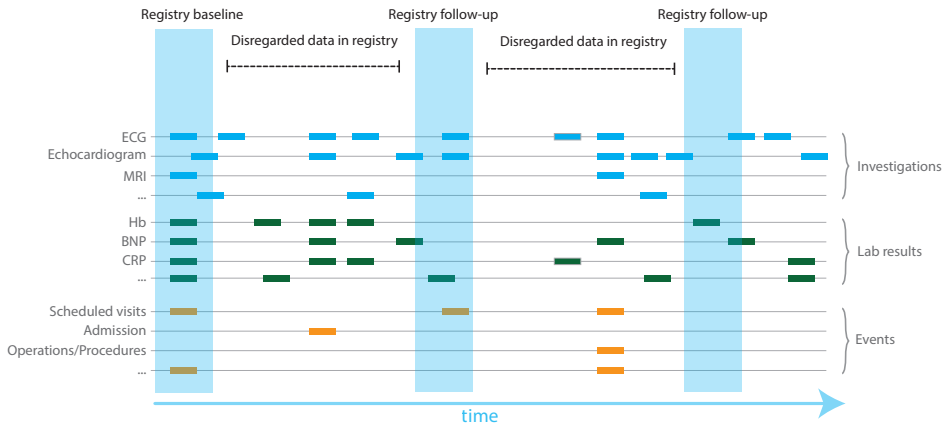

FIGURE 2. Temporal character of health care data. Schematic overview of a temporal window in which patients visit the centres. In contrast to manually maintained registries where data may be disregarded, the UNRAVEL research data platform includes all (meta)data and investigations. ECG electrocardiogram, MRI magnetic resonance imaging, Hb haemoglobin, BNP brain natriuretic peptide, CRP C-reactive protein

Outcomes

The UNRAVEL RDP contains multiple outcome measures that can be used for primary or secondary outcome analyses. All-cause death and date of death are extracted from the EHR and retrieved from the municipality registry [11]. Other outcome measures such as diagnoses, date of diagnosis, occurrence of clinical events such as acute heart failure, arrhythmia or hospitalisation, ventricular assist device implantation and clinical interventions, including heart transplantation, can be extracted from the UNRAVEL RDP.

Sample ECG output *(n = 18,565)*

LeadIDText_ECG	ECG_LeadID	P_OnsetAmpl_ECG	P_PeakAmpl_ECG	P_Duration_ECG	P_Area_ECG
I	0	14	146	130	1018
II	1	73	200	130	1222
III	8	58	122	63	349
V1	2	-5	-117	130	-528
V2	3	0	97	130	456
V3	4	39	136	130	744
V4	5	43	131	130	806
V5	6	39	122	130	860
V6	7	24	107	130	810
aVF	11	63	161	116	732
aVL	10	-20	19	18	24

Sample echocardiogram *(n = 3619)*

easName_ECH	MeasAbstractNumber_ECHO	Value_ECHO	UnitName_ECHO
Ao V2 max	14	91.478282996	cm/s
Ao max PG	13	3.347310504	mm[Hg]
Ao max PG (full)	43	1.5946550851	mm[Hg]
BSA	55	1.7834161914	m2
BSA(Haycock)	56	1.7705933178	m2
BZI_BMI	52	21.469150482	kg/m2
BZI_Metric_Height	203	174	cm
BZI_Metric_Weight	193	65	kg
EDV(MOD-bp)	158	100.45469807	mL

FIGURE 3. Two data tables from the UNRAVEL research data platform as samples of electrocardiogram and ultrasound output in SAS enterprise guide. ECG electrocardiogram, ECH echocardiogram

Text mining

The UNRAVEL RDP includes all structured data from the EHR. However, some data remain unstructured, such as free text. These texts might harbour valuable variables to extract, such as New York Heart Association (NYHA) class or other clinical symptoms. To enrich the UNRAVEL RDP with these unstructured data from clinical notes, a text-mining prototype tool was developed. In short, we defined pre-set variables for the tool to extract from clinical notes, e.g. NYHA classification and cardiovascular risk factors such as diabetes, hypercholesterolaemia and hypertension. The pre-set variables are now in accordance with the variables in the TORCH registry but can be defined at the discretion of the researcher [12]. The algorithm and further explanation are provided open source on www.unravelrdp.nl. Since the tool is under development, it should only be used with caution and under the supervision of medical and text-mining experts until further evaluation. A sample output of this automated tool is presented in Fig. 4. Future perspectives include the use of natural language processing for automated standardised diagnosis registration from clinical notes based on the International Classification of Disease (ICD) 10 classification mapped to the diagnosis thesaurus and reimbursement codes set by the project group DHD diagnosis

thesaurus-DBC-ICD 10 of the Dutch Society of Cardiology [13]. Data standardisation will be harmonised with the OMOP Common Data Model to allow for systematic analysis of disparate observational databases [14].

Blood biobank

All patients are asked concerning the collection of biomaterials for the UNRAVEL Blood Biobank. The exact laboratory protocol is available on www.unravelrdp.nl. In short, the standardised biobank protocol consists of one 10 ml serum, one 4.5 ml citrate, one 2 ml ethylenediaminetetraacetic acid (EDTA), one 10 ml EDTA and one 10 ml Na-heparin blood collection tube. These are processed and aliquoted to two vials of 0.5 ml whole blood from EDTA tubes, four vials of 0.5 ml plasma from citrate tubes, six vials of 0.5 ml plasma from EDTA and heparin tubes and six vials of 0.5 ml serum. All samples are stored at -80°C. Availability, type and storage of material is linked to the RDP for easy accessibility.

Cardiac tissue database

Cardiac tissue of patients that have received a left ventricular assist device or undergone heart transplantation, and received donor spleen tissue during heart transplantation are routinely stored by the Department of Pathology. Samples are paffin embedded and frozen at -80°C. All samples are stored according to protocol available on www.unravelrdp.nl and explanted hearts are divided into slides and cubes accordingly. The registration of these samples is performed using an electronic case registration form in Redcap in the cardiac tissue database which is linked to the UNRAVEL RDP. Further information can be found on www.unravelrdp.nl.

Preliminary results

An overview of the preliminary results is provided in Table 1. By October 2018, 1928 individuals had been asked to participate in the UNRAVEL RDP. Of these, 828 individuals provided consent, of which 58% are male. Median current age is 57 years [interquartile range (IQR) 45-67]. Overall, the available data comprises 18,565 ECGs with a median of 74 per patient (IQR 32-105), 3619 different echocardiograms with a median of 12 per patient (IQR 5-18), over 20,000 radiological examinations including 389 cardiac MRI scans and 650,000 individual laboratory results. Data from other non-cardiac examinations, e.g. orthopaedic MRI or endoscopy, are also available. In 356 participants, a diagnosis of heart failure had been registered according to the diagnosis thesaurus described earlier: 222 have dilated CMP, 38 hypertrophic CMP. Blood from 267 patients has thus far been stored in the biobank according to protocol. To date, 323 mutations have been identified, primarily in PKP2 (23%), PLN (17%) and TTN (13%).

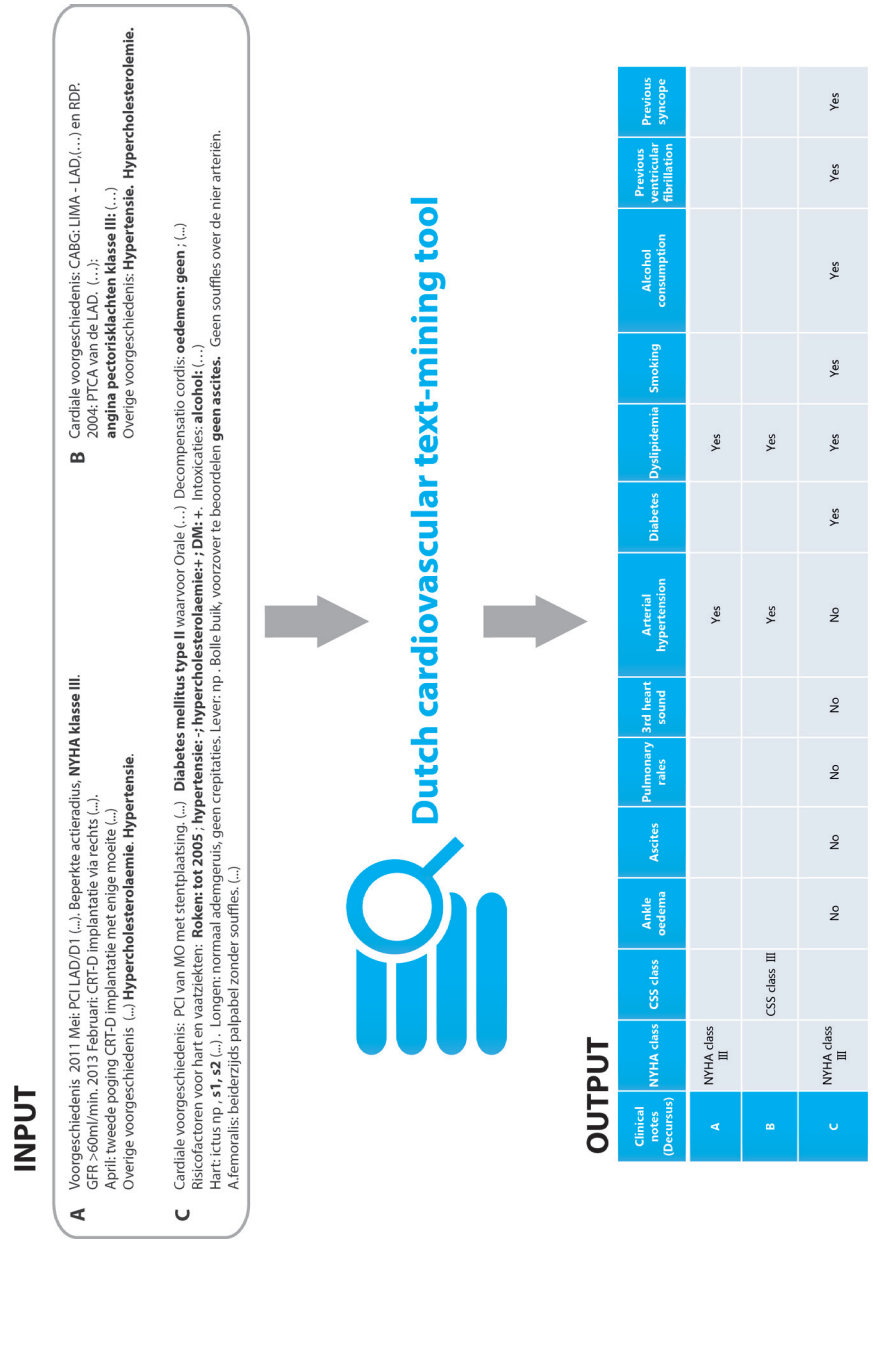

FIGURE 4. Sample data from the text-mining tool, where based on the clinical notes in the EHR (DECURSUS) an output file is created with different standardised variables, such as arterial hypertension, diabetes and dyslipidaemia. Variables are harmonised with the German TORCH registry, but can be changed as deemed necessary. The application is written for Dutch cardiovascular notes

TABLE 1. Clinical characteristics and available tests of 828 patients included in UNRAVEL. Data are presented as number (median, IQR)

Men		480 (58%)
Median age		57 years (IQR 45-67)
Diagnosis as registered in EHR		
	Heart failure	356
	DCMP	222
	HCMP	38
	Cardio-oncology	95
	Not specified	308
	Cardiogenetic screening	165
Cardiac ultrasound images		3619 (12, IQR 5-18)
Electrocardiograms		18,565 (74, IQR 32-105)
Radiological examinations		20,318
	Chest radiography	512
	CT thorax	274 (7, IQR 3-15)
	MRI cardiac	389 (2, IQR 1-3)
Laboratory tests		650,000
Biobanking		267
Device therapy		241
	LVAD	46
	ICD/CRT	195
Heart transplantation		72
Genes mutated		323
	PKP2	76
	PLN	54
	TTN	41
	MYBPC3	38
	MYH7	13
	LMNA	10
	Other	91

IQR interquartile range, EHR electronic health record, DCMP dilated cardiomyopathy, HCMP hypertrophic cardiomyopathy, CT computed tomography, MRI magnetic resonance imaging, LVAD left ventricular assist device, ICD internal cardiac defibrillator, CRT cardiac resynchronisation therapy
MRI cardiac includes both MRI cardiac and stress MRI (adenosine/dobutamine). Radiological examinations include all examinations performed in-house, e.g. chest, abdominal, thyroid radiography etc.

DISCUSSION

There is still limited knowledge on the aetiology, diagnostic performance of clinical investigations and disease modifiers in CMPs, complicating the clinical care of these patients [2, 6, 7]. Research databases based on large numbers of patients provide the infrastructure for new insights into these diseases. To date, patient registries have typically often had fixed time points at which data are manually inputted, data entry is at the discretion of the researcher and a vast amount of (meta)data gathered during routine clinical care is inherently disregarded. The current advanced EHR systems provide exciting opportunities to access all data gathered in routine clinical care which can be linked to research data. The resulting datasets will have larger resolution and may provide new insights into disease penetrance, risk assessment and disease pathophysiology [8, 15]. The UNRAVEL RDP incorporates these large automated and standardised datasets of CMP patients, enriched with language processing and text retrieval. Advantages include (1) automation and efficiency, (2) featuring temporal or sequential data, (3) allowing for EHR-embedded trials and (4) mining unstructured data using text analysis.

EHR data are extracted and standardised in the UNRAVEL RDP, which has thus far led to a dataset comprising 828 patients with a total of 18,565 ECGs, 3619 echocardiograms, 389 cardiac MRI scans and 323 patients with mutated genes (Table 1). The RDP automatically provides these raw (meta)data. This obviates the laborious need for manually maintained registries, saving the precious time of (medical) experts and reducing transcription errors. Furthermore, since outcomes such as admission, heart transplantation and (cardiac) death are automatically extracted from the EHR, obtaining follow-up will be less time-consuming, thereby reducing costs [11].

With the RDP, these data can be integrated into a detailed longitudinal picture of the clinical course of a patient, a 'human phenome sequence' [8]. In previous studies, (semi-)supervised and unsupervised machine learning on linked EHR data was able to solve problems in prediction and pattern recognition [8, 16, 17]. However, routine clinical records can be sparsely filled and (ontological) definitions of disease may differ over time. To counter these issues, a semi-supervised machine learning method has been proposed by Beaulieu-Jones et al. [18] to analyse these high-dimensional EHR data, constructing phenotypes based on unsupervised learning, then clustering these patients in sub-phenotypes and performing survival analyses. Furthermore, large datasets such as the UNRAVEL RDP are prone to generate associations with uncertain causal relevance. To address causality, the addition of our stem-cell informed consent serves as a stepping stone for functional follow-up studies using induced pluripotent stem cells. Additional statistical frameworks such as instrumental variables and Mendelian randomisation, or further research in randomised clinical trials may also provide further support to observed associations [19].

To embed clinical trials, data in the UNRAVEL RDP can be used for trial feasibility, patient recruitment, but also for remote data monitoring, potentially reducing clinical trial costs and selection bias (pragmatic trials). Using the UNRAVEL RDP, it is possible to perform interventions and measure outcomes during routine health care, ranging from life-style interventions to logistical questions on how often a patient should be followed up. EHR can be an alternative to electronic case registration forms providing data is consistently collected in routine clinical care, including data on (adverse) events [20].

Structured EHR data such as encoded diagnosis and cardiac ultrasound are the easiest data sources to process, but advances in text mining have made it possible to also use unstructured clinical data, such as patient medical histories, discharge summaries and clinical notes [10, 14]. Using a text-retrieval algorithm, we have developed a tool to extract standardised data from clinical notes. This tool is, however, still under development and was implemented on clinical notes from the Department of Cardiology at the UMC Utrecht. Therefore, the tool should be used with caution and under the supervision of a medical expert in other centres.

EHR data that are subjected to robust pre-processing and cleaning have been shown to offer a common scaffold upon which research questions can be built and linked to datasets, enabling new areas of research [9, 21]. With these 'big' EHR data, however, great challenges and responsibilities arise: data governance, data access, public trust, definitions of disease and development of replicable scientific tools. Furthermore, these large datasets are prone to generating associations with great uncertainty regarding causality. Therefore, analysis of data and interpretation must be performed by a multidisciplinary team including medical experts, epidemiologists and data scientists. Only if the data are understood and carefully evaluated can new models explaining onset and progression of disease be developed [8].

In conclusion, the UNRAVEL RDP is an enriched data platform for CMPs that combines EHR data with a standardised blood biobank and text-mining tools. This integration of EHR data into the RDP allows novel analysis of the onset and progression of disease and can embed performance measures in clinical practice. Laboratory protocols, informed consent forms and algorithms are available on www.unravelrdp.nl. Protocols have been shared thus far with the University Medical Centre Groningen, Amsterdam University Medical Centre and Bergman Clinics, and we explicitly welcome national and international cooperation with the UNRAVEL team to harmonise protocols.

Conflict of interest

A. Sammani, M. Jansen, M. Linschoten, A. Bagheri, N. de Jonge, H. Kirkels, L.W. van Laake, A. Vink, J.P van Tintelen, D. Dooijes, A.S.J.M. te Riele, M. Harakalova, A.F. Baas and F.W. Asselbergs declare that they have no competing interests.

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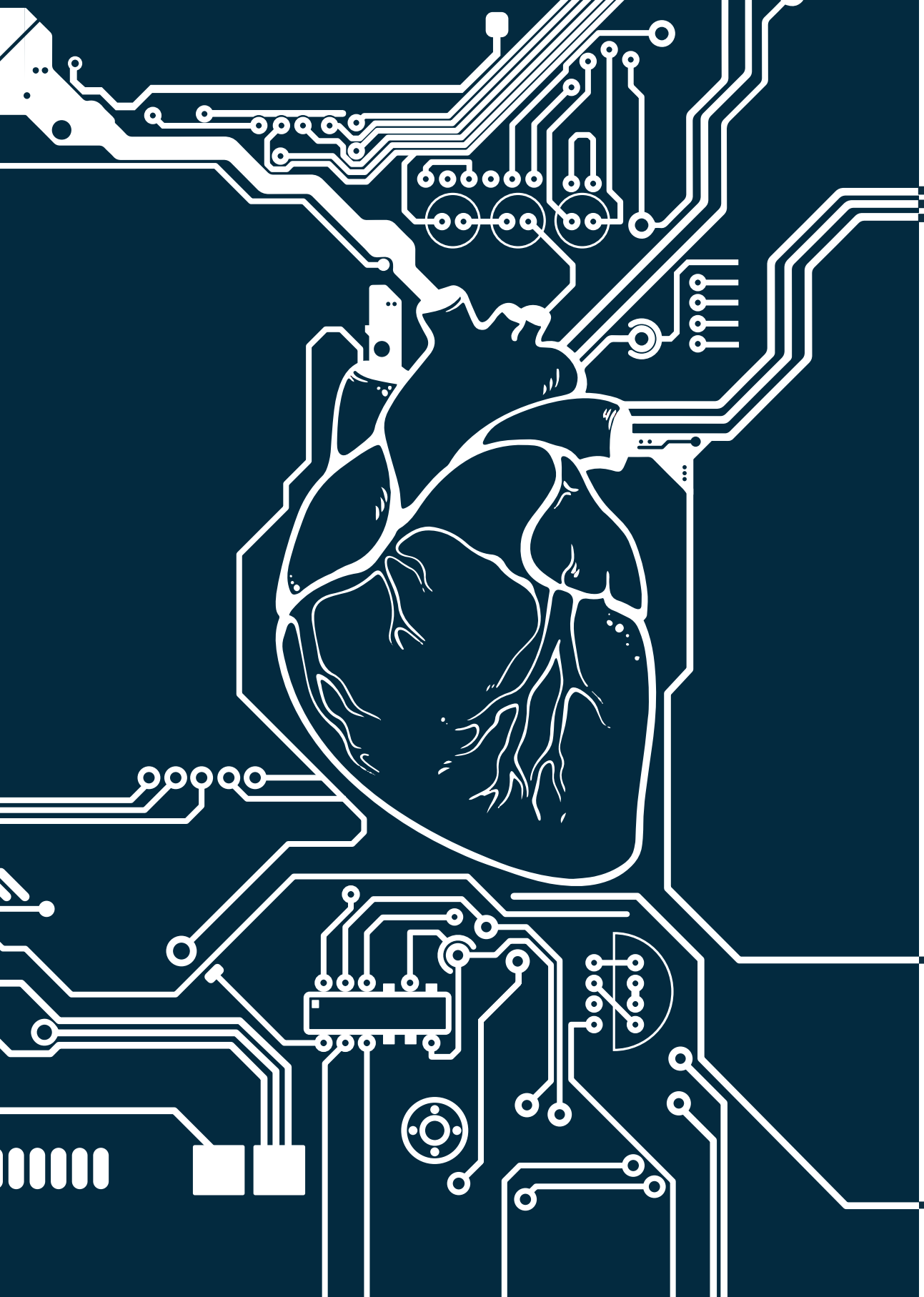

CHAPTER 7

Automatic multilabel detection of ICD10 codes in Dutch cardiology discharge letters using neural networks

Arjan Sammani*, Ayoub Bagheri*, Peter GM van der Heijden, Anneline SJM te Riele, Annette F Baas, CAJ Oosters, Daniel Oberski, Folkert W Asselbergs

*contributed equally as first authors

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ABSTRACT

Standard reference terminology of diagnoses and risk factors is crucial for billing, epidemiological studies and inter/intranational comparisons of diseases. The International Classification of Disease (ICD) is a standardized and widely used method, but manual classification is an enormously time-consuming endeavour. Natural language processing together with machine learning allows automated structuring of diagnoses using ICD-10 codes, but limited performance of machine learning models, the necessity of gigantic datasets and poor reliability of terminal parts of these codes restricted clinical usability. We aimed to create a high performing pipeline for automated classification of reliable ICD-10 codes in free medical text in cardiology. We focussed on frequently used and well defined three- and four-digit ICD-10 codes that still have enough granularity to be clinically relevant such as atrial fibrillation (I48), acute myocardial infarction (I21) or dilated cardiomyopathy (I42.0). Our pipeline uses a deep neural network known as a Bidirectional Gated Recurrent Unit Neural Network and was trained and tested with 5,548 discharge letters and validated in 5,089 discharge and procedural letters. As in clinical practice discharge letters may be labelled with more than one code, we assessed the single- and multilabel performance of main diagnoses and cardiovascular risk factors. We investigated using both the entire body of text and only the summary paragraph, supplemented by age and sex. Given the privacy sensitive information included in discharge letters, we added a de-identification step. Performance was high, with F1 scores of 0.76 – 0.99 for three-character and 0.87-0.98 for four-character ICD-10 codes and was best by using complete discharge letters. Adding variables age/sex did not affect results. For model interpretability, word coefficients were provided and qualitative assessment of classification was manually performed. Because of its high performance, this pipeline can be useful to decrease administrative burden of classifying discharge diagnoses and may serve a scaffold for reimbursement and research applications.

INTRODUCTION

Electronic health records enable fast information retrieval and contain both structured (e.g. laboratory values, numeric measurements) and unstructured data (free text in clinical notes).[1] Clinical discharge letters are an important source of information, but the translation from free text to structured data remains challenging.[2] To structure diagnoses, the international classification of diseases (ICD-10) coding system was created. This classification system is hierarchical and multiple codes may be assigned to a single discharge letter (multilabel). ICD-10 is alphanumerically structured, with seven possible digits arranged hierarchically as shown in Figure 1.[3] The classification is performed by practitioners, managers or medical coders and serves worldwide in clinical practice (e.g. medical history and billing), research (e.g. trial recruitment) and (inter)national epidemiological studies.[2–5] Manual classification is an enormously costly endeavour, its quality depends on the expertise of who is performing the classification task and the reliability for terminal parts of ICD-10 codes can be poor, even among trained medical coders.[5]

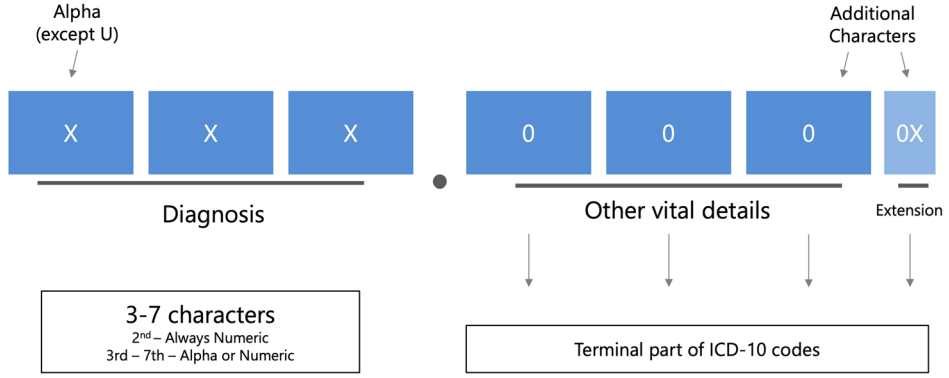

FIGURE 1. ICD-10 structure

Natural language processing (NLP) together with machine learning allows to automate ICD-10 coding for discharge letters.[2] This task is particularly challenging because of: (i) the unstructured nature of free text, (ii) the multilabel setting of ICD10 codes and (iii) the large number of terminal ICD-10 codes.[4] Several attempts have been made to automatically assign ICD-10 codes to medical documents ranging from rule-based to machine learning approaches.[2,6] Generally speaking, rule-based methods have good performance, which is however restricted to conditions that seldomly occur in free-text clinical notes (given possibly ambiguous wording/spelling, multilabel classification and sparsity). Machine learning techniques on the other hand have shown increasingly promising results.[2,4,6,7] Supervised classification can often be simplified by considering only top-level “chapters”

of ICD-10 hierarchy or by only considering a single label or disease groups as output. By doing so, some models do not depict a real-world situation and are less applicable in daily clinical practice.[4,7–16]

More recently, multilabel classification of detailed ICD-10 codes has been improved greatly with deep learning, showing better performance when using recurrent neural networks. These improved models however rely on enormous labelled datasets (Table 1).[2,4,6,17] Unsupervised or semi-supervised classification algorithms are not dependent on curated Electronic Health Record (EHR) datasets and may even reduce bias from practice and coding behaviour. Recent work by Sonabend and colleagues illustrated an unsupervised knowledge integration algorithm by using pre-existing clinical knowledge sources such as Medscape, and mapped identified terms to concept unique identifiers. This resulted in a well-performing classification algorithm for six entities.[8] In general, clinically relevant granularity in predicted labels and reliability of terminal parts of ICD-10 codes is challenging to model performance (Table 1).[2,4,6–16] Contextual word embeddings (ELMo and BERT) are derived from pre-trained bidirectional language models and show substantial performance improvements in many NLP tasks.[18,19] Fine-tuning of these pre-trained models is, given the language and context of the training data, in essence efficient and performant but poses challenges when contextual embeddings in a subdomain and language are lacking.[6,18,20] Furthermore, patient privacy may be compromised if these language models are published online. [21]

In our prior work, we assessed the performance of different machine and deep learning models from literature to this dataset. We employed two vectorization methods (bag of words and word embeddings) and used support vector machines for each of the representations. We also employed several neural network architectures, from which the Bidirectional Gated Recurrent Unit (BGRU) performed best.[2] In this work, we focus on clinical usability which requires high performance, sufficient clinical granularity and interpretability. We focussed on well-defined and frequently used three- and four-character ICD-10 codes that are clinically relevant such as atrial fibrillation (I48), acute myocardial infarction (I21) or dilated cardiomyopathy (I42.0). Since privacy sensitive clinical data is being used, we embedded a pseudonymization algorithm in the pipeline for GDPR compliance. The main contributions of this work are: (i) addressing imbalanced data by using a binary relevance method for multiclass/multilabel classification and a combination of binary classifiers into a multilabel clinically relevant presentation, (ii) a combination of word embeddings and bi-directional gated recurrent unit neural network that encompasses neighbourhood and context of words and (iii) “explainability” of the model with word coefficients and manual assessment of classification. We assessed three- and four-character performance using solely the summary paragraph of discharge letters (conclusion), adding clinical variables (age/sex) and multilabel classification, as is the case in clinical practice and compared our proposed embedding to ELMo as a contextual embedding layer in the neural network model.

TABLE 1. Performance of machine learning classifiers in literature

Author (reference)	F1-score	Classifier	Dataset
Atutxa 2019 (4)	0.84 – 0.95	RNN	Death certificates from CépiDc (France), ISTAT (Italy) and a Hungarian database*
Blanco 2020 (6)	0.70	RNN	Osakidetza Spanish basque public health system
Cao 2019 (9)	0.68	HCAML	Internal Chinese EHR dataset
Chen 2017 (10)	0.63	Longest Common Subsequence	ICD-10 National Chinese dataset
Lin 2019 (14)	0.73	CNN	Tri-service General Hospital Taipei dataset with ICD-10 labels
Du 2019 (11)	0.43	CNN	Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC II)#
Duarte 2018 (12)	0.65	“combined neural network”	Cause of death autopsy reports (three-character)
Karimi 2017 (13)	0.81	CNN	ICD-9 radiology reports
Koopman 2015 (7)	0.94	binary SVM classifier for 4 different codes	Australian Bureau of Statistics dataset with ICD-10 cause of deaths%
Pakhomov 2006 (15)	0.54	Naïve Bayes Classifier	Random sample of HICDA (A mayo-clinics adaptation of ICD-8) dataset
Perotte 2014 (16)	0.40	Hierarchy-based SVM	Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC II)#
Singh 2020 (17)	0.86	BERT model implemented in PyTorch	Medical Information Mart for Intensive Care III (MIMIC III)
Sonabend 2020 (8)	0.71	“unsupervised knowledge integration (UNITE)”	Medical Information Mart for Intensive Care III (MIMIC III) and Partners HealthCare (PHS) Biobank$

RNN: Recurrent Neural Network | HCAML: Hierarchical Convolutional Attention for Multi-Label classification | EHR: Electronic Health Record | ICD: International Classification of Disease | SVM: Support Vector Machine | CNN: Convolutional Neural Network | HICDA: Hospital Adaptation of the International Classification of Diseases. *Using 128•000 training data. #Using the same dataset. %Using 447•336 training data and only four ICD-10 codes to predict as outcome. $193•677 and 52•691 training data for six disease groups

RESULTS

Datasets

In total, 5,548 discharge letters from in-house cardiology patients were included in the dataset with an average of 4.7 codes per letter (cardinality). Median age at discharge was 68 years (1st and 3rd quartiles [58-77]) and 36% of patients were female. For sanity check, Cohen's Kappa was calculated for three- and four-character ICD-10 codes and was high: 0.78 (95% Confidence Intervals (CI) [0.72-0.84]) for four-character codes and 0.85 (95%CI [0.79-0.89]) for three-character codes. Table 2 summarizes the characteristics and an example (box 1) is given after de-identification. 64 different ICD-10 codes have at least 200 records in this dataset. Most common ICD-10 code was I25 (Chronic ischemic heart disease) followed by Z95, I10 and I48 (Presence of cardiac vascular implants and grafts, primary hypertension and atrial fibrillation/flutter, respectively) with all at least 1000 individual counts. The validation dataset contained an additional 5,089 discharge and procedural letters from cardiology. Most common ICD-10 code in the validation set were comparable to the training set (I25, followed by Z95, I10, I48, I50, etc) and are depicted in supplementary file (Supplementary Figure 1).

Box 1: An example of a Dutch discharge letter from the dataset

Bovengenoemde patiënt was opgenomen op <DATUM-1> op de <PERSOON-1> voor het specialisme Cardiologie.
Reden van opname *STEMI inferior*
Cardiale voorgeschiedenis *. Blanco*
Cardiovasculaire risicofactoren *: Roken(-) Diabetes(-) Hypertensie(?) Hypercholesterolemie (?)*
Anamnese*. Om 18.30 pijn op de borst met uitstraling naar de linkerarm, zweten, misselijk. Ambulance gebeld en bij aansluiten monitor beeld van acuut onderwandinfarct.*
AMBU overdracht. 500 mg aspegic iv, ticagrelor 180 mg oraal, heparine, zofran eenmalig, 3× NTG spray. HD stabiel gebleven.Medicatie bij presentatie.Geen.
Lichamelijk onderzoek*. Grauw, vegetatief, Halsvenen niet gestuwd. Cor s1 s2 geen souffles.Pulm schoon. Extr warm en slank.*
Aanvullend onderzoek*. AMBU ECG: Sinusritme, STEMI inferior III)II C/vermoedelijk RCA.Coronair angiografie. (...). Conclusie angio: 1-vatslijden..PCI*
Conclusie en beleid
Bovengenoemde <LEEFTIJD-1> jarige man, blanco cardiale voorgeschiedenis, werd gepresenteerd vanwege een STEMI inferior waarvoor een spoed PCI werd verricht van de mid-RCA. Er bestaan geen relevante nevenletsels. Hij kon na de procedure worden overgeplaatst naar de CCU van het <INSTELLING-2>...Dank voor de snelle overname...Medicatie bij overplaatsing. Acetylsalicylzuur dispertablet 80 mg; oraal; 1× per dag 80 milligram; <DATUM-1>. Ticagrelor tablet 90 mg; oraal; 2× per dag 90 milligram; <DATUM-1>. Metoprolol tablet 50 mg; oraal; 2× per dag 25 milligram; <DATUM-1> . Atorvastatine tablet 40 mg (als ca-zout-3-water); oraal; 1× per dag 40 milligram; <DATUM-1>
Samenvatting
Hoofddiagnose: STEMI inferior wv PCI RCA. Geen nevenletsels. Nevendiagnoses: geen. Complicaties: geen Ontslag naar: CCU <INSTELLING-2>.

TABLE 2. UMCU Cardiology Dataset

Variable	Description
Taxonomy	International Classification of Disease version 10
Language	Dutch
Number of unique records	5,548
Number of unique tokens	148,726
Average number of tokens per record	936
Number of rolled-up labels (i.e. I42)	608
Average number of codes per letter	4,7
% of labels with >50 letters	8,03%
Cohen's Kappa	4-character: 0.78, 95% CI [0.72, 0.84] 3-character: 0.85, 95% CI [0.79, 0.89]
Age. Median (IQs)	68 (1st: 58, 3rd: 77) years
Sex (% Female)	36% Female

Performance of models

The performance in test and validation (F1-score) of our best performing model (BGRU) is summarized in Figure 3. Overall, performance was remarkably high for all selected ICD-10 codes in both test and validation and was optimal using the entire corpus of the discharge letters rather than using just the conclusion/summary section. Adding variables age and sex did not affect performance. Leveraging the model by using ELMo as the embedding layer did not improve performance (figure 4). The performance of multilabel three-character classification in the test set was 0.75 for sensitivity, 0.92 for specificity with an F1-score of 0.74 and decreased in external validation (0.72, 0.61, 0.69 respectively, Supplementary Table 5).

Three and four-character ICD-10 labels

Table 3 contains a description all three and four-character ICD-10 labels. Performance for main diagnosis (I21, I25, I42, I48, I50) and cardiovascular risk factors (I10, E11, E78) was high (Figure 3 and Supplementary table 2) in both test and validation. F1-scores range from 0.76 (I10) to 0.99 (N18). Performance for the four-character codes was also high, with F1 scores ranging from 0.87 (Z95.5: presence of coronary angioplasty implant graft and I25.1: atherosclerotic heart disease of native coronary artery) to 0.98 for I48.1 (persistent atrial fibrillation). Sensitivity in external validation ranged from 90% for presence of cardiac and vascular implants and grafts (Z95) to 100% for cardiomyopathy (I42) (supplementary tables 3 and 4). Specificity was lower in the validation set which would indicate false positives, or over-classification by our model. For all three-character ICD-codes these putative "false" positives were assessed. Many (83% on average) of the putative "false" positives were in fact true positives after manual review, indicating that the model had successfully identified additional cases. Of the putative "false" positives, 93% were correct for E11, 87% were correct for E78, 60% were correct for I10 and 97% correct for I21. This pattern was seen for the rest of the codes as well (supplementary table 7).

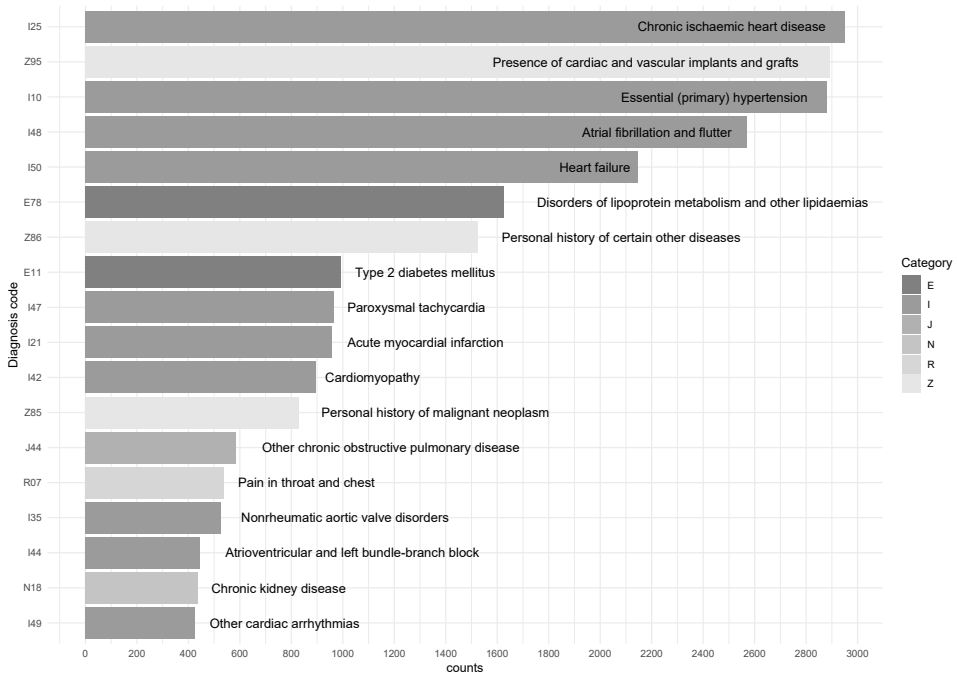

FIGURE 2. Codes with more than 400 appearances in the dataset

TABLE 3. Selected three-character and four-digit ICD-10 codes

ICD10 code three digit and (four digit)	Description of codes
E11* (E11.9)	Type 2 diabetes mellitus (Type 2 diabetes mellitus without mention of complications)
E78* (E78.0)	Disorders of lipoprotein metabolism and other lipidemias (Pure hypercholesterolemia)
I10*	Primary hypertension
I21 (I21.1, I21.4)	Acute myocardial infarction (ST elevation myocardial infarction, Non-ST elevation myocardial infarction)
I25 (I25.1, I25.1, I25.5)	Chronic ischemic heart disease (Atherosclerotic heart disease of native coronary artery, Old myocardial infarction, Ischemic cardiomyopathy)
I42 (I42.0)	Cardiomyopathy (Dilated cardiomyopathy)
I48 (I48.0, I48.1, I48.2, I48.9)	Atrial fibrillation and flutter (Paroxysmal atrial fibrillation, Persistent atrial fibrillation, Chronic atrial fibrillation, Unspecified)
I50 (I50.1)	Heart failure (Left ventricular failure)
N18*	Chronic kidney disease
Z95 (Z95.0, Z95.1, Z95.5)	Presence of cardiac and vascular implants grafts (Presence of cardiac pacemaker, Presence of aortocoronary bypass graft, Presence of coronary angioplasty implant and graft)

* Risk factor for cardiovascular disease

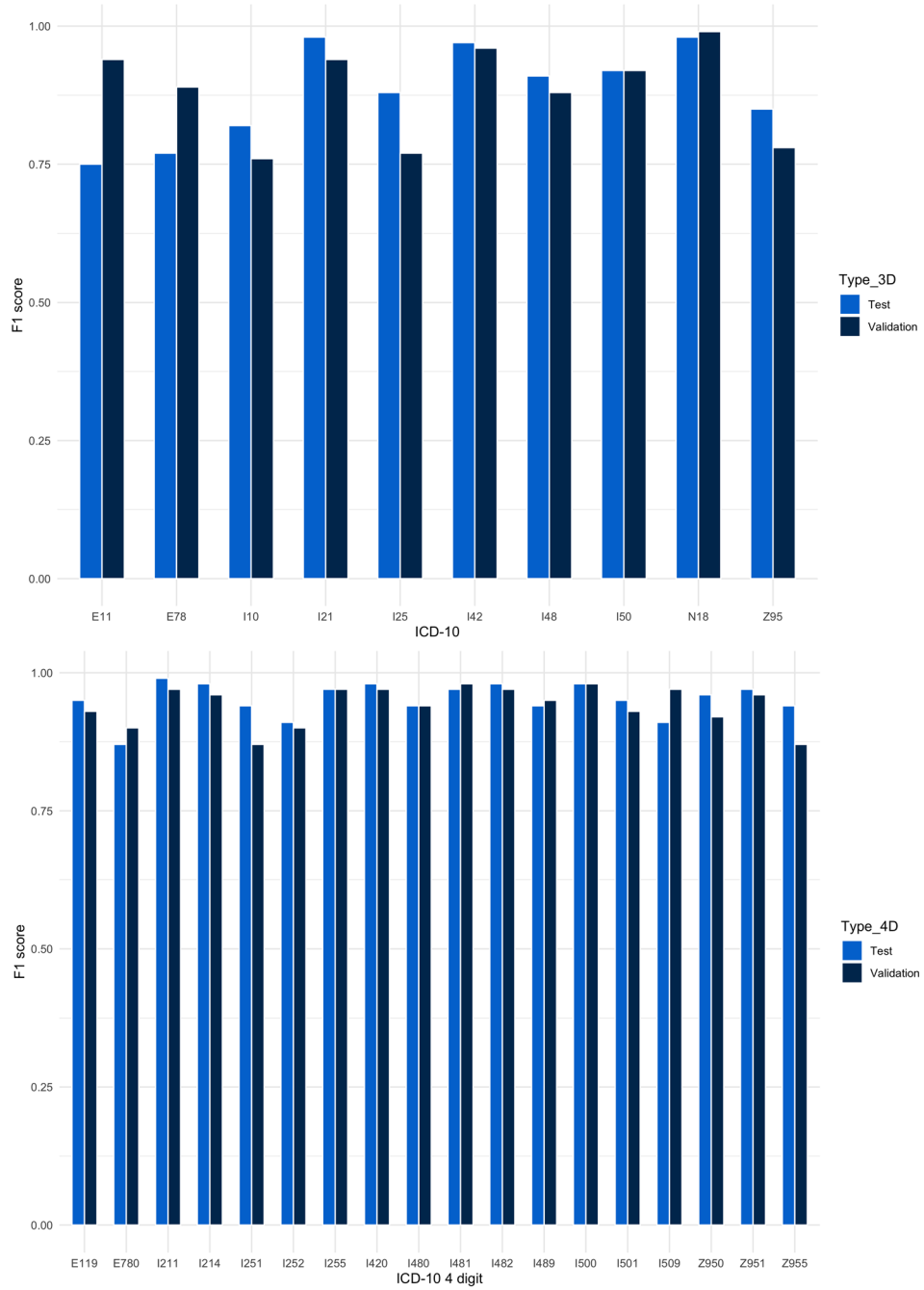

FIGURE 3. F1 scores for test and validation for three- and four-digit ICD-10 codes

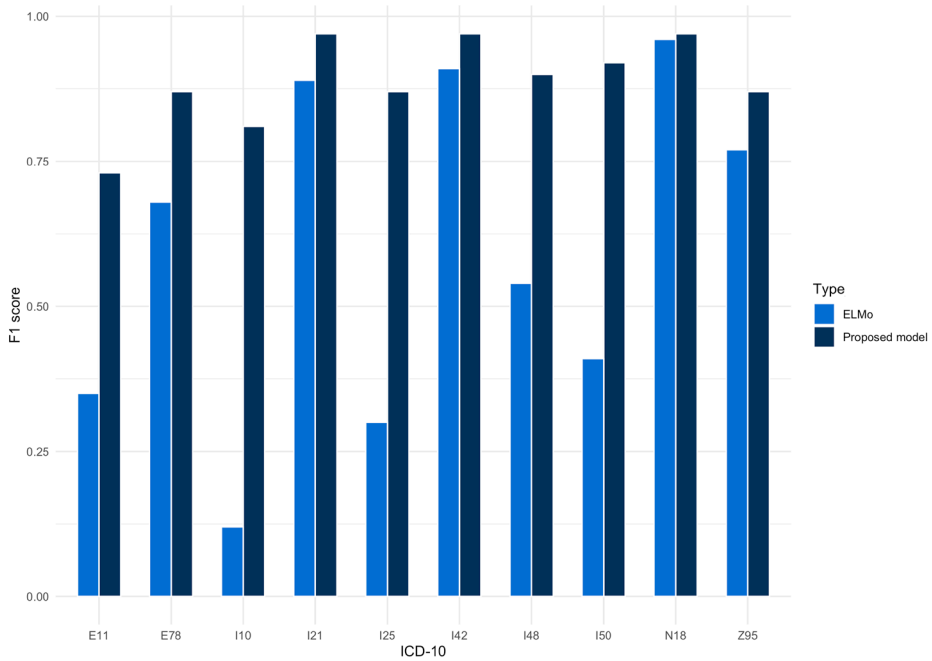

FIGURE 4. Comparison between ELMo and our proposed method

Word coefficients

To interpret the model, word coefficients have been plotted per ICD-10 code. Words that increase the prediction probability are delineated in green. For Type 2 diabetes (E11) these words are either related to the use of medication ("metformin", "gliclazide", "insulin"), are synonyms for E11 ("diabetes", "mellitus", "dmii") or are words that co-occur with cardiovascular risk factors ("overgewicht" (*translation: overweight)*, "stenoses"). For hypertension (I10), the highest coefficients were reached with the synonyms and medication for hypertension as well ("hypertensie", "amlodipine", "valsartan", "ht"). This pattern can be seen for all ICD-10 codes. The words "blanco", "normale" and "nee" all have negative coefficients which illustrates the negative effect of these words in the ICD-10 codes E11, E78, I10, I21, Z95. The coefficients of all ICD-10 codes are visible in the supplementary files.

Manual qualitative assessment of classification

For qualitative assessment of over-, under- and improved classifications all three-character ICD-10 codes were investigated manually by a clinical doctor. The model performed remarkably well in prediction ICD-10 codes of patients in case medication use indicated specific diagnoses. For E11 (Type 2 diabetes) for example, in case metformin or gliclazide were prescribed, the model accurately identified them whereas the medical coders missed them in the validation set. The model seemed to overestimate the probability of type 2 diabetes when "type ii" was used in another context (type 2 ischemia or type 2 atrial septal defect). This detection of prescribed medication in text was also present for hypertension (I10) and dyslipidemias (E78). The detection of medication however also led to over-classification, since some prescribed drugs (amlodipine, perindopril or rosuvastatin) are often also prescribed as a means of treatment or primary/secondary prevention in other diseases than hypertension, for example in heart failure or ischemic heart disease. In case of acute myocardial infarction (I21), the model accurately identified procedures for which acute ischemia was an indication (STEMI and non-STEMI). Our model seemed to struggle with shorter ambiguous procedural letters. In case of I50 (heart failure) relatively short discharge letters (e.g., for device implantation) may include an abbreviation of cardiac decompensation *("decomp cor")* but was missed by our model. As expected, if more words were used to describe the patient's condition (*"CRT-D replacement for non-reversible perfusion defects that led to a dilated and poorly functioning asynchronous LV")* the model did accurately predict the ICD-10 class. Over-classification was present in case of other reasons for decompensation than cardiac (pulmonary, hepatic or renal), or in case a cardiomyopathy was not yet diagnosed but the discharged patient was still undergoing the work-up. Supplementary table 8 contains a description of all three-character ICD-10 codes and their qualitative assessments.

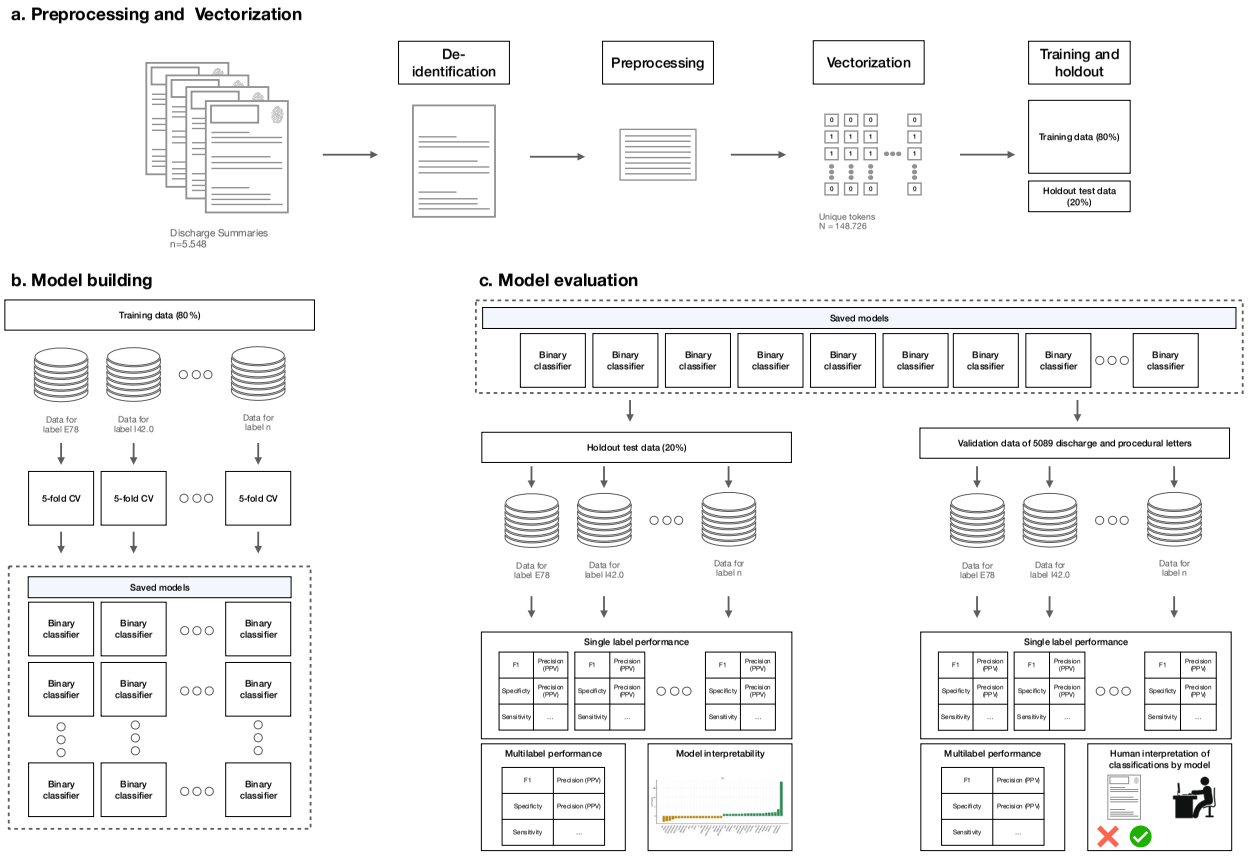

FIGURE 5. Summary of training, validation and model interpretation pipeline
Data was pre-processed, vectorized and split into a training (80%) and holdout (20%) set as shown in panel a. Binary classifiers were trained in panel b and the model was evaluated in panel c. Model interpretability was provided by using word coefficients and human interpretation of misclassification.

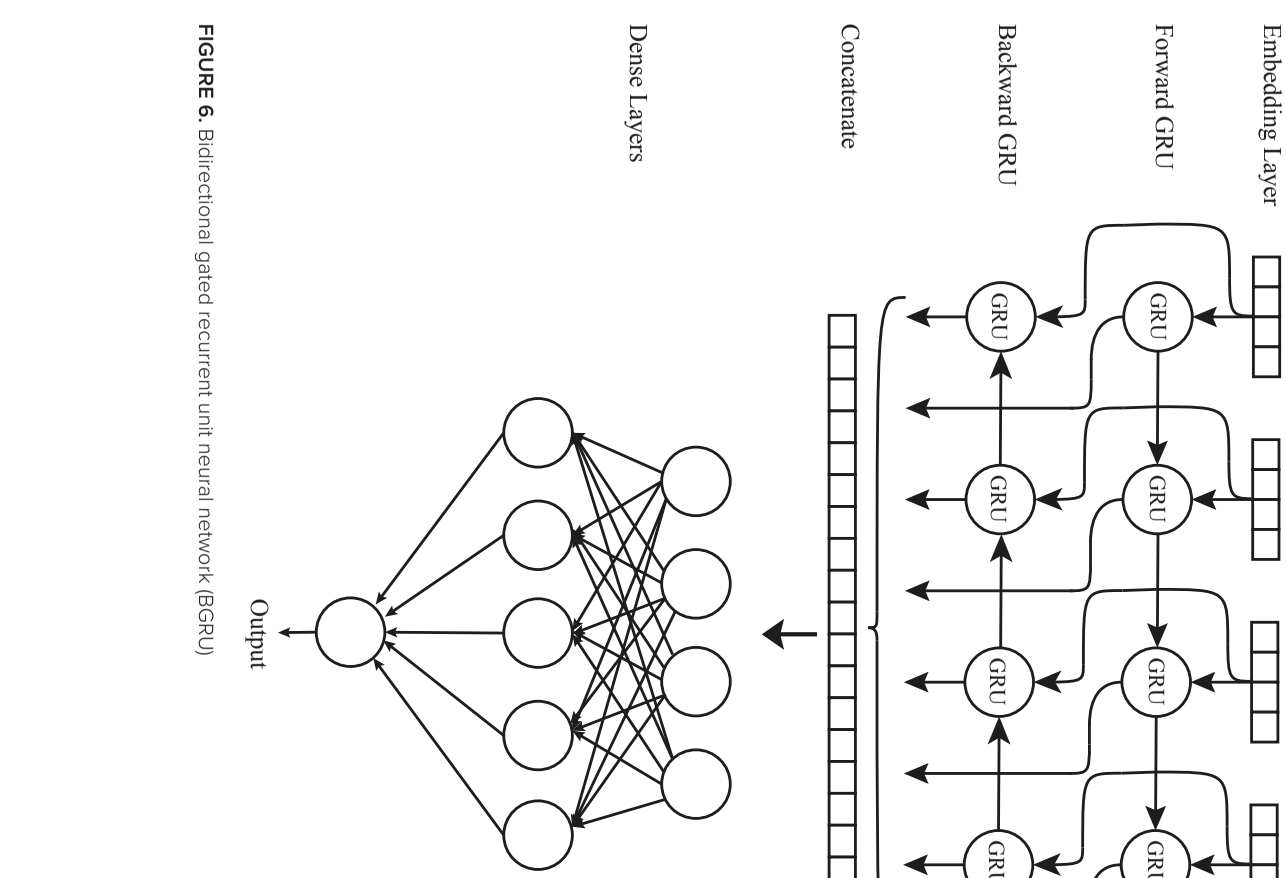

FIGURE 6. Bidirectional gated recurrent unit neural network (BGRU)

DISCUSSION

We created a deep learning pipeline for automatic multilabel ICD-10 classification in free medical text using Dutch cardiology discharge letters. Given the sensitive nature of these data, we included a de-identification step.[22]

Prior work on NLP in cardiology was focussed on specific relevant indicators such as hypertension, algorithms to identify Framingham heart failure signs and symptoms or identification of cardiovascular risk factors and outcomes.[23] The use of Recurrent Neural Networks (RNN) for cardiovascular diagnoses, risk factors and complications, however, remained relatively uncharted. Partially, this is due to rather low performance of some models limiting clinical usefulness.[7,9–16] Recent methodological developments in neural networks lead to high performing models, but they rely on limiting the number of codes (four) to predict, or require huge datasets of up to 128,000 training data points (Table 1).[4,7] Limited performance of some models, the necessity of gigantic datasets for (pre-)training and lack of interpretability withhold them from replacing or aiding a human coder.

In this work, we used a deep neural network and focussed on clinical usefulness with both single and multilabel prediction in a relatively small dataset of 5,548 clinical discharge notes. We extracted frequently used, well defined and clinically relevant three- and four-digit ICD-10 codes.[5] These three-character codes still have enough granularity to include relevant diagnoses such as atrial fibrillation (I48) or acute myocardial infarction (I21). Next, we assessed and improved an already potent type of RNN (BGRU) by using semi-structured parts of text, by adding clinical variables (age and sex) and by adding an ELMo embedding layer. We then sought to explain our model using word coefficients and manual review of misclassifications. Even though our dataset focussed on cardiology, the pipeline is generalizable and may be trained with data from any other speciality.

A comparison of several state-of-the-art RNN ICD coding systems reported that classification performance is higher for ICD chapters than rolled-up codes. The previously reported F1-scores of ICD-10 chapters for this dataset were around 50-60% at best and limited to 20-30% for rolled-up, more terminal codes.[2] BGRU has been promising for classification of medical text and prior experiments advocate either reducing granularity or increasing training data to improve performance.[2,4,6] Additionally, the use of co-occurrences (association rule mining) for the initialization weights also positively impacted performance.[12] Unfortunately, in most settings training data are limited. Therefore, we tried reducing granularity of our dataset whilst remaining clinically relevant without reducing the label-set size. By doing so, our pipeline reached F1 scores for rolled-up codes of 97%. Using the entire corpus of text rather than semi-structured parts also improved classification performance, especially for conventional risk factors such as diabetes and hypertension that are seldomly mentioned in the summary paragraph of discharge letters. By building on prior work and using BGRU which is computationally less expensive, our reported performance is substantially higher than previously seen in smaller datasets, making it a useful and scalable tool for administrative and research support.[2,4,12] We argue that this is caused by the high-quality of the selected training data, our pre-processing pipeline and the binary classification method together with a potent BGRU. Contextual word embeddings (ELMo and BERT) have shown substantial performance improvements in many NLP tasks.[6,18,19] Recently, Blanco and colleagues assessed the performance of a BGRU combined with ELMo, showing an improvement in model performance. Their trained language was in Spanish which in terms of NLP is under strong growth and therefore they were able to train their embedding sets on the strong Spanish Billion Word Corpus.[6] In this regard however, the lack of large Dutch (medical) language models for embeddings poses an important challenge. This is especially understandable as in our case privacy sensitive information in the medical field may be compromised if these language models are published online.[21] Interestingly, ELMo did not positively affect our results which may be due to a variety of reasons. First, our pipeline was already optimized for this specific task of medical ICD-10 labelling and included word-embedding in the first layer of the BGRU, performing quite well with a binary relevance method. Next, given the fact that our model is trained and validated in a specific field of expertise (cardiology), there is little word ambiguity to be expected (the case when contextual word embeddings would be most beneficial). Third, the ELMo pipeline may still be suboptimal and have room for improvement for this task. Using language specific pre-trained embeddings in the field of medicine, multi-language support or by trying meta-embeddings as proposed by Blanco may further improve performance of these pipelines.[6,24] A recently published standardized benchmarking by Peng and colleagues evaluated BERT and ELMo on ten datasets, showing substantial better performance using pre-trained BERT models than other state-of-the-art models.[25] Sing and colleagues implemented BERT as well on de-identified data from the MIMIC-III dataset (58.000 admissions). They demonstrated that with fine tuning based transfer learning of a pretrained bidirectional transformer language model, very high overall performances can be reached for both top 10 and top 50 ICD-10 codes. They advocate working on interpretability for models' prediction and further deployment to more coding systems (e.g. CPT and SNOMED).[17]

An important consideration is model interpretability. State-of-the-art deep learning models are challenging to grasp with no specialised knowledge in neural networks, and practice has shown that the easier the model, the wider its acceptance. There has been a significant increase in the use of machine learning methods but a notable proportion of works still use relatively simple methods: shallow classifiers, or combined with rule-based methods for higher interpretability.[23] Interpretable results however may provide experts with supporting evidence when confronted with coding decisions.[4] We therefore attempted to provide insight into the model by using word coefficients and manual assessment of

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classifications. These results illustrate that synonyms of ICD-10 diagnoses or medication specifically prescribed for these diseases have the highest positive probabilities. Negative words (negation), such as “normal” or “no” decrease the probability of ICD-10 diagnoses, more noticeably for cardiovascular risk factors. Interestingly, in a recent study published by Lin and colleagues, their results also suggest that BERT subsumes domain adaptation for negation detection and further fine-tuning on specific corpora does not lead to much overfitting.[20]

Most ICD-10 codes are used rarely in clinical practice, while a small amount of diagnoses comprise the majority of patients seen in cardiology clinics.[3,5] To aid administrative support, our focus was directed towards multilabel classification and we argue that the model is interpretable and its performance is high enough to aid medical coders. From a clinical perspective, the high single label performance allows for patient identification in EHRs by using only the clinical discharge letters as a first step towards building research cohorts of interest. Less frequent ICD-10 codes, for rare diagnoses for instance, still require datasets large enough for machine learning and deep learning algorithms to perform well in ICD-10 classification.[2] For these diagnoses, rule-based methods may be a more viable option, given that the terms in text follow regular patterns and the task is limited to single-label classification.[4] To accurately capture rare diagnoses, other more structured parts of the EHR may be useful such as laboratory results. A well-performing example is a simple classification algorithm for identification of patients with Systemic Sclerosis in the EHR by using positive antinuclear antibody titre thresholds.[26]

7

Automated coding system that combine simple classifiers with machine learning models are not new, as they have been successfully implemented in 2006 at the Mayo Clinic and resulted in an 80% reduction of staff engaged in manual coding.[15] More recently, a similar system for veterinary electronic health records (VetTag) was built, which classified veterinary clinical notes with diagnosis codes. Authors argue that processing these clinical notes has a tremendous impact on (veterinary) clinical data sciences.[27] Nonetheless, these promising results have not led to widespread use of automatic coding systems for discharge letters.[23] It is clear that human coders can benefit by reviewing suggested ICD-10 codes rather than reading all discharge letters and translating them to proper ICD-10 codes.[15] Saved time can then be used to dive deeply into the correct terminal and detailed coding or additional structuring of data, leading to better research infrastructure. However, there are two long-term concerns: the first is the actual implementation of these algorithms into software. Implementation is more than solely installing an automation pipeline. It requires new software which is embedded in existing workflows and prolonged maintenance. The second is the improvement of technology to for more complex and less frequent ICD-10 codes ICD-10 codes with high accuracy, which would require larger datasets and feedback algorithms. We underline the importance of further efforts to focus on implementation, rather than solely focusing on methodological fine-tuning as suggested by Singh and colleagues.[17]

Our proposed model may be limited by the quality of the data. Even though they were coded by an experienced medical coder, given the character of the dataset it is prone to have human error. As this work involves privacy sensitive data, we are restricted by the Dutch version of the European GDPR (AVG) which inhibits us from using external Dutch datasets. Nonetheless, within this small country and the fact that medical staff rotate we do not believe this poses a major limitation to the validation. Future studies may improve this model by using contextual word embeddings pre-trained on Dutch medical corpora, assess performance in other datasets as well as the use of other coding systems.

We propose a novel automated ICD-10 classifier BGRU pipeline with a de-identification step. Interpretation of the BGRU pipeline is made possible by using word coefficients. Because of its high performance, this pipeline can be useful to decrease administrative burden of classifying discharge diagnoses and may serve a scaffold for reimbursement and research applications.

7

METHODS

Medical ethical regulations and GDPR

This study was exempt from medical ethical regulations by the Medical Ethical Committee of the University Medical Center Utrecht (UMCU) (*no. 18-446*). A data management plan was created and reviewed by the privacy security board to meet institutional and national requirements in the Netherlands for GDPR compliance.

Dataset

Discharge letters were retrieved from the electronic health records in the University Medical Centre Utrecht (UMCU) and were available from the start of the electronic health record on 08-09-2013 until data extraction on 30-06-2018, written by a total of 84 different medical doctors. All letters were manually classified with multilabel/multiclass ICD-10 codes by an experienced medical coder that works solely in the field of cardiology. The discharge letters were matched to the corresponding ICD-10 classification by using patient ID and dates of admission/discharge from within the UMCU Research Data Platform. We removed ICD-10 codes with less than 50 observations.[28] Since the reliability of terminal codes is poor, simplification of ICD-10 codes is important to receive a valid image of health care reality.[5] Selection of specific ICD codes was based on availability and clinical usability (sufficient granularity) of higher level rolled-up codes (e.g. I42 (cardiomyopathy) rather than I42.3 (endomyocardial (eosinophilic) disease)). The 10 selected codes account for six main diagnoses (acute myocardial infarction, chronic ischemic heart disease, cardiomyopathy, atrial fibrillation/flutter, heart failure and presence of cardiovascular implant grafts) and four cardiovascular risk factors (type 2 diabetes, hyper/dyslipidemia, primary hypertension, chronic kidney disease). To not oversimplify the task, from these 10 selected codes, further four-character ICD-10 codes (e.g. I48.0 (paroxysmal atrial fibrillation) rather than I48) were also considered to assess performance for very granular labels with at least 100 appearances in both the training and validation set. The ICD-10 codes are depicted in Table 3. Dataset quality for both three- and four-character ICD-10 codes was manually assessed using an adaptation of Cohens Kappa previously described and used for ICD-10 codes (AS).[5] 100 clinical discharge notes were randomly selected, stripped from patient-IDs and reclassified by a medical coder (DK) that was blinded to the correct codes.

Validation

To assess the performance of the model in a new dataset, a non-overlapping temporal validation dataset was created consisting of letters and ICD-10 codes. This validation set contains new clinical discharge and procedural letters written by 46 different medical doctors. Given GDPR restrictions and the nature of this privacy sensitive work, extracting letters from other hospitals was not possible. However, because clinical staff in the Netherlands rotate from hospitals within the country frequently, the letters were written by other clinicians and teams. Additionally, sentence structures as well as diagnosis coding structures are interchangeable in hospitals. Therefore, this temporal dataset was deemed fit for external validation. For this set, clinical letters from 01-07-2018 until 04-09-2019 were included. Because the dataset is solely constructed on discharge letters and ICD-10 codes, the pipeline is not EHR system or vendor specific and may be interoperable.

Machine learning pipeline for ICD-10 classification.

The pipeline is summarized in Figure 5. Before feeding data into the different machine learning or deep learning algorithms, we first applied the following steps:

(i) We de-identified the letters using *DEDUCE*. [22]
(ii) We pre-processed the text (trimmed whitespaces, numbers and converted all characters to lowercase) using the *tm* and *tidytext* packages in *R*.[29]

To transform text into data a machine can understand (text representation), the output of our pre-processed text was then vectorised using word embedding. This method allows to represent words in such a way that it captures meanings, semantic relationships and context that words are used in. It is a dense feature representation in a low dimensional vector and has been proven to be a robust solution for most NLP issues. Word embedding is also the first layer in a neural network (NN) based classifier. After k-fold cross-validation (*k = 5)* we implemented a bidirectional gated recurrent unit (BGRU) neural network.

Bidirectional Gated Recurrent Unit (BGRU) Neural Network

The general architecture of a BGRU model is shown in Figure 6. In this model, the input layer is the text from discharge letters and the output layer is the ICD-10 label. The model uses deep recurrent neural networks (RNN) in its hidden layers, called gated recurrent units (GRUs). GRU is a type of RNN that can model sequential data. The GRU network receives an input at each timestep, updates its hidden state, and makes a prediction. By using recurrent connections, information can cycle inside these networks for an arbitrarily long time. However, RNNs are known to have difficulties learning the interactions between distant words because of long-range dependencies. This problem is known as the vanishing gradient problem. Extensions for neural networks, such as Long-Short Term Memory (LSTM) and GRU were specifically designed to combat this issue through a gating mechanism. Using GRUs also leads to a reduced number of parameters, faster convergence and a more generalizable model in comparison to other methods.[12]

We used the *Keras* library to implement the BGRU model for automated ICD-10 coding.[30] Vector dimensionality was set to 300, windows size to five and we discarded words that only appeared once in the training set. We experimented with the model directly on the

word sequence of all the discharge letters. As in previous studies on textual data, the fact that our data contains long texts creates a challenge for preserving the gradient across thousands of words. Therefore, we used dropout layers to mask the network units randomly during the training.[31] We set the number of hidden units in the RNN layers at 100. Dropout and recurrent dropout were added to avoid overfitting, both at a 0.2 rate. On the output of the recurrent layer, a fully connected neural network (two dense layers) was applied for the classification of the ICD-10 codes. The hidden dense layer contains 128 units and uses the *relu* activation function, and the output layer uses a softmax function to determine if the ICD code should be assigned to the letter.

Contextual Word Embeddings

A dense neural network using word vectors from contextual embeddings based on ELMo has been used for the comparison study.[19] These word vectors are learned functions of the internal states of a deep bidirectional language model trained on our original dataset. In this representation, the vector obtained for each word depends on the entire context in which it is used. Using a bi-directional LSTM, instead of a fixed embedding for each word, ELMo looks at the entire sentence before assigning each word an embedding (Supplementary figure 2).

Assessment of performance and experiments

We investigated performance by randomly splitting the dataset in a training (0.80) and testing (0.20) set. The model was then again evaluated in external validation. Sensitivity (recall), specificity, positive predictive value (PPV, precision), negative predictive value (NPV), and F1-score (a harmonic mean between sensitivity and positive predictive value) were calculated. We performed four experiments with different input variables: (I) using only the summary paragraph parts of discharge letters (conclusion), (II) using the entire corpus of discharge letters, (III) using the entire corpus of discharge letter and adding the variables age and sex, and (IV) multilabel classification of experiment III. For an administrative support tool, it is important to suggest the right diagnoses, ranked by the prediction probabilities. For multilabel assessment we considered every ICD label above a probability threshold as a positive. We assigned this threshold in such a way that the label cardinality for the test set is similar to the label cardinality in the training set. When performance discrepancies were present, a clinical doctor (AS) manually assessed these errors in a descriptive manner. False positives were either all manually assessed, or a subset of 100 letters in case of >100 putative false positives.

Data availability

The dataset is not available due to patient privacy restrictions. However, the model may be shared to qualified researchers from academic or university institutions upon request via the corresponding author.

Code availability

The code used in this study can be found at GitHub: https://github.com/bagheria/cardio-icd-assignment

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Author Contributions

Arjan Sammani and Ayoub Bagheri designed the experiments, supervised by Daniel Oberski, Peter van der Heijden and Folkert Asselbergs. Arjan Sammani drafted the manuscript. Ayoub Bagheri programmed the design and experiments and the scripts were checked together by Arjan Sammani and Ayoub Bagheri. Arjan Sammani and Caj Oosters designed the dataset. Manuscript was revised by all authors.

Competing interests

Authors have nothing to disclose.

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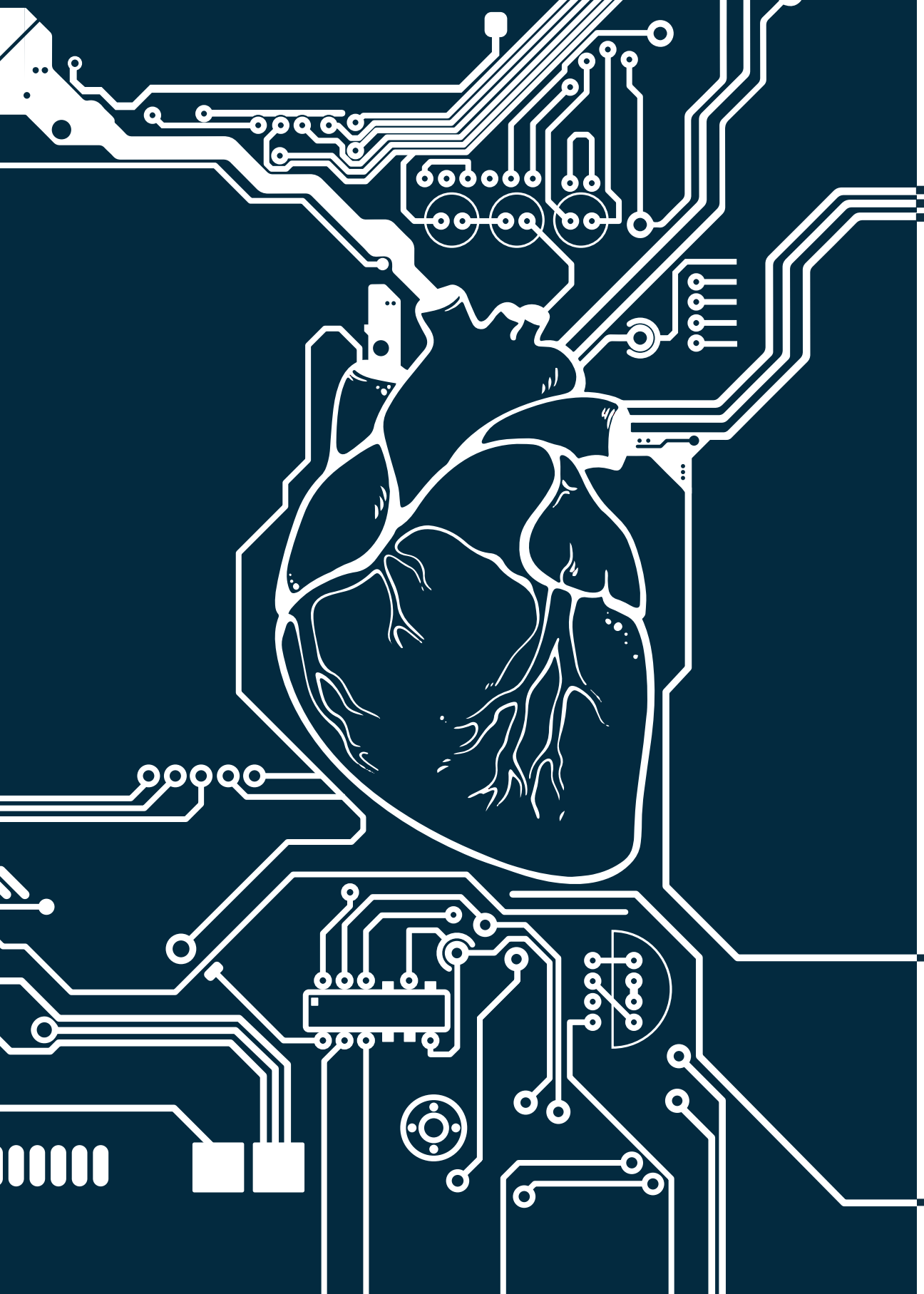

CHAPTER 8

Automatic identification of patients with unexplained left ventricular hypertrophy in electronic health record data to improve targeted treatment and family screening

Arjan Sammani*, Mark Jansen*, Nynke de Vries , Nicolaas de Jonge, Annette F. Baas, Anneline S.J.M. te Riele, Folkert W. Asselbergs, Marish I.F.J. Oerlemans

- submitted
*authors contributed equally

ABSTRACT

Background

Unexplained Left Ventricular Hypertrophy (ULVH) may be caused by genetic and non-genetic aetiologies (e.g. sarcomere variants, cardiac amyloid or Fabry's disease). Identification of ULVH patients allows for early targeted treatment and family screening.

Aim

To automatically identify patients with unexplained LVH in electronic health record (EHR) data using two computer methods: text-mining and machine learning (ML).

Methods

Adults with echocardiographic measurement of interventricular septum thickness (IVSt) were included. A text-mining algorithm was developed to identify patients with ULVH.
An ML algorithm including a variety of clinical, ECG and echocardiographic data was trained and tested in an 80%/20% split. Clinical diagnosis of ULVH was considered the gold standard. Misclassifications were reviewed by an experienced cardiologist. Sensitivity, specificity, positive and negative likelihood ratios (LHR+ and LHR-) of both text-mining and ML were reported.

Results

In total, 26954 subjects (median age 61 years, 55% male) were included. HCM was diagnosed in 204/26954 (0.8%) including 56 patients with amyloidosis and two with Fabry. Text-mining flagged 8192 patients with possible ULVH, of whom 159 were true positives (sensitivity, specificity, LHR+ and LHR-of 0.78, 0.67, 2.36 and 0.33). Machine learning resulted in a sensitivity, specificity, LHR+ and LHR- of 0.32, 0.99, 32 and 0.68 respectively. Important variables included IVSt, systolic blood pressure and age.

Conclusions

Automatic identification of patients with ULVH is possible with both Text-mining and ML. Text-mining may be a comprehensive scaffold but can be less specific than machine learning. Deployment of either method depends on existing infrastructures and clinical applications.

INTRODUCTION

Left ventricular hypertrophy (LVH) is a condition characterised by thickening of the left ventricular (LV) wall and can be identified using echocardiography (defined as an LV wall thickness of >12mm). The disease has a prevalence of ±15% in the normal population.(1–3) LVH in the absence of abnormal loading conditions (i.e. hypertension or valvular disease) has an estimated prevalence of ±0.2% and is named as unexplained LVH (ULVH) or hypertrophic cardiomyopathy (HCM).(3,4) ULVH is an important cause of sudden cardiac death and is caused by autosomal dominant genetic mutations in genes encoding proteins of the cardiac sarcomere in 40-60% of patients.(5–7) Some ULVH cases are explained by a variety of rare, genetic and non-genetic aetiologies that may produce isolated or syndromic LVH, such as cardiac amyloidosis (CA) in an estimated 5-10% and Fabry's disease in 0.5-1% of cases.(3,8–11) These specific aetiologies are also referred to as phenocopies.

Identification of patients with ULVH is important to allow risk stratification for sudden cardiac death and screening of at-risk family members.(12–14) Early identification of cardiac amyloidosis and Fabry's disease is essential to initiate targeted treatment to slow disease progression and improve patient prognosis.(15–17) However, timely identification is hampered by low disease prevalence, intrinsic phenotypic heterogeneity, presence of comorbidities or absence of an indicative family history.(18–22)

Electronic Health Records (EHR) consist of a variety of data including both structured tables with results from clinical investigations and unstructured text data (i.e., discharge letters, clinical consultation notes, etcetera). Text-mining is a method to extract data from unstructured datasets while machine learning (ML) algorithms can be deployed on structured datasets. Both approaches rely on research infrastructures, however the research infrastructure for text-mining may be easier to deploy than ML because it only needs one data source (clinical discharge letters) whereas ML requires a multitude of standardized clinical measurements (i.e., laboratory values, electrocardiograms, and echocardiography). Both text-mining and ML have been proposed as methods to extract diagnoses and assist in classification of patients using real-life EHR data.(23–26) In this proof-of-concept-study, we aimed to assess the performance of (i) a text-mining approach and (ii) a data-driven ML approach to identify patients with ULVH, such as amyloidosis and other phenocopies.

MATERIALS AND METHODS

Subject inclusion

In this single-centre, retrospective study, consecutive patients referred to Department of Cardiology of the University Medical Centre Utrecht (UMCU) were included. Inclusion criteria were an age ≥18 years and availability of an echocardiographic interventricular septum thickness measurement before 6 December 2019 (date of text-query deployment). This study was conducted in accordance with the principles laid out in the Declaration of Helsinki and in line with guidelines provided by ethics committees and national GDPR legislature. Due to its retrospective nature and the large number of participants, this study was exempt from the Medical Research Involving Human Subjects Act (WMO) as per judgement of the Medical Ethics Committee (18/446 and 19/222 UMCU, the Netherlands) including the requirement for informed consent. Patients who had opted out of retrospective studies were excluded.

Study data and infrastructure

Using the research data platform, available data on diagnosis, demographics, electrocardiograms (ECG) and echocardiography parameters, and unstructured text were retrieved from the EHR in a standardised research data platform. The design of this infrastructure has been previously published.(27) Data for the ML model were restricted to a basic set of variables on these modalities to comply with a standard diagnostic workup for patients presenting for cardiological screening and to minimize the chance of data leakage. An overview of the intended parameters, methods used to handle outliers and missingness is provided in Supplemental Table 1.

Gold standard (study outcome)

The outcome of this study was ULVH diagnosis or related phenocopies cardiac amyloidosis and Fabry's disease. Three reference lists were used to adjudicate diagnoses: first, patients with ULVH diagnosis codes were extracted from the EHR (I42.1 and I42.2, International Statistical Classification of Diseases (ICD10) codes).(28) This list was then supplemented by a retrospective list of genetically-confirmed ULVH patients from the Department of Genetics. Patients were considered genetically-confirmed if a pathogenic or likely-pathogenic variant was identified, in accordance with the 2015 American College of Medical Genetics and Genomics and the Association for Molecular Pathology Standards and guidelines for the interpretation of sequence variants(29), in one or more genes with definitive, strong or moderate evidence for an association to ULVH (by M.J. and A.F.B).(30) Third, a list of consecutive patients with cardiac amyloidosis in accordance with the recently published 2021 ESC position statement on diagnosis and treatment of cardiac amyloidosis (by M.I.F.J.O.).(18) Echocardiographic LVH was defined as a maximum wall thickness of >12 mm or a left ventricular mass indexed to body surface area >115g/m^2 in males and >95g/m^2 in females, in line with current guidelines.(3,18,21)

Computer algorithms

Two computer algorithms were used in this study: one computer algorithm used text-mining, and the other used machine learning. The details of these algorithms are available in the Supplemental Materials. In short, the text-mining algorithm was designed using CTCue (a Boolean retrieval text-mining tool) to identify patients with unexplained LVH, defined as LVH excluding hypertension and aortic stenosis using clinical discharge letters and notes. The ML algorithm was trained on patients with echocardiographic LVH to identify patients with unexplained LVH. Parameters for the ML algorithm are depicted in supplemental Table 1. As ML algorithms require training on one dataset and testing in another, the model was trained on a random selection of 80% of data (stratified by outcome) and tested in 20%. To assess the added value of text-mining, "identification by text-mining" was also investigated as a dichotomous (yes/no) variable in the ML algorithm.

Statistical analysis

Data are presented as counts (percentages) for count data and means ± standard deviation for normally distributed or medians (interquartile range) for non-normally distributed continuous data. Performance of the ML models was assessed on the holdout set (20% of patients, stratified on outcome) after manual review of overclassified (false-positive) and missed (false-negative) subjects. Manual review was performed by a panel of experienced cardiologists in the fields of ULVH and amyloidosis (M.I.F.J.O. and F.W.A). Qualitative assessment of reasons for misclassification by the text-mining algorithm was performed by A.S.. Sensitivity, specificity, positive likelihood ratio (LHR+) and negative likelihood ratio (LHR-) were reported for the models. Positive and Negative predictive values (PPV and NPV) are provided in the supplements. All analyses were performed in R version 4.0.3 (R Development Core Team, 2020) using RStudio version 1.3.1093 (RStudio Team, 2020).

RESULTS

Study population

From the electronic health record (n = 40,598), adult patients were included in the dataset if a measurement of interventricular septal thickness (IVSt) was available (n = 26,954). A flow diagram of subject inclusion is provided in Figure 1. Subject characteristics are provided in Table 1. In total, 204 patients (1 in ±130) were diagnosed with ULVH of which 56 patients were diagnosed with CA and two with Fabry disease. Genotypes of ULVH patients are summarised in Supplemental Table 2, with a total of 41 genotype positive patients and most pathogenic variants in MYBPC3 (56%) and MYH7 (20%). Most patients with ULVH were male (69%) and had a significantly lower mean systolic blood pressure compared to non-ULVH patients (121 vs 129 mmHg, p<0.001). ECG measurements associated with LVH were also more present in ULVH (R and S amplitudes, p < 0.007) as well as septal hypertrophy (1.69 vs 1.03 cm, p<0.001). All the patients with an IVSt measurement available (n = 26,954) were included in the text-mining dataset. To mimic clinical work-up, only patients with LVH on echocardiography were included in the ML dataset (n = 12,281) resulting in an exclusion of eight patients that were diagnosed with ULVH according to our gold standard (of whom 2 had CA, 3 had genetically proven ULVH and 3 were identified using ICD-10 coding).

TABLE 1. Patient characteristics

	ULVH (n = 204)	No ULVH (n = 26,750)	p-value
Demographics			
Male sex	141 (69.1)	14792 (55.3)	**<0.001**
Age (years)	62.05 [53.75, 69.90]	61.06 [46.88, 72.10]	0.591
Body surface area (m^2)	1.92 [1.82, 2.10]	1.92 [1.76, 2.07]	0.053
Mean systolic blood pressure (mmHg)	121.14 (18.37)	129.10 (17.85)	**<0.001**
Mean diastolic blood pressure (mmHg)	71.76 (10.53)	74.43 (10.57)	**0.001**
Electrocardiography			
Atrial rate (bpm)	71.00 [61.00, 84.00]	72.00 [62.00, 84.00]	0.675
Ventricular rate (bpm)	70.00 [61.00, 82.00]	71.00 [62.00, 83.00]	0.383
P axis (°)	54.00 [30.00, 70.50]	54.00 [37.00, 68.00]	0.982
R axis (°)	19.00 [-38.00, 68.00]	31.00 [-8.00, 63.00]	0.114
T axis (°)	94.00 [46.00, 135.50]	51.00 [30.00, 72.00]	**<0.001**
PQ interval (ms)	176.00 [152.00, 206.00]	160.00 [142.00, 182.00]	**<0.001**
QRS duration (ms)	118.00 [98.00, 148.00]	96.00 [86.00, 110.00]	**<0.001**
QT interval (ms)	432.00 [394.00, 465.00]	396.00 [370.00, 422.00]	**<0.001**
QTc (Fredericia) (ms)	448.00 [425.25, 484.00]	417.00 [400.00, 439.00]	**<0.001**
R amplitude V6 (μV)	693.00 [363.50, 1176.00]	937.00 [634.00, 1274.00]	**<0.001**
S amplitude V2 (μV)	1254.00 [649.00, 2094.00]	1098.00 [717.00, 1557.00]	**0.007**
Echocardiography			
IVS thickness (cm)	1.69 [1.38, 2.00]	1.03 [0.89, 1.20]	**<0.001**
IVS/LV posterior wall ratio	1.32 [1.09, 1.69]	1.09 [0.99, 1.24]	**<0.001**
LV posterior wall thickness (cm)	1.31 [1.16, 1.54]	0.98 [0.86, 1.12]	**<0.001**
LV mass (g)	275.10 [219.59, 326.55]	177.34 [140.01, 225.58]	**<0.001**
Indexed LV mass (g/m^2)	144.21 [116.27, 177.16]	91.76 [74.82, 114.39]	**<0.001**
LV end-diastolic diameter (cm)	4.58 (0.87)	4.93 (0.80)	**<0.001**
LV end-diastolic volume (mL)	96.93 [74.49, 119.04]	109.99 [87.55, 137.02]	**<0.001**
LV end-systolic diameter (cm)	3.00 [2.41, 3.63]	3.16 [2.72, 3.72]	**0.003**
LV end-systolic volume (mL)	39.64 [28.30, 57.71]	42.57 [30.14, 61.62]	**0.048**
LV ejection fraction (%)	55.87 [45.07, 66.53]	58.58 [48.98, 67.44]	**0.026**
LV fractional shortening (%)	32.77 [24.01, 43.53]	34.94 [27.18, 41.74]	0.226
LV outflow tract gradient (mmHg)	5.14 [3.36, 8.21]	4.02 [3.01, 5.33]	**<0.001**
Aortic valve gradient (mmHg)	8.42 [5.42, 14.33]	7.08 [5.26, 10.56]	**0.01**
LA diameter (cm)	4.51 [4.02, 5.09]	3.92 [3.48, 4.47]	**<0.001**
E/A	1.21 [0.83, 1.89]	1.02 [0.77, 1.41]	**<0.001**
Average E/e'	12.95 [9.85, 18.27]	8.06 [6.41, 10.69]	**<0.001**
Lateral E/e'	10.54 [6.96, 15.29]	6.87 [5.33, 9.32]	**<0.001**
Septal E/e'	14.74 [11.06, 19.46]	9.15 [7.19, 12.13]	**<0.001**
MV deceleration time (s)	0.17 [0.14, 0.22]	0.18 [0.15, 0.22]	**0.009**
TAPSE (cm)	2.05 (0.54)	2.21 (0.52)	**<0.001**
Criterium on which "outcome" was defined			
Echocardiographic LV hypertrophy	196 (96.1)	12085 (45.2)	**<0.001**
Maximum wall thickness >12 mm	174 (85.3)	6010 (22.7)	**<0.001**
Indexed LV mass >115 (males) or >95 (females) g/m^2	170 (90.4)	10408 (45.2)	**<0.001**
Identified by CTCue population finder	159 (77.9)	8033 (30.0)	**<0.001**

Patient characteristics, shown as means (standard deviation), medians [interquartile range] or counts (%), stratified by ULVH diagnosis according to the reference lists (amyloidosis, genetically confirmed and classified based on World Health Organization International Statistical Classification of Diseases and Related Health Problems, tenth revision). P-values <0.05 are shown in bold. IVS, interventricular septum; LV, left ventricular; LA, left atrial; MV; TAPSE, tricuspid annular plane systolic excursion.

Text-mining

From the 26,954 subjects, the CTCue population finder algorithm flagged a total of 8,192 patients with possible ULVH, of whom 159 had ULVH and incorrectly excluding 45 ULVH cases. Patient characteristics stratified by identification by the CTCue population finder are provided in Supplemental Table 3. Patients that were identified by CTCue had characteristics that were comparable to patients with ULVH, for example with larger IVSt (1.14cm vs 1.00 cm (p<0.001), larger LA dimensions (4.00cm vs 3.90 cm (p<0.001) and longer PQ intervals (165ms vs 158 ms, p<0.001). Given the identified 159 patients and missed 45 ULVH cases, Sensitivity, specificity, LHR+ and LHR- of the CTCue text-mining algorithm was 0.78, 0.67, 2.36 and 0.33 respectively. Manual reclassification revealed one additional case of unexplained LVH which was not present in our gold standard. Reasons for under classification are provided in Supplemental Table 4, and were mostly a diagnosis of (pulmonary) hypertension (n=15,

33%) and ambiguous notation of LVH (i.e. “important hypertrophy”; n=7, 16%). However, in 22 patients (49%) the reason for under classification was not apparent which is discussed in the study limitations.

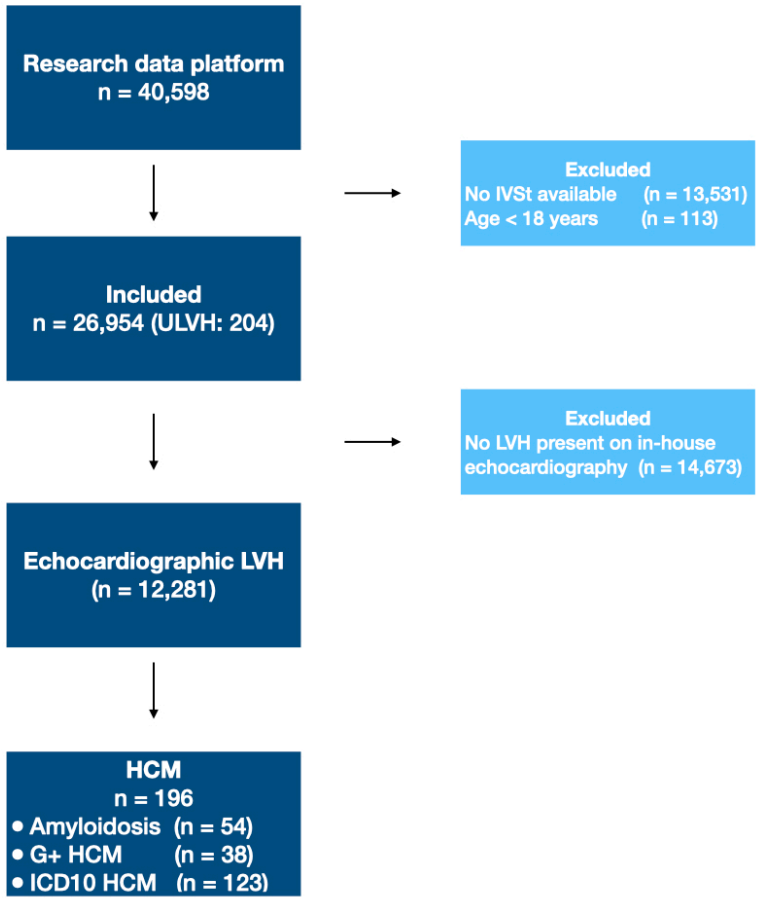

FIGURE 1. Flow diagram of patient inclusion
Flow diagram showing the patients excluded in each step. For the text-mining algorithm, 26,954 patients were included. The machine learning algorithm was trained on patients with echocardiographic LVH. IVSt, interventricular septum thickness; LVH, left ventricular hypertrophy; ULVH, Unexplained Left Ventricular Hypertrophy; HCM: Hypertrophic Cardiomyopathy; G+, genetically-confirmed; ICD10, World Health Organization International Statistical Classification of Diseases and Related Health Problems, tenth revision.

Machine learning

From the 12,281 patients with echocardiographic LVH, 196 patients were previously diagnosed with ULVH. Subject characteristics stratified by echocardiographic LVH are provided in Supplemental Table 5. Patients with echocardiographic LVH were more frequently male (66.1 vs 46.7%, p<0.001), with larger LA dimensions (4.23cm vs 3.69cm, p<0.001), longer PQ interval (166ms vs 154ms, p<0.001) and longer QRS duration (102ms vs 92ms, p<0.001). The tuned hyperparameters for the trained models are provided in Supplemental Table 6. The performance of the machine learning models is shown in Table 6. The test set included 39 patients with ULVH, in which machine learning correctly identified 10 out of 39 (26%) patients with ULVH and 2412 (99.8% of total) without ULVH. Manual review of overclassified (false-positive, n = 5) cases in the test-set revealed that three were in fact true positives and missed by our golden standard list. Manual review of the misclassified (false-negatives, n = 29) in the test-set revealed that one case of the false-negatives was in fact sufficiently explained by hypertension resulting in a true-negative by the model. This led to a total of two false positives and 28 false negatives. Additionally, one novel case of ULVH was also identified that, in retrospect, required further work-up of LVH. Final sensitivity, specificity, LHR+ and LHR- after manual review were 0.32, 0.99, 32 and 0.69 respectively. Important variables for classification included IVSt, systolic blood pressure and age (Figure 2).

Added value of text-mining

As shown in Supplemental Table 6, including identification by CTCue as a dichotomous variable (yes/no) did not improve performance over the baseline ML model (sensitivity, specificity, LHR+ and LHR- of 0.18, 0.99, 18, 0.83 respectively). Coefficients and explanation of Lasso logistic regression were provided in Supplemental Table 7 and showed that including identification by CTCue as a dichotomous variable (yes/no) slightly decreased performance, correctly identifying the same number of subjects with ULVH and misclassifying one.

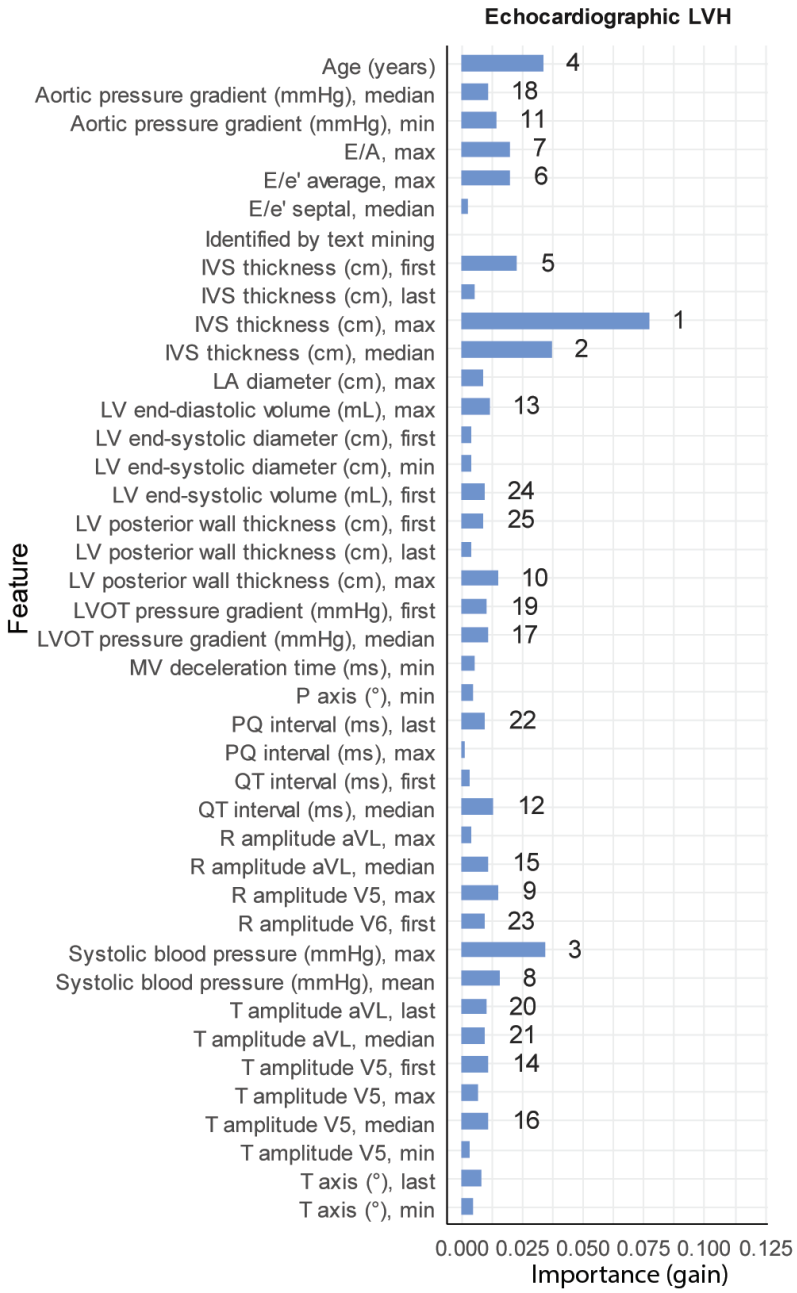

FIGURE 2. Feature importance
Relative importance for the top 25 variables of each of the three XGBoost models (41 variables in total), measured by gain. Numbers denote the rank of the top 25 variables for each model (1 being the most important). LVH, left ventricular hypertrophy.

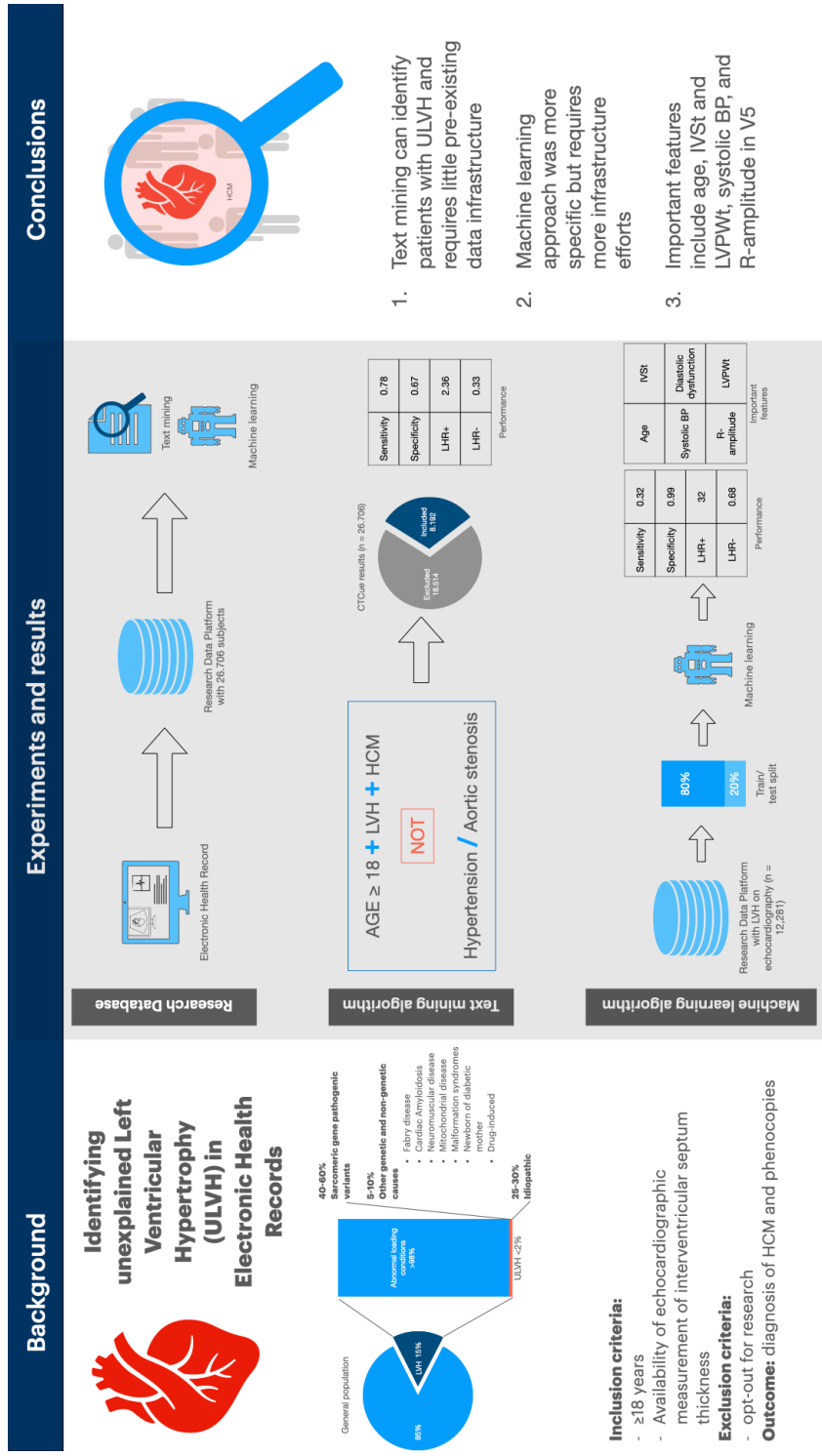

FIGURE 3. Summary figure
Summary figure of the study. BP, blood pressure. IVSt, interventricular septum thickness; LVH, left ventricular hypertrophy; LVPWt, left ventricular posterior wall thickness; LHR, likelihood ratio; ULVH, unexplained LVH

DISCUSSION

In this study, we evaluated computer methods (text-mining and machine learning) in EHR data to identify patients with unexplained LVH. These methods are feasible strategies to assist in patient screening for research databases, trial recruitment or clinical follow-up. (26,31,32). Our results suggest that both methods can reduce the bulk of patients needed to screen with a high negative predictive value.

Unexplained LVH

LVH is an echocardiographic abnormality often encountered in the normal population (±15%).(1–3) As abnormal loading conditions, such as hypertension and valvular disease are also quite common, the distinction between LVH that is sufficiently explained by these conditions and ULVH requires further investigation.(3,4) Early detection of ULVH is essential to initiate targeted treatment, for instance in Fabry's disease and cardiac amyloidosis, for risk stratification of sarcomeric HCM and for family screening.(3,5–11) As Fabry's disease and cardiac amyloidosis are rare and therefore difficult to detect, the imperative to recognize them largely depends on availability of specific therapeutic workflows.(11,17,20) More likely, patients present to non-experts with their initial symptoms, leading to an operational challenge to construct systems that can facilitate identification of these rare phenocopies. (33) Automatic strategies to augment unexplained LVH detection can therefore provide a systematic framework for further cardiogenetic screening of patients and relatives. With accessible EHR data approaches like text-mining or machine learning are practicable.(34)

Computer algorithms

Text-mining is the process of deriving high quality information from text, in this case from clinical discharge letters. It can range from simple rule-based algorithms, to complex computer models that understand semantics and word ambiguity.(26) State-of-the-art deep neural networks offer the best performance but require large amounts of language specific training data, mostly lacking for rare diseases and especially in Dutch.(26,35–37) For less-frequent diagnoses such as ULVH, rule-based methods may be a more viable option, given that the terms in text follow regular patterns.(26,31) A well-performing example is a simple classification algorithm to identify patients with systemic sclerosis using data from the EHR.(31) However, the broad definition of ULVH, including phenocopies and allowing presence of concomitant abnormal loading conditions (not explaining the degree of left ventricular hypertrophy), makes precise identification of ULVH an especially challenging task.(3) Furthermore, Dutch terminology for ULVH is heterogeneous, including different ways of denoting hypertrophy and spelling of hypertrophic cardiomyopathy. By using a Boolean retrieval algorithm software (CTCue), clinical criteria for unexplained LVH were entered: excluding cases when patients had hypertension or aortic stenosis. These retrieval algorithms may be hampered by ambiguous spelling in the EHR whereas medical experts would easily identify cases when presented to them (as illustrated in the reasons for under-classification, Supplemental Table 4). In our study, text-mining identified patients with ULVH with reasonable sensitivity and LHR- which, given the epidemiology of unexplained LVH, translates to identification of most patients with ULVH while reducing the number of patient files needed to be screened (high negative predictive value). Our results are in line with other studies using the same approach, for instance reducing the number of patients that needed to be screened for trial inclusion by 80% and a yield of 2-5% for inclusion. (25) Other applications for such algorithms include retrospective cohort building, further emphasizing the supportive role of text-mining applications rather than a comprehensive solution replacing human assessment of patient inclusions.(25,38,39) Whether queries for specific phenocopies (such as Cardiac Amyloidosis and Fabry's disease) can be improved by ancillary search terms (e.g., neuropathy for amyloidosis and kidney failure for Fabry's disease) remains to be investigated.

Machine learning algorithms build a model based on training data to make decisions on new data without being explicitly told how to do so (learning). Our existing research data platform provided structured and standardised data to train our machine learning (XGBoost) algorithm.(27) It identified ULVH patients with high specificity, however at the cost of sensitivity compared to the text-mining algorithm. Artificial intelligence (AI) models have previously been developed to identify patients with heart failure, or to identify patients with PLN p.Arg14del cardiomyopathy.(40,41) Our final model was efficient in identifying patients with ULVH, with a specificity of 0.99, LHR+ of 32 resulting in a positive predictive value of 0.72. Moreover, the model identified a previously undiagnosed patient with ULVH. A highly specific model like this would be better suited for clinical applications that require high degrees of certainty, e.g., when selecting patients to perform expensive diagnostic testing (such as Whole Genome Sequencing) or in the context of ethical considerations (whether to inform family members of a potentially inheritable phenotype).(3) As expected, coefficients were generally positive for echocardiographic characteristics of ULVH ((septal) wall thickness, LV outflow tract pressure gradient, diastolic dysfunction, and LA diameter) and negative for variables associated with abnormal loading conditions (age, blood pressure and aortic pressure gradient).

Infrastructure and clinical considerations

Big-data infrastructures improve accessibility of EHR data and methods such as machine and deep learning can model complex interactions, find new phenotype clusters, or predict prognosis.(34,42) The phenotypic data usually included in EHR systems complies with the definitions of big data and include detailed laboratory, investigations, ECG data, device data, questionnaires and (unstructured) text.(27,34,43) Importantly, text-mining requires little data infrastructure: it requires only one database (clinical discharge letters) and can already be implemented using a single piece of open-sourced software.(44) This advantage enables

easier dissemination to other centres than complex machine learning pipelines which often require a multitude of standardized data. Future developments for data infrastructures should focus on interoperability between EHR systems to enable validation of (complex) machine and deep learning models.(34,45)

While using text-mining and machine learning for patient identification and possible treatment, there are considerations limiting widespread adoption in clinical setting which including (i) algorithm performance and (ii) clinical follow-up of identified patients.(42,46) AI-algorithms may fail if selection bias occurred in dataset, reducing external validity and performance of the model. Dealing with rare diseases may for instance lead to underrepresentation in training data and subsequently be missed by AI algorithms.(46) While algorithms with high positive predictive value and LHRs would accurately capture true cases, this is usually at the expense of sensitivity.[32] By focussing on the needle in the haystack, the learning metric for AI algorithm must encompass a combination of both positive predictive value and sensitivity, both summarized in the F1-score. External validation in non-tertiary centres may also be necessary in rare diseases to compare effectiveness of screening algorithms. Furthermore, clinical follow-up of selected cases within a common care pathway may improve effective implementation of these algorithms compared to fragmented clinical care.(47,48)

Study limitations

As we used real-world data, it is possible that values in our dataset were wrong or biased due to clinical, billing, or administrative interests. Even though our centre employs specialised coders to classify cardiology diagnoses (kappa of 0.78)(26), given the nature of this work, human errors in classifying disease may have added noise to the training data which is resembled by the fact that 3 genotype positive patients were diagnosed with ULVH without LVH. As the CTCue population finder algorithms remain proprietary (essentially a black box), this poses a major limitation in assessing algorithm shortcomings, exemplified by the fact that in 22 (49%) of patients the reason for under classification was not apparent. Additionally, our manual review was restricted to misclassified subjects. The (academic) single-centre study design with internal validation may limit external validity. Given GDPR compliance and the use of privacy sensitive clinical text, external validation was not available. However, our aim was not to train and publish a model that can be used, but rather to assess the feasibility of such a pipeline. Further work may be specific for data capturing systems per EHR/hospital system.

Conclusion

In this study, we investigated two methods (text-mining and machine learning) to identify ULVH patients using EHR data. Our results suggest that these methods are viable options to reduce the bulk of patients needed to screen. We conclude that (i) text-mining can be easily set-up in terms of infrastructure and observed that it had reasonable sensitivity when deployed to identify patients with ULVH, (ii) machine learning was more specific and could be used to efficiently identify patients with ULVH though at the cost of sensitivity and infrastructure needs. Deployment depends on specific requirements of pre-existing data infrastructure, clinical framework, and ethical considerations.

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Contribution to the field

Left ventricular hypertrophy is a commonly found echocardiographic abnormality in the normal population (±15%). The absence of abnormal loading conditions (such as hypertension and valvular disease) however suggests other aetiologies, such as sarcomeric pathogenic variants, Fabry disease and cardiac amyloidosis. Early detection of these diseases is essential to initiate targeted treatment, risk stratification and for family screening. As some causes are rare, the imperative to recognize them largely depends on availability of therapeutic workflows and expertise. Automatic strategies to augment unexplained left ventricular hypertrophy can provide a systematic framework for further cardiogenetic screening of patients and relatives. With electronic health record data now accessible, we investigated text-mining and machine learning methods to identify patients with unexplained left ventricular hypertrophy. Our results suggest that these methods are viable options to reduce the bulk of patients needed to screen. We conclude that (i) text-mining can be easily set-up in terms of infrastructure and observed that it had reasonable sensitivity when deployed to identify patients with ULVH, (ii) machine learning was more specific and could be used to efficiently identify patients with ULVH though at the cost of sensitivity and infrastructure needs. Deployment depends on specific requirements of pre-existing data infrastructure, clinical framework, and ethical considerations.

Conflicts of interest

M.J., A.S. and F.W.A. received consultancy fees from Sanofi Genzyme. M.I.F.J.O received consultancy fees from Alnylam, Pfizer and Novartis paid to the University Medical Center Utrecht.

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SUPPLEMENTAL METHODS

Text-mining

For the text mining method, an algorithm was created using the software program: CTcue population finder version 2.0.12 (CTcue, Amsterdam, The Netherlands). This tool uses Boolean retrieval method to search through unstructured EHR data such as clinical discharge letters and in-hospital consultations. The output of the tool is a list of flagged patients that meet the inclusion criteria or the query using a proprietary (black box) algorithm. The query was designed to identify patients with unexplained LVH, defined as LVH excluding hypertension and aortic stenosis and can be summarised as: ([Age > 17] AND [LVH-synonyms OR ULVH-synonyms] AND [patient at cardiology]) NOT ([hypertension-synonyms] OR [aortic stenosis-synonym]). Synonyms included suggestions by the built-in synonym expander supplemented with commonly used synonyms and abbreviations.

Machine learning algorithm

Within subjects with LVH on echocardiography, an XGBoost algorithm was trained. The model was trained on a random selection of 80% of data (train set, stratified on outcome). Echocardiographic LVH was defined as a maximum wall thickness of >12 mm or a left ventricular mass indexed to body surface area >115 in males and >95 in females, in line with current guidelines.[3,21,31] An additional model was built using identification by CTCue as a dichotomous variable (yes/no) to address added value of CTCue in identifying ULVH within this subset dataset with LVH. XGBoost is an ensemble ML algorithm that uses extreme gradient boosting framework to convert a set of weak tree classifiers into a single strong classifier. It iterates through a process of re-weighting, adding terminal node penalisation (gamma) to allow variability in the numbers of terminal nodes per tree, additional regularisation of terminal node weights, Newton boosting to fit subsequent trees and column subsampling as an additional randomisation parameter.[1,2] Hyperparameters were tuned using consecutive 5-fold cross-validated grid-searches (provided in the Supplemental Methods) with the *caret* package.[3] The model was tested in 20% of the data. To provide a readily interpretable model, logistic regression was fitted on the train set using the top 50 best performing variables. Missing data were imputed using iterative Random forest imputations consisting of 100 trees per forest and a maximum of 10 iterations, using the *missForest* package.[4] Logistic regression was performed using 5-fold cross-validated Lasso regression to attenuate multicollinearity effects, using the *caret* and *glmnet* packages.[5]

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XGBoost hyperparameter tuning

Hyperparameter tuning was performed using grid searches in five steps, as detailed on Pelkoja (2018). "Visual XGBoost Tuning with caret." (Retrieved 19-10-2020, from https://www.kaggle.com/pelkoja/visual-xgboost-tuning-with-caret).

Step 1. Temporarily fixing learning rate

Number of iterations	200 to 1000, per 50
Learning rate	0.025, 0.05, 0.1, 0.3
Maximum tree depth	2, 3, 4, 5, 6
Gamma	0
Subsample ratio of columns	1
Subsample ratio of rows	1
Minimum sum of instance weight required in a child	1

Step 2. Maximum tree depth & minimum sum of instance weights required in a child

Number of iterations	50 to 1000, per 50
Learning rate	Step 1 best
Maximum tree depth	2-4 step 1 best was 2, otherwise step 1 best -1 to step 1 best +1
Gamma	0
Subsample ratio of columns	1
Subsample ratio of rows	1
Minimum sum of instance weight required in a child	1, 2, 3

Step 3. Subsample ratios

Number of iterations	50 to 1000, per 50
Learning rate	Step 1 best
Maximum tree depth	Step 2 best
Gamma	0
Subsample ratio of columns	0.4, 0.6, 0.8, 1.0
Subsample ratio of rows	0.5, 0.75, 1.0
Minimum sum of instance weight required in a child	Step 2 best

Step 4. Gamma

Number of iterations	50 to 1000, per 50
Learning rate	Step 1 best
Maximum tree depth	Step 2 best
Gamma	0, 0.05, 0.1, 0.5, 0.7, 0.9, 1.0
Subsample ratio of columns	Step 3 best
Subsample ratio of rows	Step 3 best
Minimum sum of instance weight required in a child	Step 2 best

Step 5. Reducing the learning rate eta & determining number of iterations

Number of iterations	100 to 10,000, per 100
Learning rate	0.01, 0.015, 0.025, 0.05, 0.1
Maximum tree depth	Step 2 best
Gamma	Step 4 best
Subsample ratio of columns	Step 3 best
Subsample ratio of rows	Step 3 best
Minimum sum of instance weight required in a child	Step 2 best

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Final model	
Number of iterations	Step 5 best
Learning rate	Step 5 best
Maximum tree depth	Step 2 best
Gamma	Step 4 best
Subsample ratio of columns	Step 3 best
Subsample ratio of rows	Step 3 best
Minimum sum of instance weight required in a child	Step 2 best

SUPPLEMENTAL TABLE 1. Parameters & outlier handling

Variable	Outlier handling	Values	Missingness
Demographics			
Sex	-	-	0.000
Age (years)	Values < 18 excluded	At last echo	0.000
Mean systolic blood pressure (mmHg)	Values < 1 & > 300 excluded	Min, mean, max	0.255
Mean diastolic blood pressure (mmHg)	Values < 1 excluded	Min, mean, max	0.255
Body surface area (m^2)	Values > 5 & < 0.5 excluded	First, last, min, median, max	0.102
Electrocardiography			
Atrial rate (bpm)	-	First, last, min, median, max	0.013
Ventricular rate (bpm)	-	First, last, min, median, max	0.013
P axis (°)	-	First, last, min, median, max	0.037
R axis (°)	-	First, last, min, median, max	0.014
T axis (°)	-	First, last, min, median, max	0.014
PQ interval (ms)	-	First, last, min, median, max	0.037
QRS duration (ms)	-	First, last, min, median, max	0.013
QT interval (ms)	-	First, last, min, median, max	0.013
QTc (Bazett) (ms)	-	First, last, min, median, max	0.013
QTc (Fredericia) (ms)	-	First, last, min, median, max	0.047
P peak amplitude (II)	-	first, last, min, median, max	0.013
PP peak amplitude (V1)	-	first, last, min, median, max	0.013
Q peak amplitude (aVL, V5, V6)	-	First, last, min, median, max	0.013
Q peak area (I-III, aVF/-L, V5, V6)	-	First, last, min, median, max	0.013
R max. amplitude (I, aVL, V5, V6)	-	First, last, min, median, max	0.013
S max. amplitude (III, aVR, V1-3)	-	First, last, min, median, max	0.013
ST minimum (I, aVL, V5, V6)	-	First, last, min, median, max	0.013
T peak amplitude (I, aVL, V5, V6)	-	First, last, min, median, max	0.013
Echocardiography			
IVS thickness (cm)	Values < 0.2 & >4.0 excluded	First, last, min, median, max	0.010
IVS/LV posterior wall ratio	Values < 0.2 & >4.0 excluded	First, last, min, median, max	0.031
LV posterior wall thickness (cm)	Values < 0.1 & >5.0 excluded	First, last, min, median, max	0.016
LV mass (g)	Values < 20 & > 400 excluded	First, last, min, median, max	0.023
Indexed LV mass (g/m^2)	Values < 10 & > 300 excluded	First, last, min, median, max	0.132
LV end-diastolic diameter (cm)	Values < 0 & > 15 excluded	First, last, min, median, max	0.012
LV end-diastolic volume (mL) *	Values <30 & > 1000 excluded	First, last, min, median, max	0.012
LV end-systolic diameter (cm)	Values < 0 & > 10 excluded	First, last, min, median, max	0.200
LV end-systolic volume (mL) *	Values < 5 & > 500 excluded	First, last, min, median, max	0.151
LV ejection fraction (%) *	Values < 10 & > 80 excluded	First, last, min, median, max	0.193
LV fractional shortening (%)	Values < 5 & > 80 excluded	First, last, min, median, max	0.206
LV outflow tract gradient (mmHg)	Values < 0 & > 200 excluded	First, last, min, median, max	0.100
Aortic valve gradient (mmHg)	Values < 0 & > 200 excluded	First, last, min, median, max	0.073
LA dimension (cm)	Values < 1 & > 9.9 excluded	First, last, min, median, max	0.409
LA volume (mL)	Excluded (missingness)		0.617
Indexed LA volume (mL/m^2)	Excluded (missingness)		0.629
E/A	Values < 0 & > 5 excluded	First, last, min, median, max	0.143
Average E/e'	Values < 0 & > 40 excluded	First, last, min, median, max	0.260
Lateral E/e'	Values < 0 & > 40 excluded	First, last, min, median, max	0.252
Septal E/e'	Values < 0 & > 40 excluded	First, last, min, median, max	0.253
MV deceleration time (s)	Values < 0.030 & 0.600 excluded	First, last, min, median, max	0.257
TAPSE (cm)	Values < 1 & > 40 excluded	First, last, min, median, max	0.232

List of the variables (a priori) intended for modelling, showing outlier handling strategies, values taken from longitudinal measurements and missingness. Missingness >0.50 is indicated in red.
* Taken from available methods, in the following order: (i) Modified Simpson, (ii) 3D-methods, (iii) other biplane methods, (iv) Teichholz's/cubed formula.
IVS, interventricular septum; LV, left ventricular; LA, left atrial; MV, mitral valve; TAPSE, tricuspid annular plane systolic excursion.

SUPPLEMENTAL TABLE 2. Genotypes

	All G+ HCM (n = 41)		G+ Echocardiographic LVH (n = 38)		G+ Text mining (n = 35)	
	P	LP	P	LP	P	LP
Definitive						
MYBPC3	22 (56.4) *†		21 (56.8) *†		19 (57.6) *†	
MYH7	4 (11.1)	3 (8.6)	3 (9.1)	3 (9.1)	4 (13.3)	3 (10.3)
TNNT2		1 (2.8)		1 (2.9)		0 (0.0)
TNNI3	1 (2.8)		1 (2.9)		0 (0.0)	
MYL3	1 (2.9)	1 (2.9)	1 (3.0)	1 (3.0)	1 (3.4)	1 (3.4)
MYL2	1 (2.8)		0 (0.0)		1 (3.3)	
GLA (Fabry disease)	2 (5.6)		2 (5.9)		2 (6.7)	
TTR (amyloidosis)	1 (2.7)		1 (2.9)		1 (3.2)	
Moderate						
CSRP3	4 (11.1) *		4 (11.8) *		4 (13.3) *	
ACTN2		2 (5.6) †		2 (5.9) †		1 (3.3) †

Number of patients with pathogenic or likely pathogenic variants (per gene), showing variants identified in the overall study population and in the subpopulations identified by selecting patients with echocardiographic left ventricular hypertrophy or using text mining.
* including one patient with a pathogenic variant in *MYBPC3* and a pathogenic variant in *CSRP3*; † including one patient with a pathogenic variant in *MYBPC3* and a likely pathogenic variant in *ACTN2*.
G+, genetically-confirmed; HCM, hypertrophic cardiomyopathy; P, pathogenic; LP, likely pathogenic; LVH, left ventricular hypertrophy

SUPPLEMENTAL TABLE 3. Baseline characteristics stratified by CTCue

	Identified by CTCue (n = 8,123)	Not identified by CTCue (n = 18,583)	p-value
Demographics			
Sex (male)	4744 (58.4)	10027 (54.0)	**<0.001**
Age (years)	63.43 [50.81, 73.01]	59.86 [45.20, 71.52]	**<0.001**
Body surface area (m^2)	1.93 [1.78, 2.09]	1.91 [1.75, 2.06]	**<0.001**
Systolic blood pressure (mmHg)	132.15 (17.83)	127.42 (17.70)	**<0.001**
Diastolic blood pressure (mmHg)	75.71 (10.77)	73.74 (10.40)	**<0.001**
Electrocardiography			
Atrial rate (bpm)	70.00 [62.00, 81.00]	72.00 [63.00, 85.00]	**<0.001**
Ventricular rate (bpm)	70.00 [62.00, 80.00]	72.00 [63.00, 84.00]	**<0.001**
P axis (°)	54.00 [36.00, 67.00]	54.00 [38.00, 68.00]	**0.01**
R axis (°)	24.00 [-13.00, 58.00]	34.00 [-6.00, 65.00]	**<0.001**
T axis (°)	53.00 [31.00, 75.00]	50.00 [29.00, 71.00]	**<0.001**
PQ interval (ms)	164.00 [146.00, 186.00]	158.00 [140.00, 180.00]	**<0.001**
QRS duration (ms)	98.00 [88.00, 110.00]	96.00 [86.00, 110.00]	**<0.001**
QT interval (ms)	398.00 [376.00, 424.00]	394.00 [368.00, 422.00]	**<0.001**
QTc (Fredericia) (ms)	417.00 [401.75, 439.00]	416.00 [399.00, 440.00]	**0.034**
Echocardiography			
IVS thickness (cm)	1.14 [0.98, 1.32]	1.00 [0.86, 1.14]	**<0.001**
IVS/LV posterior wall ratio	1.14 [1.02, 1.31]	1.07 [0.97, 1.21]	**<0.001**
LV posterior wall thickness (cm)	1.06 [0.92, 1.20]	0.96 [0.84, 1.08]	**<0.001**
LV mass (g)	195.66 [154.39, 246.17]	171.43 [135.78, 218.29]	**<0.001**
Indexed LV mass (g/m^2)	99.82 [81.06, 123.98]	88.10 [72.33, 109.34]	**<0.001**
LV end-diastolic diameter (cm)	4.83 (0.76)	4.97 (0.83)	**<0.001**
LV end-diastolic volume (mL)	106.69 [84.82, 133.81]	111.27 [88.53, 138.11]	**<0.001**
LV end-systolic diameter (cm)	3.12 [2.68, 3.65]	3.17 [2.74, 3.74]	**<0.001**
LV end-systolic volume (mL)	42.49 [29.67, 60.52]	42.39 [30.16, 62.04]	**0.006**
LV ejection fraction (%)	58.81 [50.17, 68.37]	59.86 [49.36, 69.62]	0.137
LV fractional shortening (%)	34.90 [27.25, 41.92]	34.81 [26.67, 41.58]	**0.029**
LV outflow tract gradient (mmHg)	3.60 [2.64, 4.89]	3.55 [2.59, 4.68]	**<0.001**
Aortic valve gradient (mmHg)	6.97 [5.05, 10.90]	6.37 [4.78, 9.03]	**<0.001**
LA dimension (cm)	4.00 [3.56, 4.54]	3.90 [3.45, 4.45]	**<0.001**
E/A	0.95 [0.73, 1.32]	1.07 [0.79, 1.46]	**<0.001**
Average E/e'	8.45 [6.75, 11.21]	7.89 [6.28, 10.51]	**<0.001**
Lateral E/e'	7.22 [5.58, 9.74]	6.72 [5.23, 9.17]	**<0.001**
Septal E/e'	9.62 [7.57, 12.80]	8.96 [7.04, 11.91]	**<0.001**
MV deceleration time (s)	0.19 [0.16, 0.23]	0.18 [0.15, 0.21]	**<0.001**
TAPSE (cm)	2.21 (0.53)	2.19 (0.54)	**0.022**
Outcome criteria			
Left ventricular hypertrophy	4767 (58.7)	7090 (38.2)	**<0.001**
Maximum wall thickness ≥13 mm	2491 (30.7)	2483 (13.4)	**<0.001**
LV mass/BSA >115 (male), >95 (female) g/m^2	4241 (57.0)	6336 (40.2)	**<0.001**
ULVH diagnosis	159 (2.0)	45 (0.2)	**<0.001**
Amyloidosis	37	19	
G+ HCM	35	6	
ICD10	100	26	

Subject characteristics, shown as means (standard deviation), medians [interquartile range] or counts (%), stratified by identification by text mining. P-values <0.05 are shown in bold. IVS, interventricular septum; LV, left ventricular; LA, left atrial; MV; TAPSE, tricuspid annular plane systolic excursion; ICD10, World Health Organization International Statistical Classification of Diseases and Related Health Problems, tenth revision; ULVH:Unexplained Left Ventricular Hypertrophy.

SUPPLEMENTAL TABLE 4. Qualitative assessment of under classification by CTCue

LVH not mentioned	Ambigious writing	Hypertension	Aortic stenosis	LVH clearly mentioned	Notes	Missed, and can be explained logically	Missed, without apparent explanation	HCM diagnosed by cardiologist?
	yes				"duidelijke hypertrofie", but left ventricle not mentioned	yes	no	yes
				yes	hypertrofie linkerventrikel, should not have been missed	no	yes	yes
				yes	"linkerventrikelhypertrofie " should not have been missed	no	yes	yes
				yes		no	yes	yes
yes						yes	no	no
		yes		yes	Restrictive CMP with amyloid and LVH, also essentiele hypertensie	yes	no	no
				yes	hypertensie: nee	no	yes	yes
yes					Cardio file without cardio consultation, no mention of LVH	yes	no	no
						no	yes	yes
				yes		yes	no	yes
		yes			First controls: geen HOCM, but developed it later on	yes	no	yes
		yes	yes		No HCM but explained LVH	yes	no	no
				yes	geringe LVH, hypertensie: nee	no	yes	yes
				yes	linker ventrikelhypertrofie	no	yes	yes
	yes				belangrijke hypertrofie	no	yes	yes
	yes				concentrische hypertrofie van de linkerventrikelwand	yes	no	yes
		yes		yes	HCM	yes	no	yes
				yes	HOCM	no	yes	yes
				yes	HCM	no	yes	yes
				yes	hypertrophische cardiomyopathiemutatie and LVH mentioned in letters	no	yes	yes
				yes	HCM	no	yes	yes
				yes	hypertrofische cardiomyopathie	no	yes	yes
				yes	hypertrofische cardiomyopathie	no	yes	yes
	yes				AL amyloidose met RCM "en wanden vrij fors zijn"	yes	no	no
				yes	hypertrofische cardiomyopathie	no	yes	yes
				yes	HCM	no	yes	yes
		yes	yes	yes	"lichte hypertrofie"	no	yes	yes
				yes	LVH	no	yes	no
		yes		yes	hypertrofe cardiomyopathie; pulmonale hypertensie	yes	yes	yes
				yes	hypertrofische obstructieve cardiomyopathie	no	yes	yes
	yes				biventriculaire hypertrofie	no	yes	yes
		yes		yes	linker ventrikel hypertrofie	no	yes	yes
		yes		yes	HCM and hypertension	no	yes	yes
no					restrictieve cmp met geringe deel hypertrofie	no	yes	no
				yes	beginnende LVH	no	yes	yes
		yes		yes	hypertensie not negated in text	yes	no	yes
				yes	hypertrofe obstructieve cardiomyopathie	no	yes	yes
				yes	hypertrofische cardiomyopathie	no	yes	yes
				yes	hcm	no	yes	yes
	yes				hypertrofische biventriculaire cardiomyopathie	yes	no	yes
		yes		yes	pulmonale hypertensie; toont duidelijke LVH	no	yes	yes
		yes		yes	pulmonale hypertensie	yes	no	yes
				yes	hypertensieve CMP	yes	no	no
				yes	hypertrofische cardiomyopathie	yes	no	yes
		yes		yes	hypertrofische cardiomyopathie	yes	no	yes

SUPPLEMENTAL TABLE 5. Baseline characteristics stratified by left ventricular hypertrophy

	Left ventricular hypertrophy (n = 11857)	No left ventricular hypertrophy (n = 14849)	p-value
Demographics			
Sex (male)	7841 (66.1)	6930 (46.7)	**<0.001**
Age (years)	66.30 [54.35, 75.35]	56.29 [41.03, 68.34]	**<0.001**
Body surface area (m^2)	1.94 [1.79, 2.09]	1.88 [1.74, 2.04]	**<0.001**
Systolic blood pressure (mmHg)	129.72 (18.46)	128.42 (17.32)	**<0.001**
Diastolic blood pressure (mmHg)	74.18 (10.79)	74.63 (10.36)	**0.003**
Electrocardiography			
Atrial rate (bpm)	72.00 [62.00, 85.00]	72.00 [63.00, 84.00]	0.134
Ventricular rate (bpm)	71.00 [62.00, 83.00]	71.00 [63.00, 83.00]	0.633
P axis (°)	54.00 [35.00, 68.00]	55.00 [38.00, 67.00]	0.098
R axis (°)	17.00 [-22.00, 57.00]	40.00 [4.00, 66.00]	**<0.001**
T axis (°)	56.00 [29.00, 89.00]	48.00 [30.00, 65.00]	**<0.001**
PQ interval (ms)	166.00 [146.00, 190.00]	154.00 [138.00, 174.00]	**<0.001**
QRS duration (ms)	102.00 [92.00, 128.00]	92.00 [84.00, 102.00]	**<0.001**
QT interval (ms)	404.00 [378.00, 436.00]	390.00 [366.00, 414.00]	**<0.001**
QTc (Fredericia) (ms)	425.00 [406.00, 454.00]	411.00 [396.00, 429.00]	**<0.001**
Echocardiography			
IVS thickness (cm)	1.20 [1.05, 1.38]	0.93 [0.82, 1.04]	**<0.001**
IVS/LV posterior wall ratio	1.15 [1.02, 1.32]	1.05 [0.96, 1.18]	**<0.001**
LV posterior wall thickness (cm)	1.11 [0.99, 1.25]	0.90 [0.80, 1.00]	**<0.001**
LV mass (g)	229.74 [198.44, 274.01]	145.78 [121.43, 171.08]	**<0.001**
Indexed LV mass (g/m^2)	115.55 [102.54, 136.77]	75.63 [65.10, 84.90]	**<0.001**
LV end-diastolic diameter (cm)	5.18 (0.94)	4.72 (0.63)	**<0.001**
LV end-diastolic volume (mL)	123.63 [95.20, 156.26]	102.16 [83.59, 123.08]	**<0.001**
LV end-systolic diameter (cm)	3.43 [2.89, 4.18]	3.00 [2.62, 3.40]	**<0.001**
LV end-systolic volume (mL)	51.17 [34.76, 79.80]	37.47 [27.34, 50.23]	**<0.001**
LV ejection fraction (%)	55.78 [42.91, 66.99]	62.02 [54.12, 70.62]	**<0.001**
LV fractional shortening (%)	32.54 [22.62, 40.76]	36.17 [29.91, 42.32]	**<0.001**
LV outflow tract gradient (mmHg)	4.09 [2.98, 5.65]	3.97 [3.02, 5.16]	**<0.001**
Aortic valve gradient (mmHg)	8.06 [5.68, 14.27]	6.55 [5.02, 8.85]	**<0.001**
LA dimension (cm)	4.23 [3.78, 4.82]	3.69 [3.30, 4.11]	**<0.001**
E/A	0.96 [0.71, 1.37]	1.08 [0.81, 1.44]	**<0.001**
Average E/e'	9.23 [7.09, 12.69]	7.44 [6.03, 9.32]	**<0.001**
Lateral E/e'	7.79 [5.85, 10.92]	6.35 [5.05, 8.20]	**<0.001**
Septal E/e'	10.44 [7.97, 14.57]	8.39 [6.76, 10.63]	**<0.001**
MV deceleration time (s)	0.19 [0.15, 0.23]	0.18 [0.15, 0.21]	**<0.001**
TAPSE (cm)	2.12 (0.57)	2.27 (0.51)	**<0.001**
Outcome criteria			
Identified by CTCue population finder	4767 (40.2)	3356 (22.6)	**<0.001**
ULVH diagnosis	193 (1.6)	11 (0.1)	**<0.001**
Amyloidosis	53	3	
G+ HCM	38	3	
ICD10	121	5	

Subject characteristics, shown as means (standard deviation), medians [interquartile range] or counts (%), stratified by presence of echocardiographic left ventricular hypertrophy (maximum wall thickness of >12 mm or a left ventricular mass indexed to body surface area >115 in males and >95 in females). P-values <0.05 are shown in bold. IVS, interventricular septum; LV, left ventricular; LA, left atrial; MV; TAPSE, tricuspid annular plane systolic excursion; ICD10, World Health Organization International Statistical Classification of Diseases and Related Health Problems, tenth revision.

SUPPLEMENTAL TABLE 6. Performance measures XGBoost

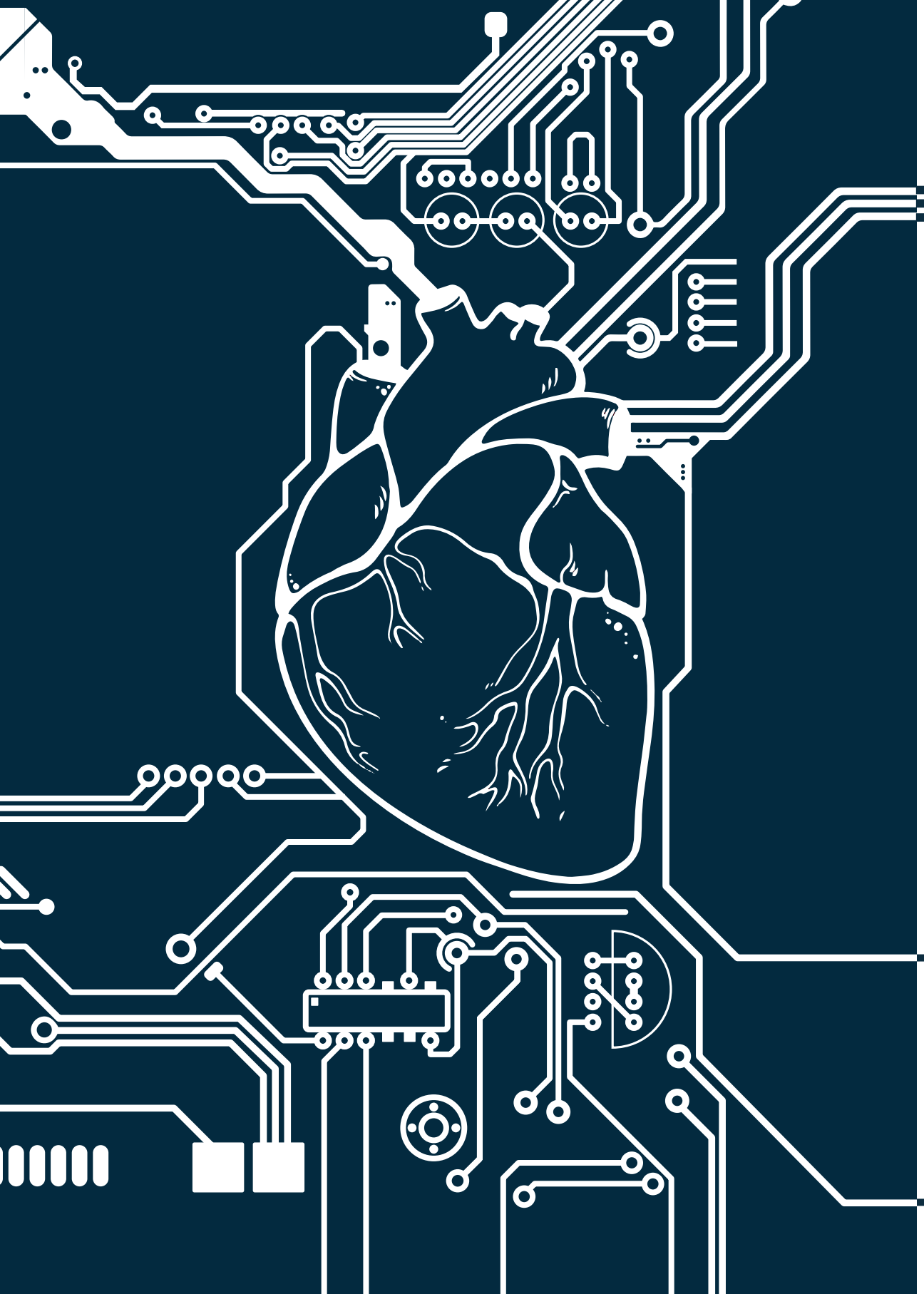
	Echocardiographic LVH (n = 2,456)	Echocardiographic LVH (text mining as variable) (n = 2,456)	Text mining (n = 1,637)
Before manual review			
Sensitivity	0.2564	0.1795	0.1290
Specificity	0.9979	0.9979	0.9988
Positive predictive value	0.6667	0.5833	0.6667
Negative predictive value	0.9881	0.9869	0.9834
Likelihood ratio +	26	18	13
Likelihood ratio -	0.75	0.83	0.88
After manual review			
Sensitivity	0.32		
Specificity	0.99		
Positive predictive value	0.72		
Negative predictive value	0.99		
Likelihood ratio +	32		
Likelihood ratio -	0.69		

Performance of the three hypertuned XGBoost models on the holdout set (20% of total subjects identified through each method), before and after reclassification by manual review. LVH, left ventricular hypertrophy.

SUPPLEMENTAL TABLE 7. Performance measures Lasso regression

	Coefficients without text mining variable	Coefficients with text mining variable
Intercept	-10.2	-12.5
Age (years)	-0.0212	-0.0186
Systolic blood pressure (mmHg), max	-0.0157	-0.0165
Systolic blood pressure (mmHg), mean	-0.0117	-0.0151
P axis (°), last	-1.64E-04	-
T axis (°), first	2.17E-03	2.30E-03
T axis (°), last	3.03E-03	3.67E-03
PQ interval (ms), median	2.76E-03	2.24E-03
QT interval (ms), median	0.0118	0.0103
QTC Fredericia (ms), last	1.50E-03	3.17E-03
P area II, max	-	2.54E-06
P area II, median	4.04E-04	4.24E-04
Q amplitude aVL, max	5.73E-05	1.02E-04
R amplitude aVL, median	-2.25E-04	-3.11E-04
R amplitude I, first	2.07E-04	2.02E-04
R amplitude V6, first	-4.10E-04	-4.18E-04
S amplitude V3, first	-5.76E-05	-9.40E-05
T amplitude aVL, last	-2.35E-04	-2.30E-04
T amplitude aVL, median	-4.89E-04	-3.03E-04
T amplitude V5, first	-5.05E-04	-5.29E-04
T amplitude V5, median	-6.49E-04	-4.54E-04
IVS thickness (cm), first	0.274	0.472
IVS thickness (cm), max	1.02	0.768
IVS thickness (cm), median	0.816	0.699
LV posterior wall thickness (cm), first	0.556	0.259
LV posterior wall thickness (cm), max	1.04	0.705
LV posterior wall thickness (cm), median	0.152	0.903
LV end-diastolic diameter, median	-8.05E-03	-
LV end-diastolic volume (mL), max	-	-2.51E-03
LV end-diastolic volume (mL), median	-5.21E-03	-2.25E-03
LV end-systolic volume (mL), first	-7.33E-03	-5.66E-03
LVOT pressure gradient (mmHg), first	7.41E-03	0.0103
LVOT pressure gradient (mmHg), median	1.86E-03	2.60E-03
Aortic pressure gradient (mmHg), median	-0.0351	-0.0381
LA diameter (cm), max	0.187	0.225
E/A, max	0.292	0.305
E/e' average, max	7.24E-03	0.0129
E/e' lateral, median	9.83E-03	0.0121
E/e' septal, max	0.0309	0.0297
MV deceleration time (ms), min	-0.386	-0.814
Identified by text mining	-	1.60

Coefficients of the logistic Lasso regression fitted to the train data of the subjects with echocardiographic left ventricular hypertrophy (n = 9,825). Coefficients correspond to each unit increase of variable. The Lasso logistic regression fitted on the subjects with echocardiographic LVH (best lambda = 0.001) using the top 50 XGBoost variables correctly identified 6 out of 39 subjects with and 2,412 out of 2,417 subjects without ULVH (sensitivity 0.154, specificity 0.998, PPV 0.545, NPV 0.987). Inclusion of text mining as a variable (best lambda = 0.001) slightly decreased performance, correctly identifying the same numbers of subjects with ULVH but misclassifying one additional subject without ULVH (2411 out of 2417; specificity 0.998, PPV 0.500).



CHAPTER 9

Life-threatening ventricular arrhythmia prediction in patients with dilated cardiomyopathy using explainable electrocardiogram-based deep neural networks

A Sammani*, R.R. van de Leur*, M.T.H.M. Henkens, M. Meine, K.P. Loh, R.J. Hassink, DL. Oberski, S.R.B. Heymans, PA. Doevendans, F.W. Asselbergs, A.S.J.M. te Riele§, R. van Es§

- submitted

* Contributed equally as first authors, § Contributed equally as last authors

ABSTRACT

Aims

While electrocardiogram (ECG) characteristics have been associated with life-threatening ventricular arrhythmias (LTVA) in dilated cardiomyopathy (DCM), they typically rely on human derived parameters. Deep neural networks (DNN) can discover complex ECG patterns, but interpretation is hampered by their 'black-box' characteristics. We aimed to detect DCM patients at risk of LTVA using an inherently explainable DNN.

Methods and Results

In this two-phase study we first developed a variational auto encoder DNN on more than 1 million 12-lead median beat ECGs, compressing the ECG into 21 different factors (F): factorECG. Next, we used two cohorts with a combined total of 695 DCM patients and entered these factors in a Cox regression for the composite LTVA outcome, which was defined as sudden cardiac arrest, spontaneous sustained ventricular tachycardia, or implantable cardioverter-defibrillator treated ventricular arrhythmia. Most patients were male (n=442, 64%) with a median age of 54 years [interquartile range (IQR) 44-62], and median left ventricular ejection fraction of 30% [IQR 23-39]. A total of 115 patients (16.5%) reached the study outcome. Factors F_8 (prolonged PR-interval and P-wave duration, $p < 0.005$), F_{15} (reduced P-wave height, $p = 0.04$), F_{25} (increased right bundle branch delay, $p = 0.02$), F_{27} (P-wave axis $p < 0.005$) and F_{32} (reduced QRS-T voltages $p = 0.03$) were significantly associated with LTVA.

Conclusion

Inherently explainable DNNs can detect patients at risk of LTVA which is mainly driven by P-wave abnormalities.

INTRODUCTION

Patients with non-ischaemic dilated cardiomyopathy (DCM) have an estimated annual risk of life-threatening ventricular arrhythmias (LVTAs) of 4.5% and may potentially benefit from implantable cardioverter-defibrillator (ICD) implantation.[1,2] A novel risk model (DCM-SVA risk) for predicting LTVA was recently published and includes easily accessible clinical parameters, such as history of non-sustained ventricular tachycardia (VT), QRS duration and left ventricular ejection fraction (LVEF).[3] More complex electrocardiogram (ECG) characteristics such as fragmented QRS waves, heart rate variability and t-wave alternans have also been associated with LTVA, but rely on manually derived ECG parameters that remain difficult to standardize, hampering their integration into daily clinical practice.[2,4] By using raw ECG signals and machine learning techniques, manual feature extraction is not necessary, and novel, more subtle parameters may be detected.[5]

Deep neural networks (DNN) have proven to be potent machine learning algorithms for diagnostic classification tasks using raw ECGs signals. Previous studies using DNNs on raw ECG signals in cardiomyopathies report high performance in disease classification and triaging.[6–9] However, because of the inherent lack of "explainability" of DNNs, clinical implementation remains limited.[10] Different techniques may assist in interpreting DNNs. A recently introduced pipeline for fully explainable DNNs for ECG analysis uses variational auto-encoders (VAE)[11,12], that can compress the ECG into a lower number of explanatory and independent generative factors (factorECG), which can subsequently be used in interpretable algorithms (such as Cox regression).[9]

In this study, we aimed (i) use an inherently interpretable DNN for predicting potentially LTVA based on ECGs in patients with non-ischemic DCM, assess its added value above conventional ECG parameters and current guidelines, and (ii) interpret the model by visualizing pivotal ECG features.

METHODS

Study Design

This was a two-phase study with a pre-training step, followed by a training step. In the pre-training phase, we first developed a VAE DNN (factorECG) on ECGs of patients from the University Medical Centre (UMCU). Next, the results of the factorECG were entered in an interpretable statistical model (Cox-regression), for patients with DCM from two different centres: UMCU and Maastricht University Medical Centre (MUMC+) for the outcome of LTVA. The complete pipeline is illustrated in figure 1.

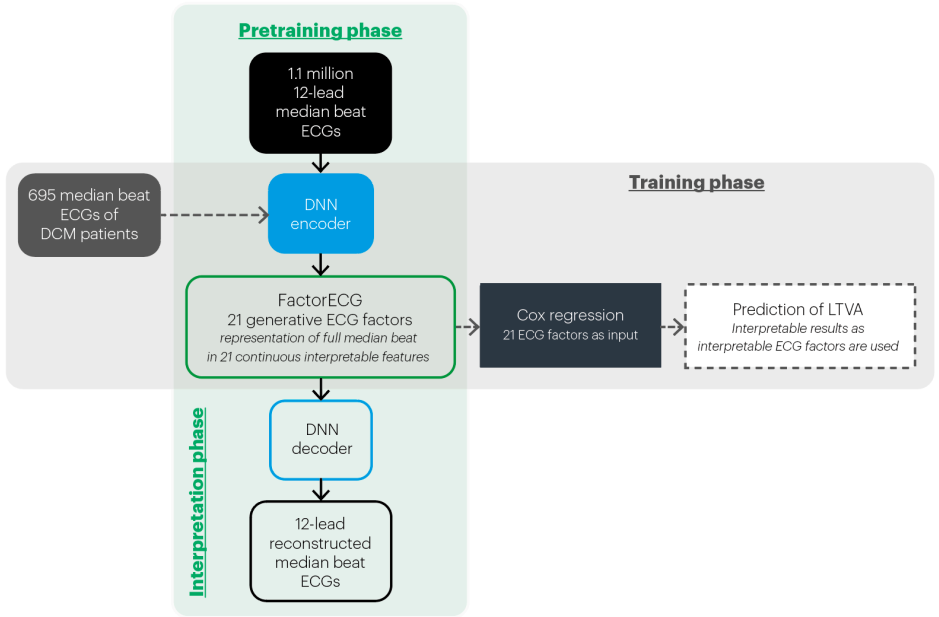


FIGURE 1. General training architecture of the VAE model and generative factors
The general architecture of the Variational Auto Encoder (VAE) is depicted here. In the pre-training phase, 1.1 million 12-lead median beat ECGs were included in the training of the VAE. The VAE network is enforced with a specific function to reach maximum disentanglement of lower-dimensional representation (i.e. to produce generative factors in the ECG that operate independently). Of the 695 patients, median beat ECGs were encoded into 21 generative factors, that were used as an input in an explainable statistical model: Cox regression. These factors were used for both prediction of life-threatening ventricular arrhythmias and reconstructions of these factors were used for interpretation.

Variational auto encoder

VAEs are unsupervised deep learning encoder-decoder convolutional neural networks that are optimized to reconstruct their training data with a lower-dimensional representation (i.e., using less data) than the original training data (in this case ECGs). The VAE network is enforced with a specific function to reach maximum disentanglement of lower-dimensional representation (i.e., to produce generative factors in the ECG that operate independently: factorECG).[11] Resting 12-lead 10-second ECGs of 251,473 unique patients (1,114,331 ECGs) were exported from the UMCU ECG system and trained in an encoder-decoder convolutional DNN architecture. In a prior study, the optimal number of dimensions was set to 21, considering the trade-off of good reconstruction disentanglement and encoding for visible ECG abnormalities.*(van de Leur et al, submitted)* Visualisation of these individual dimensions was obtained by varying their values while reconstructing median beat ECGs. By starting every visualization with zeros for all representations, a mean ECG was reconstructed (as the embedding space was forced to be a Gaussian distribution with zero mean and standard deviation of one). Then, for every individual representation, values between -5 and 5 were assigned, while keeping others at zero. The architecture and model training process were implemented using PyTorch (version 1.7.0+cu110) in Python (version 3.6.7). All training was performed using an NVIDIA Xp GPU.

DCM Subject inclusion

In the training phase, we included consecutive adult patients with DCM as defined by the European Society of Cardiology (ESC) guidelines if a baseline non-paced 12-lead ECG was available before Left Ventricular Assist Device (LVAD) implantation or Heart Transplantation (HTx) from the UMCU and MUMC+.[1] Patients that opted-out for research were excluded. Patients with a cardiac resynchronisation therapy (CRT) were also excluded, as it positively affects reverse remodelling which may reduce arrhythmias.[13] This study was conducted in accordance with the principles laid out in the Declaration of Helsinki and in line with guidelines provided by ethics committees and national GDPR legislature. The UMCU cohort was exempt from the Medical Research Involving Human Subjects Act (WMO) as per judgement of the Medical Ethics Committee (18/446 and 19/222 UMCU, the Netherlands) including the requirement for informed consent. The participants of the Maastricht cohort signed informed consent at enrolment.

Outcome definitions

The primary study outcome was LTVA with similar definitions to a prior study, defined as the composite outcome of sustained ventricular tachycardia (VT) >100 bpm lasting >30sec or with hemodynamic compromise, ventricular fibrillation (VF), sudden cardiac death (SCD) or appropriate ICD therapy.[3]

Data acquisition

For all subjects, the ECG closest to the date of diagnosis was obtained, which was considered “baseline” for the purpose of this study. All ECGs were exported from the MUSE ECG system (version 8; GE Healthcare, Chicago, IL, USA) in raw voltage format. The recordings were made using a General Electric MAC V, 5000 or 5500 device and acquired

at either 250 or 500 Hz. Resampling to 500 Hz was performed via linear interpolation and transformation into 1.2-second median beats was achieved by aligning all QRS-complexes of the same shape (e.g., excluding premature ventricular complexes) and taking the median voltage to generate a representative P-QRS-T complex. Echocardiographic measurements were extracted from the electronic health record using methods described before.[14]

Statistical analyses

For interpretability of FactorECG, each baseline ECG's generative factors (as computed by the VAE encoder) were included in a Cox proportional hazards model (Figure 1). The proportional hazards assumption was tested. Hazard Ratio's (HR) were reported, and 95% confidence intervals were computed using 2000 bootstrap samples. To rule out that the VAE model was solely considering already established ECG characteristics (ventricular rate, PR-interval, P-wave duration, QRS-duration and Bazett corrected QT-interval), a baseline Cox proportional hazard model was also fitted using these variables in a complete case analysis. The correlations of the significant ECG factors were plotted against the left atrial (LA) dimension and left atrial volume index (LAVI) measured on standard care clinical echocardiography using both the first (closest to baseline) and last (closest to follow-up) available measurements.[13] Additionally a Kaplan Meier curve was plotted for one of the significant VAE generative factors. These analyses were performed using Python (version 3.8.5).

RESULTS

Patient characteristics

Baseline characteristics stratified by centre and outcome are depicted in Table 1. A total of 695 patients were included from the UMCU and MUMC+, which were predominantly male (n=442, 64%) with a median age of 54 years [interquartile range (IQR) 44-62] and median LVEF of 30% [IQR 23%-39%]. A total of 115 (17%) reached the study outcome. In summary, patients from the MUMC+ cohort had less severe symptoms at baseline with primarily New York Heart Association classes I and II as opposed to the UMCU cohort with primarily II and III, and a median LVEF of 33% [IQR 25-40]. During a median follow-up of 4.3 years [IQR 2.0 – 7.5], a lower proportion of MUMC+ patients (25, 6%) reached the study outcome of LTVA compared to 90 (28%) UMCU patients.

TABLE 1. Patient characteristics at baseline (first evaluation) stratified by centre and outcome

	UMCU all (n=317)	UMCU without LTVA (n=227)	UMCU with LTVA (n=90)	MUMC all (n=378)	MUMC without LTVA (353)	MUMC with LTVA (25)
Age, median [Q1-Q3]	52 [42 – 61]	51 [41 – 60]	52 [42-62]	55 [47 – 63]	56 [47-63]	54 [49-63]
Male Sex	195 (62%)	129 (57%)	66 (74%)	247 (65%)	228 (65%)	19 (76%)
NYHA-class						
I	53 (17%)	36 (16%)	17 (19%)	158 (42%)	150 (43%)	8 (32%)
II	102 (32%)	71 (31%)	31 (19%)	175 (46%)	163 (47%)	12 (48%)
III	79 (25%)	56 (25%)	23 (26%)	37 (10%)	32 (9%)	5 (20%)
IV	27 (9%)	36 (16%)	4 (4%)	8 (2%)	8 (2%)	0 (0)%
Diabetes (I and II)	42 (13%)	31 (13%)	11 (12%)	52 (14%)	50 (14%)	2 (8%)
Hypercholesterolemia	37 (13%)	26 (13%)	11 (13%)	41 (11%)	38 (11%)	3 (12%)
(Ever) smoked	203 (64%)	145 (64%)	57 (63%)	77 (20%)	72 (20%)	5 (20%)
Alcohol abuse	19 (6%)	14 (6%)	5 (6%)	n/a	n/a	n/a
History of LTVA	42 (13%)	17 (7%)	25 (27%)	8 (2%)	7 (2%)	1 (4%)
Family history of DCM	133 (42%)	97 (43%)	36 (40%)	47 (14%)	39 (11%)	8 (32%)
ICD implantation	233 (74%)	145 (63%)	88 (97%)	0 (0%)	0 (0%)	0 (0%)
LVEF, median [Q1-Q3]	25% [20%-33%]	25% [20%-33%]	25% [20%-33%]	33% [25-40%]	28 [22-37]	33 [25-41]
MRI LGE	84 (56%**)	60 (51%*)	24 (71%**)	n/a	n/a	n/a

Baseline characteristics of the included cohorts. NYHA = New York Heart Association; LTVA = Life Threatening Ventricular Arrhythmia; ICD = Implantable Cardioverter-Defibrillator; LVEF = Left Ventricular ejection fraction; MRI LGE = Magnetic Resonance Imaging Late Gadolinium Enhancement. ** = of valid, in patients with cardiac MRIs.

Prediction of LTVA with established ECG variables

Established ECG variables (such as ventricular rate, PR-interval, QRS-duration, and QTc-time) were entered in a "baseline" cox-regression model (complete case analysis (n = 577), excluding patients without a measurable PR-interval (n = 118). This baseline model had a low C-statistic of 0.59 and no significant effects of: ventricular rate (HR 1.00; 95%CI[0.98-1.01], *p = 0.61)*, QRS-duration (HR 1.01; 95%CI[1.00-1.02], *p=0.10)* and QTc-time (HR 1.00; 95%CI[0.99-1.00], *p = 0.24*). The PR-interval was however significantly associated with LTVA (HR 1.01;

95%CI[1.00-1.02], *p = 0.01*) The results of this model were depicted in supplementary table 2.

Prediction of LTVA with FactorECG

The VAE compressed the ECG data into 21 different ECG factors and their reconstructions are available in supplementary figure 1. In Cox-regression, F_8 (HR 1.60; 95%CI [1.29-1.99], *p < 0.005*), F_{15} (HR 0.81; 95%CI [0.66-0.99], *p = 0.04*), F_{25} (HR 0.77 95%CI [0.62 – 0.95], *p = 0.02*), F_{27} (HR 0.71, 95%CI[0.57–0.88], *p < 0.005*) and F_{32} (HR 1.26, 95%CI [1.03–1.55], *p = 0.03)* were significantly associated with the outcome after correcting for guideline indication (NYHA II/III and LVEF < 35%, *p = 0.84*). A reconstruction of the significant generative factors (F_8, F_{15}, F_{25}, F_{27} and F_{32}) has been illustrated in figure 2. F_8 encodes for PR-interval and P-wave morphology, where high values increase PR-interval and broaden the P-wave. F_{15} encodes for P-wave height and P/T-overlap, where low values are correlated with atrial fibrillation and third-degree AV-block. F_{25} encodes for conduction delays in the right bundle (right bundle branch block), where low values increase the block. F_{27} encodes for P- and R- axis deviation, where low values flatten out the P-wave. F_{32} encodes for QRS-T amplitudes, with low values reconstruct QRS-T microvoltages. Results of the Cox-regression model and the descriptions of the generative factors are present in Table 2 and supplementary table 1. The partial effects on outcome per significant factor have been plotted in supplementary figure 2. As an example, the ECGs and their corresponding values of the generative factors of two patients were plotted in figure 3. A summary figure of this study was depicted in figure 4.

TABLE 2. Cox proportional hazards model of generative factors in both cohorts

Factors	Factor descriptions	Hazard Ratio	95% Confidence Interval	P-value
F_1	Inferolateral ST deviation	0.91	0.72-1.14	*0.39*
F_5	Inferolateral T-wave height and orientation	1.17	0.92-1.48	*0.19*
F_6	P-wave height and/or shape	1.14	0.90-1.44	*0.27*
F_8*	PR-interval *(high values associated with first degree AV-block and reduced LVEF)*	1.61	1.29-1.99	*<0.005*
F_9	T-wave height and orientation	1.12	0.89-1.39	*0.34*
F_{10}	Ventricular rate	0.93	0.76-1.13	*0.46*
F_{11}	Subtle P- and T-wave changes	1.00	0.83-1.21	*0.97*
F_{12}	Onset of depolarisation	1.08	0.86-1.36	*0.50*
F_{13}	Anterior ST deviation	0.85	0.68-1.06	*0.14*
F_{15}*	P-wave height and P/T-overlap (*low values associated with third degree AV-block and junctional tachycardia)*	0.81	0.66-0.99	*0.04*
F_{16}	T-wave morphology	1.14	0.94-1.40	*0.19*
F_{17}	Lateral ST-deviation	1.08	0.85-1.38	*0.51*
F_{19}	Precordial R-wave progression and combined P-QRS-T-amplitude	1.07	0.87-1.33	*0.51*
F_{22}	Subtle T-wave changes	1.02	0.83-1.25	*0.85*
F_{23}	P-wave height and/or shape	1.13	0.93-1.37	*0.21*
F_{25}*	Right bundle branch delay *(low values associated with ventricular tachycardia, RBBB and reduced LVEF)*	0.77	0.62-0.95	*0.02*
F_{26}	Left bundle branch delay	1.02	0.81-1.29	*0.85*
F_{27}*	P- and R- axis deviation *(low values associated with AF, junctional bradycardia, ventricular tachycardia, and left axis deviation)*	0.71	0.57-0.88	*<0.005*
F_{30}	QR interval	0.92	0.74-1.16	*0.48*
F_{31}	QRS-T amplitudes	0.86	0.71-1.05	*0.15*
F_{32}*	QRS-T amplitudes *(high values associated with microvoltages)*	1.26	1.02-1.55	*0.03*

Results of Cox-regression and explanation of (significant) factors including their association with known electrocardiographic and echocardiographic pathologies as described in Van de Leur et al
*significant

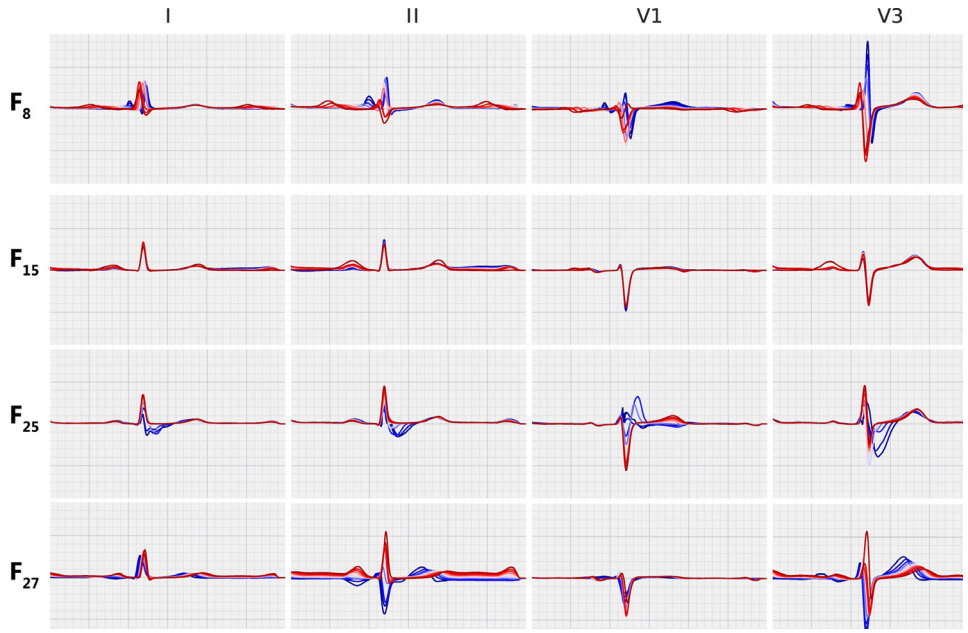
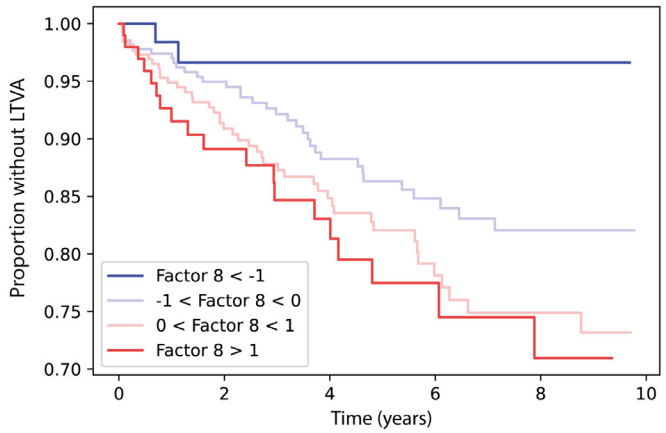


FIGURE 2. Reconstructions of the generative factors significant in Cox regression
The reconstructions of a standard ECG were made, depicting leads I, II, V1, V3 and V6. The values for each of the significant factors were set between -5 and +5 whilst all others were 0.

LA dimensions

To investigate the possibility that the identified factors were an effect of anatomical substrates of P-wave abnormalities, such as atrial remodelling, first and last LAVI and LA dimensions (by outcome) of complete UMCU cases (n = 219) were plotted (supplementary figures 4, 5, 6 and 7 respectively). LA's were significantly larger in the last echocardiography, compared to the first (p = 0.02, supplement figure 6). Next, the LA dimensions were plotted to these factors (supplement figure 8) which showed no association between F_8, F_{15}, F_{25}, F_{27} and F_{32} and LA dimensions.

A



B

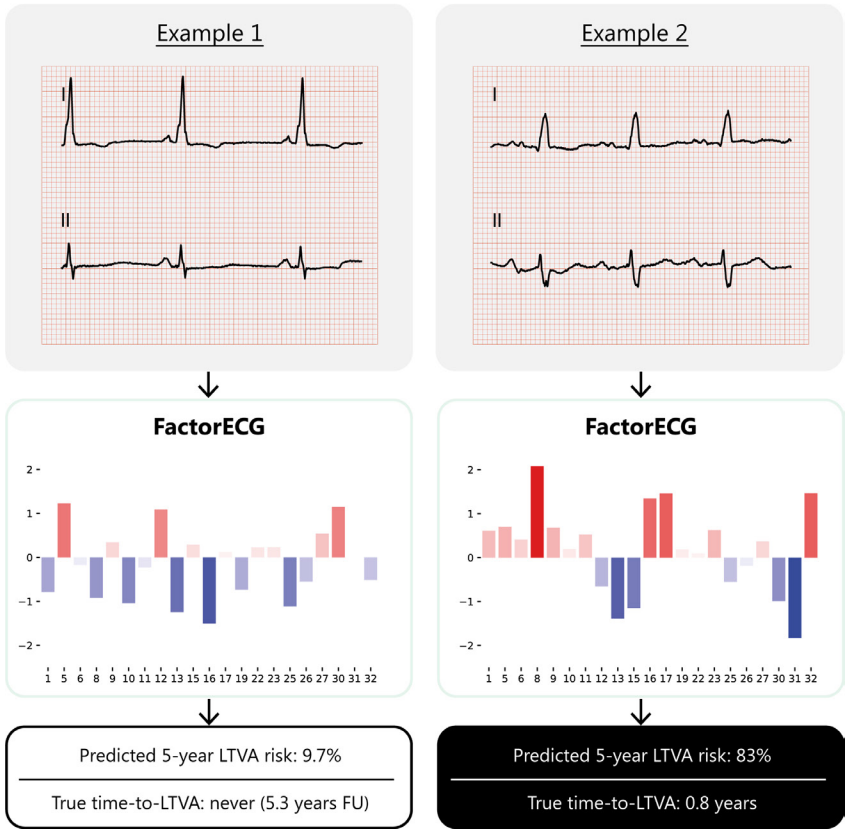


FIGURE 3. Two examples of ECGs with and their generative factor values
A Kaplan Meier (A) for factor 8 and (B) two examples with a low and high predicted five-year LTVA risk were depicted. The example on the left had a low predicted risk of LTVA and did not reach the endpoint. Factor 8 was low, which causes the short PR duration and P-wave length. The example on the right had a high predicted risk of LTVA and reached the outcome, for which factor 8 is highly positive. In the ECG we see a broad P wave with a long PR interval.

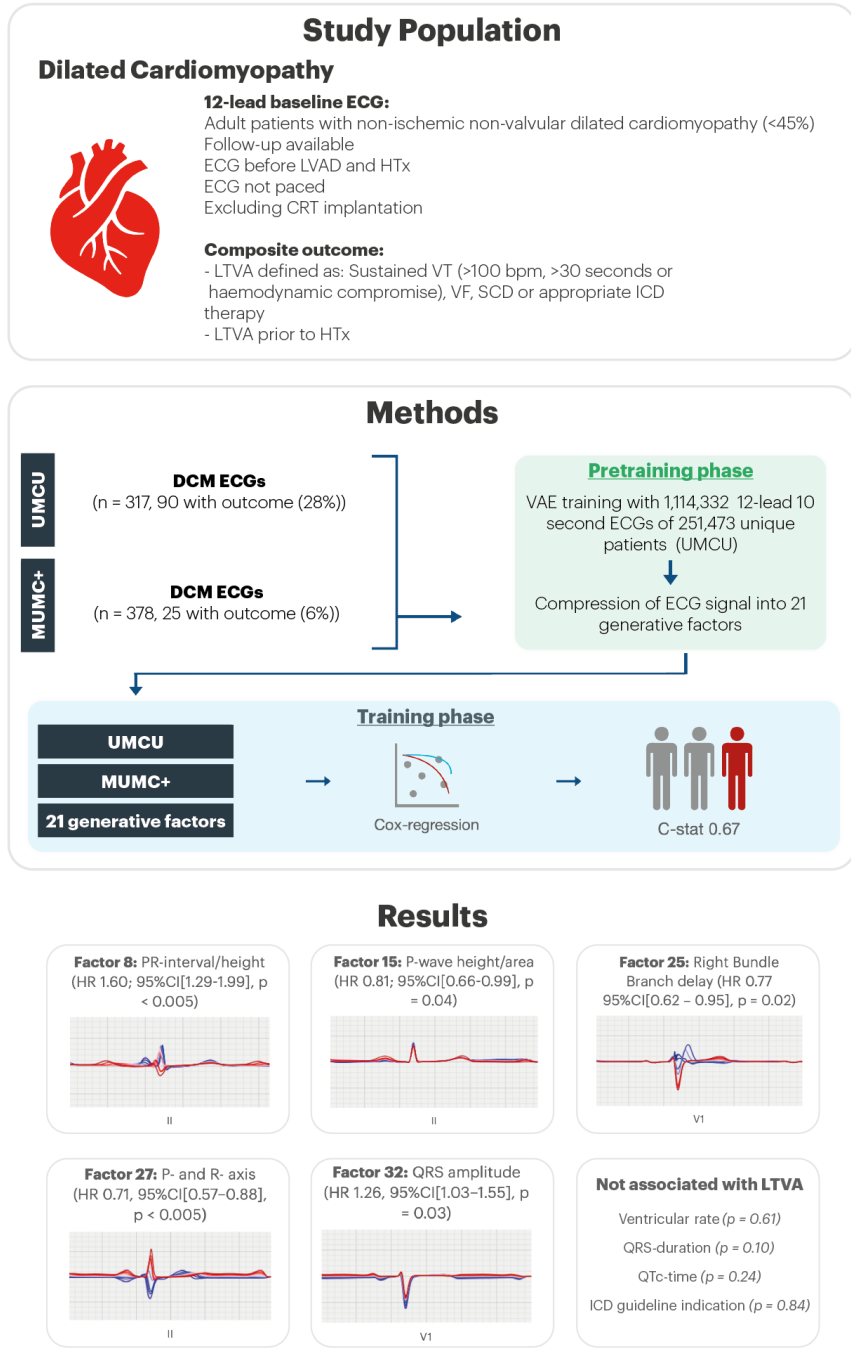


FIGURE 4. Summary figure
Study summary figure, including the methods and results. LVAD = Left Ventricular Assist Device. HTx = Heart Transplantation, CRT = Cardiac Resynchronisation Therapy. ECG = electrocardiogram. VT = Ventricular Tachycardia. VF = Ventricular Fibrillation. SCD = Sudden Cardiac Death. ICD = Implantable Cardioverter-Defibrillator. HR = Hazard Ratio. UMCU = University Medical Centre Utrecht. MUMC+ = Maastricht University Medical Centre.

DISCUSSION

This is the first study to use DNNs trained with (baseline) ECGs for LTVA prediction in DCM patients on a multicentre dataset. By using an inherently explainable DNN architecture, we were able to distinguish patients at risk for LTVA whilst allowing interpretation and visualisation of pivotal ECG features.[10] The model was able to identify patients at highest risk with a predominant network focus on P-wave abnormalities. Furthermore, these identified P-wave abnormalities did not correlate to their anatomical analogues (LA dimension/LAVI), suggesting an electrophysiological substrate.

Prior studies

There is emerging evidence suggesting that risk stratification for LTVA in DCM is a viable strategy using easily accessible clinical markers, such as LVEF, QRS duration and late gadolinium enhancement on magnetic resonance imaging.[2–4,15,16] The use of more complex ECG markers (fragmented QRS waves, heart rate variability and t-wave alternans) however is withheld by measuring and standardization difficulties which may be assisted by (automatic) interpretation using DNNs.[2,4,17,18] As these networks are generally "black-box" algorithms that need very large datasets for training, a strategy of reducing the ECG into its generative factors was used. These interpretable factors were then used in a common statistical model (Cox regression), that allowed for pivotal ECG features to be visualized.

DNN Findings

The FactorECG encompasses the entire ECG including all its features. This novel strategy allows to simultaneously evaluate all characteristics that make up an ECG, rather than using solely human derived ECG features. Nonetheless, the factors that were most predictive for LTVA primarily encoded for several P-wave characteristics, such as PR-duration, P-wave morphology, and P-wave axis (figure 2). The combination of reconstructed ECGs together with the hazard ratios allow for a novel in-depth interpretation of a DNN's features. A high value in F_8 for instance, leads to PR-prolongation with a broadened P-wave, whereas a low value in F_{27} leads to removal of the P-wave, which is associated with atrial fibrillation, a known clinical risk factor for LTVA in DCM.[3] Because the baseline model using established ECG variables performed poorly, this indicated that the VAE generative factors are more complex than solely the standard ECG intervals. The combination of the 21 generative factors as well as their interpretation allow for LTVA prediction and feature detection (figure 3).

The fact that atrial (i.e. P-wave) abnormalities predict ventricular events (i.e. LTVA) may be considered remarkable. However, this association has been described before, and has been thought to be due to shared mechanistic pathologies between atria and ventricles, such as ion-channel abnormalities, or atrioventricular fibrosis due to atrial remodelling.[2,3,19,20] In a recently published population study of 13580 participants, abnormal P-wave indices were independently associated with LTVA, after adjustment for age, sex, race and study centre.[21] As it is likely that these P-wave indices are caused by atrial remodelling, we investigated the association of anatomical LA characteristics and our identified ECG factors. As expected, LA dimensions increased significantly over time, indicating disease progression. However, we did not find any association to the significant ECG factors, suggesting an exclusive electrophysiological substrate. This is in line with other studies, in which individual ECG P-wave changes were not reliable predictors of anatomic atrial enlargement.[22,23] Future studies are warranted to prospectively validate the identified ECG abnormalities and their electrophysiological substrate for LTVA prediction in DCM.

Genotype-phenotype associations

DCM has a genetic basis in ±30-50% of cases and specific genotype-phenotype associations are known to lead to arrhythmogenic phenotypes.[2,24–26] One study analysed over 75.000 ECGs from the UK Biobank and established several genetic ECG signatures. A polygenic effect on PR-interval for instance, was identified, as well as genetic variants related to the Q-wave in DCM. The strongest Q-wave locus was discovered in *BAG3*: a gene in which pathogenic variants have been described for DCM with high penetrance and a high risk of progressive heart failure.[27,28] As our VAE model assessed the entire ECG, an interesting significant factor included QRS-T voltages (F_{32}), with high values in this factor associated with microvoltages. These microvoltages are an established ECG characteristic for phospholamban cardiomyopathy, which can lead to both a highly arrhythmogenic DCM phenotype and arrhythmogenic cardiomyopathy.[29] Integrating genome and phenome provides unique opportunities to study ECG biology in relation to genetic risk which can be explored by future studies using DNNs.[28–31] Furthermore, these studies may pave the way for using artificial intelligence models for risk prediction in DCM patients to estimate an individual's lifetime (genetic) risk of developing a specific arrhythmogenic DCM phenotype.

Limitations

The results of this study must be evaluated in light of its limitations. Even though the cohorts were consecutively constructed, data may be heterogeneous with missingness not-at-random given the nature of retrospective cohorts. As the UMCU is a heart transplantation centre, this may have caused a selection bias. To account for this, an external cohort was added from the MUMC+ (non-heart transplantation centre) of which the patients logically presented with less severe phenotypes (table 1). Since ICD shocks are not a true surrogate for sudden cardiac death in patients with DCM, the results need confirmation in a study population with fewer ICD carriers or considering only fast events (i.e., >200/min).[32] Because DCM is relatively rare, the results may be due to sample size and require confirmation in larger (prospective) studies.

Conclusion

To the best of our knowledge, this study is the first to use interpretable DNNs trained with ECGs for LTVA prediction in DCM patients. We observed that the VAE network combined with an interpretable Cox-regression can distinguish patients at risk of LTVA. The use of this inherently explainable DNN pipeline allowed interpretation and visualisation of pivotal ECG features.[10] Predictions were mainly driven by P-wave abnormalities that did not correlate with LA dimensions, suggesting an electrophysiological substrate. Future studies are warranted to validate these findings and elucidate their electrophysiological substrate for LTVA prediction in DCM.

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Conflicts of interest

Authors declare no conflicts of interest.

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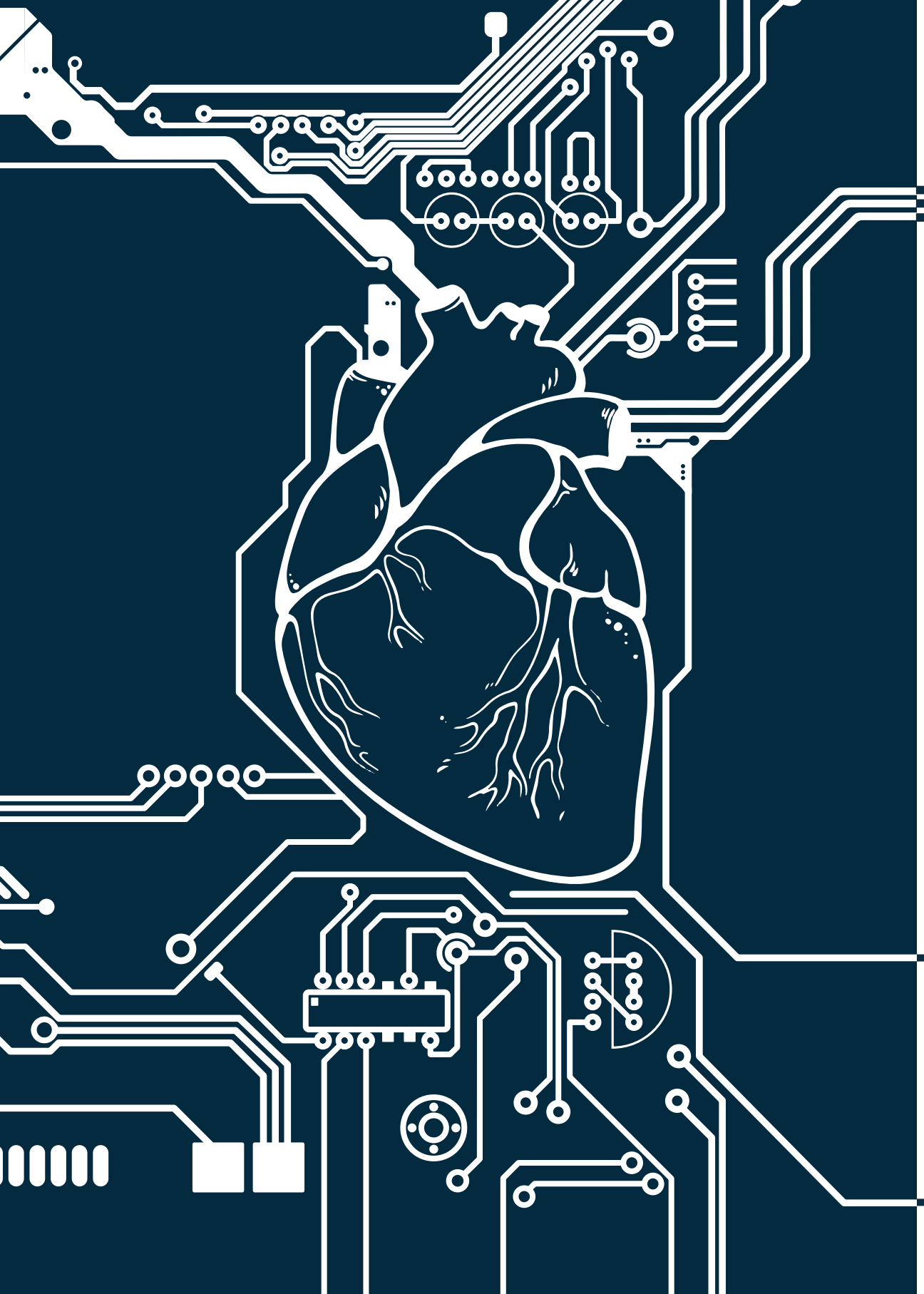
PART III

DISCUSSION



CHAPTER 10

Discussion and future perspectives

Adapted from: Sammani A, Baas AF, Asselbergs FW, te Riele ASJM.

Diagnosis and Risk Prediction of Dilated Cardiomyopathy in the Era of Big Data and Genomics. Journal of Clinical Medicine. 2021; 10(5):921.

DISCUSSION

Dilated cardiomyopathy (DCM) is characterized by systolic dysfunction in the absence of coronary artery disease. DCM affects 1:250-500 individuals and its patients harbour a risk of frequent hospitalisation, overt heart failure and life-threatening ventricular arrhythmias (LTVA).[1] The classification of DCM has been subject to change in the last decades. Its first descriptions were non-specific and included "idiopathic cardiomegaly" and "familial cardiomegaly" in the 1940's[2]. With electrocardiograms (ECG), echocardiography, and later with cardiac magnetic resonance imaging (CMR) and genetic testing, descriptions became more specific (i.e. "PLN-cardiomyopathy") and early diagnoses (i.e. hypokinetic non-dilated cardiomyopathy) became detectable.[3–5] Artificial intelligence (AI) models trained with big data from electronic health records (EHR) may be considered to be a new modality as well. Though AI models require data generated by beforementioned investigations, given the right setting and infrastructure, they may identify new phenotype clusters, predict prognosis, and shine light on novel important clinical variables, for instance by automatic feature extraction with ECGs.[6–8] In this chapter, I discuss how future studies should progress with predicting prognosis in DCM and use electronic health record (EHR) data, illustrated by the work presented in this thesis and related literature.

DCM prediction models

To facilitate prognostic assessments, several clinical prediction models have been constructed for heart failure related mortality in the general cardiology population. The Seattle Heart Failure Model (SHFM)[9], MAGGIC risk score[10], and the BCN bio-HF calculator[11] are three models with comparable risk prediction performance.[12] The performance of these models in DCM may, however, be suboptimal because their derivation also included patients with ischemic aetiology who are known to have a higher mortality risk than DCM patients (3-year mortality between 24–40%, compared to a 5-year mortality of ±20% in DCM).[12,13] Indeed, a recent comparison of these prediction models in an external DCM cohort produced an area under the curve (AUC) of ≥0.6, with the more sophisticated risk models (BCN Bio-HF and SHFM) yielding the highest accuracies.[9,11,12] As expected, the risk models typically overestimated mortality risk in DCM patients, likely caused by a difference in age (DCM patients tend to be younger (±15 years) than other heart failure aetiologies), which is one of the strongest variables affecting mortality.[12,13] Moreover, there is a distinct subgroup of DCM patients who experience LV function recovery and have a subsequent mild clinical course during follow-up.[14] These patients typically have higher LV contractile reserve and are more often women, whereas the presence of LGE on CMR in patients with DCM often represents an ominous marker.[14,15] Larger prospective studies are warranted for two purposes: (1) to discriminate patients who may recover and better understand their physiologic substrates which may impact new treatment strategies, and (2) to develop a risk stratification tool dedicated for DCM patients that also incorporates variables reflecting LV recovery.[12,15,16] To this end, (inter)national collaborations for clinical registries are imminent.

As patients harbour a risk for LTVA, we extensively investigated the risk factors for LTVA in DCM. They include Left Ventricular (LV) dilatation, decreased LV ejection fraction (LVEF), late gadolinium enhancement (LGE) on CMR, prior (non)sustained ventricular arrhythmia, and pathogenic variants in *PLN, LMNA, FLNC*, and *TTNtv*.[17–20] A recently published post hoc analysis of the MADIT trials in heart failure patients (including those with ischemic aetiology) confirmed that low LVEF (≤25%), male sex, prior non-sustained ventricular tachycardia, atrial arrhythmia, and myocardial infarction are potent predictors of LTVA.[21] An important consideration would be the confounding effect of cardiac resynchronisation therapy defibrillator (CRT-D) devices as these devices influence the risk of LTVA (including appropriate device therapy) in two ways: (1) they may decrease the risk of arrhythmia (improved LVEF with LV remodelling) and (2) they increase the detection chance ventricular arrhythmias, including self-terminating and possibly non-life-threatening ones.[22,23] In this thesis, we developed the DCM-SVA risk calculator: a multiparametric prediction model incorporating easily accessible clinical data to predict LTVA in patients with DCM.[19] As the newer techniques, such as LGE on CMR and genetic sequencing, are gaining ground in the work-up of DCM, we also provided an additional model including LGE.[19,20] It is now important to evaluate this prediction model in a prospective clinical study for DCM and specifically include high risk pathogenic gene variants.

Genetic risk scores of DCM

In up to 40% of patients with DCM a causative pathogenic variant is identified, which decreases to 10% in patients without a positive family history for DCM.[3,24–27] An explanation for the limited diagnostic yield of monogenetic causes and incomplete penetrance of DCM-associated variants is a common genetic variation and multifactorial inheritance.[28] To understand the relationship between these common genetic variants and DCM, researchers conducted several case-control genome-wide association studies (GWASs) and one exome-wide association study (EWAS).[29–32] The three GWASs identified several loci including the following genes: *HSPB7, BAG3, HCG22, SLC6A6*, and *SMARCB1*.[30–32] The EWAS reported eight loci independently associated with sporadic DCM, five of which included genes that harbour rare DCM causing variants (*TTN, ALPK3, BAG3, FLNC,* and *FHOD3*).[29] Additionally, a recent GWAS conducted in individuals from the UK Biobank investigated the role of genetic associations in CMR-derived LV measurements. They identified 45 previously unreported common genetic loci that were associated with cardiac function and dimensions in individuals without cardiovascular disease.[28] The results of these studies indicate that common genetic variation plays an important role in DCM development and progression.

To this end, genetic risk scores may be used to estimate an individual's lifetime genetic risk of a disease, which can be a useful tool to discriminate subjects that require more frequent

surveillance and more aggressive treatment.[3,33] Polygenic risk scores were constructed based on the identified loci that were linked to DCM, one of which comprised 28 single nucleotide polymorphisms that was able to predict DCM with a hazard ratio (HR) of 1.58 per standard deviation increase in the risk score. Moreover, LV end systolic volume and LVEF of *TTN*tv carriers were also shown to be influenced by this polygenic risk score.[28] This study, however, also underscored the particularly challenging clinical validation and implementation of polygenic risk scores: (1) the scores were mostly developed in patients with European/Western ancestry, and (2) interpretation was based on the distribution of risk, which may limit information on an individual's lifetime risk.[34] As previously mentioned, whether a carrier of a pathogenic variant develops DCM will also depend on the influence of environmental and cardiotoxic factors, further complicating risk predictions. Future research in large, well-phenotyped cohorts of pathogenic variants is required to define the utility of these genetic risk scores for individual prognosis.

Infrastructures, the prerequisite for artificial intelligence

Big data are usually described as data that are high in volume (e.g., by number of patients) and high in complexity (e.g., by temporality or number of variables).[35] The phenotypic data in an EHR system complies with this definition, as it may include detailed data on laboratory values, investigations, raw imaging and ECG data, device data, (unstructured) text, and questionnaires in many patients.[36] As each patient has a multitude of time-stamped events and data points that are performed upon discretion of the treating physician, these data are high dimensional, sparse (with varying intervals between data points), irregular, and temporal. Furthermore, data may be biased because of administrative or financial interests or because of a highly variable yet meaningful missingness.[37]

These challenges may be overcome by several methods. Phenotype-classifying algorithms may be able to cope with conflicting or missing data by combining multiple data sources and integrating information on treatment and comorbidities to infer diagnoses, as shown by a case study in atrial fibrillation.[38] Furthermore, clinically repetitive, or administrative tasks can be automated[39] —for instance, EchoNet is a deep learning network that can accurately extract LV volume and function, and other algorithms have been deployed for automatic CMR multi-structure segmentation.[40,41] Registration of diagnoses can also be automated, for example by interpreting clinical discharge letters and extracting diagnoses using deep learning.[42,43] Of note, these pipelines do not always need to rely on complex algorithms. Boolean retrieval methods or regular expressions are two examples of simpler algorithms that are also capable of extracting data from medical text.[44] These pipelines help creating big data research infrastructures by extracting previously messy data and structuring them for clinical research and patient care. Big data research infrastructures can also be a combination of conventional cohorts, e.g., EHR in population settings, disease registries, and trial data. BigData@Heart is an example that combines these different research and population datasets to gather real-world evidence.[45] As EHR systems are continued to be used as research data platforms, interoperability is important for continuous collaborations and validation of algorithms. When validated, these algorithms can then be entered into prospective clinical trials and implemented in clinical practice given that their big data infrastructure is already in place. Integrated data repositories and consensus-based approaches for data modelling and a variety of data models have been developed to provide standardisation, the latest being the OMOP Common Data Model and HL7 FHIR.[46]

Artificial Intelligence in Cardiomyopathy research and clinical implementation

Deep neural networks can discover complex patterns in data and be trained (and tested) to classify diseases. For example, a recent deep neural network accurately classified pathogenic *PLN* variants based on 12-lead ECGs in patients with cardiomyopathy.[6] The network showed excellent discriminatory performance and visualised both established ECG features (low QRS voltage and T-wave inversions) and a novel disease-specific ECG feature (increased PR duration) [98]. Another deep neural network was able to accurately triage ECG into four categories (normal, abnormal not acute, subacute, and acute).[47] An important consideration in these techniques is their interpretability. As they are generally black-box algorithms, their inherent lack of "explainability" hampers clinical implementation.[48] Different techniques may assist in interpreting DNNs. In this thesis, we used a recently introduced pipeline for fully explainable DNNs for ECG analysis based on variational auto-encoders (VAE)[49,50], that compressed the ECG into a lower number of explanatory and independent generative factors (factorECG).[51] We then used these factors in an interpretable algorithm for the prediction of LTVA in patients with DCM. We observed that the VAE network combined with an interpretable Cox-regression can distinguish patients at risk of LTVA and predictions were mainly driven by P-wave abnormalities. Future studies are warranted to validate these findings and elucidate their electrophysiological substrate to improve LTVA prediction in DCM.

Unsupervised clustering algorithms may also be able to help our understanding of phenotypic heterogeneity in DCM, as they can identify pathophysiologically similar individuals who may respond in a uniform and predictable way to treatment.[8] Indeed, a recent study identified four different DCM phenotype subgroups ("phenogroups") using an unsupervised hierarchical clustering algorithm, which was validated in two external registries: the Italian Trieste Registry and a cohort from Madrid.[7] The four identified phenogroups were summarised as (i) mild systolic dysfunction, (ii) auto-immune disease, (iii) arrhythmic, and (iv) severe systolic dysfunction. The latter three groups had comparable and relatively unfavourable outcome compared to the first phenogroup.[7] Whether these subgroups can be used to guide clinical decision-making remains to be investigated.[3] Since the prevalence of subtle systolic and diastolic dysfunction is present in genotype-positive phenotype-negative DCM relatives, using machine and deep learning for early detection of disease may be an important next step.[52]

Wearables

Wearables and smartphones are embedded with (and connected to) many sensors that can play a leading role in healthcare, ranging from accelerometers, temperature/heart rate detectors, and ECGs. To engage clinicians to use these data, platforms have been created to facilitate data storage and connectivity with these wearables, such as RADAR-base (an open-source mobile health platform) or the Harvard Forhealth application.[53,54] These applications allow for dynamic informed consents with patients and direct connection to researchers, while simultaneously providing the infrastructure for the assessment of telemonitoring devices. These initiatives mark the beginning of the paradigm shift from "one-size-fits-all" to personalised care supported by AI.[55]

Indeed, the last year has brought an exponential increase in studies using various forms of eHealth, which are now moving from research to implementation.[56] A recent meta-analysis estimated that telemonitoring systems reduce all-cause mortality in heart failure patients by ±20%, with optimal results if ≥3 simple biologic parameters (body weight, blood pressure, or ECG) are measured.[57] For heart failure hospitalisations in patients with CRT devices, however, older data indicate that more complex diagnostic indices are necessary: decreased intrathoracic impedance, low patient activity, and low heart rate variability (HRV).[58] More specifically, a HRV of <50 ms (standard deviation of the 5-min atrial–atrial intervals) was associated with high mortality and hospitalisation risk.[59] Non-invasive disposable patches were also shown to accurately provide early detection of impending rehospitalisation when combined with a machine learning algorithm.[60] Whether these innovative approaches can mitigate rehospitalisation (if acted upon) remains to be investigated. In addition, the benefit of wearables for arrhythmia detection or pre-clinical disease detection (e.g., by ECGs) in at-risk individuals needs to be evaluated in large prospective studies. [61]

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FUTURE PERSPECTIVES

With advancing technology, temporal EHR data, eHealth and wearables provide exciting new opportunities for patient-tailored predictive and preventive medicine (figure 1). Furthermore, because wearables are generally non-invasive, they can be used by the general population and measure the first onset of disease, creating a feasible opportunity for early detection. For example, carriers of pathogenic variants that causes cardiomyopathy may already have unnoticed arrhythmias[62] which can be detected using wearables that detect heart rhythm. Importantly, these data can be incorporated into the EHR, allowing big research data platforms to investigate AI-algorithms. However, "big data" are accompanied by "big responsibilities" and diminishing risks of biases requires a multi-disciplinary effort, including data scientists (who make the models), "hybrid physicians" (who speak the "AI language"), and information technology (IT) specialists (who provide the infrastructure).[35] The use of explainable algorithms and prospective validation of their clinical impact are imminent steps to guide further implementation.

Nonetheless, it is already possible to take advantage of IT infrastructures in research and daily clinical practice. Rather than seeing patients with the relatively scarce information preceding (outpatient) appointments, we can pro-actively start data collection from the moment of referral (or even before, with wearables). Data from their referring physicians can be automatically extracted (text-mining) to already suggest further diagnostic work-up and may include (poly)genic profiles harbouring baseline risks of disease and potential drug responsiveness in the future. With patient questionnaires, basic data (i.e. medical history and cardiovascular risk factors) may already be collected before an appointment and actively involves patients to maintain the accuracy of their EHR data. In this setting, the role of specialists will change, requiring more "hybrid physicians" that understand the complexity of healthcare data and its means to standardize them (figure 2). With validated AI models, these physicians will be selecting the right care pathways and predict patients' risk of adverse events. Furthermore, guideline adherence can be ingrained into these systems, actively guiding clinicians to their evidence-based treatment options and even retrospectively selecting cases that require further attention. Nonetheless, these "hybrid physicians" must not fail to realize the need for a human touch: using IT and AI systems to improve efficiency, whilst keeping healthcare humane.

10

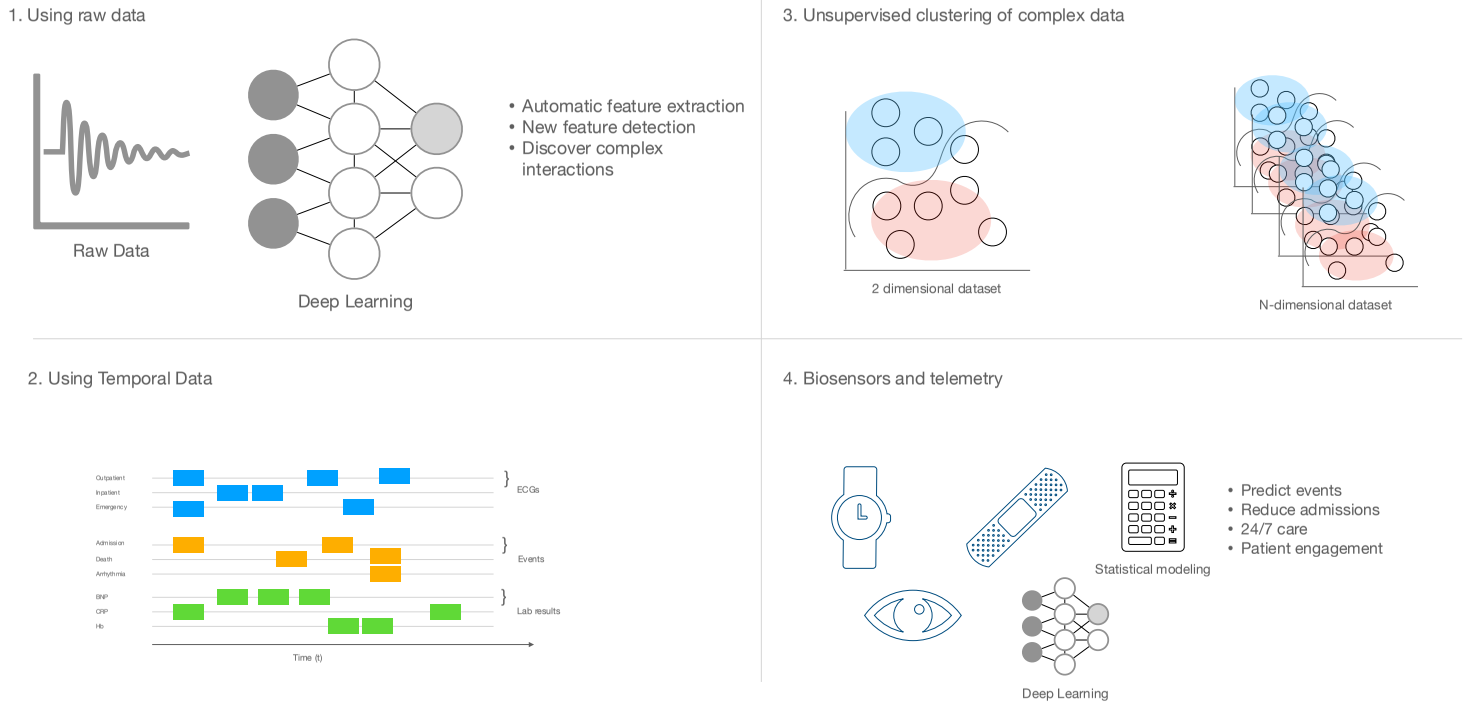

FIGURE 1. Opportunities

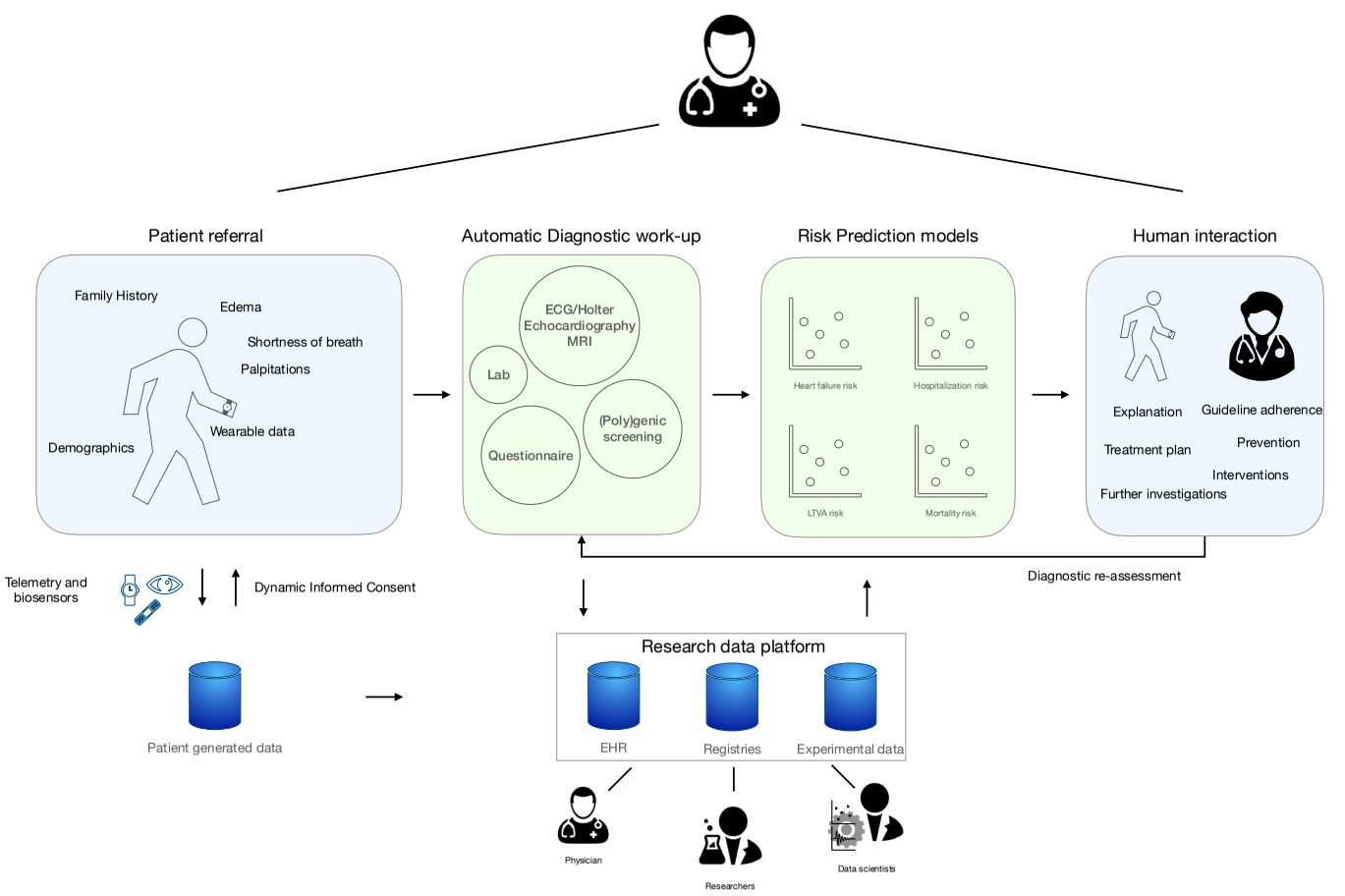

FIGURE 2. Overview by physician

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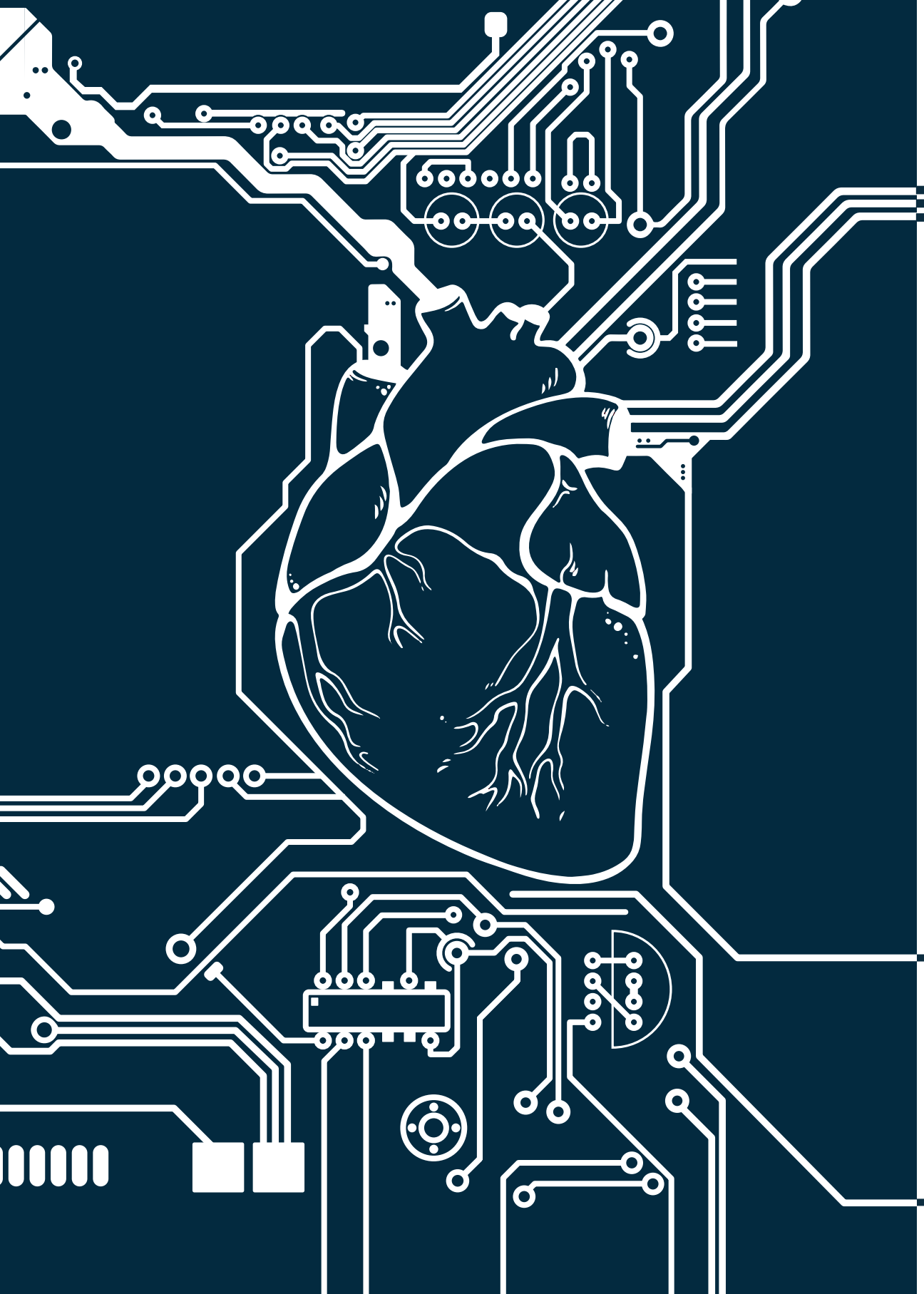

APPENDIX

ENGLISH SUMMARY

Electronic health records (EHR) have adjusted the nature of clinical medicine and research, allowing continuous capture of clinical data improving research infrastructures. These “real world” data can be manually captured in clinical registries or be used as big health records for clinical research using exciting techniques, such as text-mining and deep learning. These techniques were applied to investigate dilated cardiomyopathy (DCM): a heterogeneous common final pathway and its patients harbour a risk of life-threatening ventricular arrhythmias (LTVA).

The first chapters of this thesis focus on using “real world” data from registries to understand the clinical heterogeneity of DCM. In **Chapter 2** we used data from the University Medical Centre Utrecht Heart Transplantation cohort, focussing on end-stage heart failure. We showed that throughout the years DCM has become the primary indication of heart transplantation and that survival after heart transplantation has been increasing, possibly due to better post-transplantation care. Importantly, the lack of available donor hearts continues to lead to increased waiting lists. Ventricular assist devices offer a valuable bridge to transplantation, and more recently as “destination” therapy.

DCM is a complex disease where genetics interplay with extrinsic factors. In **Chapter 3** we investigated the phenotype, management, and outcome of familial DCM compared to non-familial (sporadic) DCM across Europe. We observed that there are important differences at baseline, such as younger age, less severe phenotypes at presentation and more favourable baseline cardiovascular risk profiles for patients with familial DCM. Logically, patients with familial DCM received more genetic testing with subsequently a higher genetic yield but remained limited for sporadic DCM. We discussed the opportunities of cardiovascular risk factors as means of treatment. Furthermore, we argued that limited genetic testing and heterogeneity throughout genetic panels throughout Europe provide a scaffold to improve genetic counselling and testing.

The risk of LTVA in patients with DCM has led to an established guideline (left ventricular ejection fraction (LVEF) <35%, NYHA class II/III) indication for implantable cardiac defibrillators (ICD). As LVEF remains the main guideline criterion for primary prophylactic ICD implantation, this could lead to overtreatment or failed detection of patients at risk of LTVA without impaired LVEF. As a first step towards a risk-calculator, we performed a systematic review and meta-analysis for predictors of LTVA in DCM in **Chapter 4**. We identified 55 studies which had an average crude annual event rate of 4.5%. We identified important risk factors (young age, hypertension, prior sustained arrhythmia, LVEF, left ventricular dilation and the presence of late gadolinium enhancement) that were associated with LTVA. Furthermore, several genotypes (Phospholamban, Lamin A/C and Filamin-C) were also associated with more events. We used these results to create an international cohort of Dutch, French, German and Polish patients with DCM, and construct a clinical risk prediction model in **Chapter 5**. We included a total of 1,393 patients that were primarily male (68%) with a mean age of ±50 years. We constructed a clinical risk model that included six independent and easily accessible clinical variables. Comparing this model to current guidelines resulted in the same protection of patients while implanting 12% fewer ICDs. We also provided a cut-off-free model that could be helpful for decision making in patients who do not fulfil ICD criteria based on existing guidelines, for instance having LVEF >35% in presence of other risk factors. Even though pathogenic variants in high-risk genes have repeatedly been associated with higher rates of life-threatening arrhythmias, we argue that genotyping DCM patients should be encouraged, despite current guideline recommendations to only do so in case of established conduction or rhythm disturbances.

In the next part of this thesis, we focussed on big health records for clinical research using exciting techniques, such as text-mining and deep learning. In **Chapter 6** we developed the UNRAVEL research data platform and biobank. This platform is an extraction of the EHR data and constitutes both structured and unstructured data in chronological sequence, such as electrocardiograms (ECG) and free text from doctors’ notes. The integration of these data into a research data platform allows efficient data collection. Furthermore, the biobank includes the use of residual material (for instance after heart transplantation), venepuncture and protocols are shared on www.unravelrdp.nl.

Standard reference terminology of diagnoses and risk factors is crucial for epidemiological studies and inter/intranational comparisons of disease. The International Classification of Disease (ICD-10) is a standardized and widely used method, where doctors’ notes are manually classified. In **Chapter 7**, we developed a natural language processing pipeline that automatically classifies ICD-10 codes in free medical text. We focussed on three- and four-digit codes, such as atrial fibrillation (I48) and DCM (I42.0). We observed that the performance was best when using the entire discharge letters and discuss implementation of this technique to decrease administrative burden and further use in research applications. Another technique is the use of more simple text-mining algorithms for the identification of rare diseases. In **Chapter 8** we described the use of a Boolean retrieval algorithm for the identification of unexplained left ventricular hypertrophy to allow for early targeted treatment and family screening. We discuss the use of computer algorithms as an exciting next era of patient identification and discuss infrastructure and clinical implications.

Using structured data from the research data platforms enables novel deep learning methods. Specific ECG characteristics have been associated with LTVA but require hand-crafted feature extraction. Deep neural networks (DNN) can discover complex patterns without the necessity of manual extraction, but clinical use is hampered by model

interpretation. In **Chapter 9**, we developed an inherently explainable DNN in patients with DCM for the outcome of LTVA. We observed that the network was able to predict events and predictions were driven by P-wave abnormalities. This paves the way for future studies to improve identification of patients at risk of LTVA and elucidate the electrophysiological substrates.

In the last chapter of this thesis (**Chapter 10)** I further discussed on how to progress with diagnosis and risk prediction of DCM using big data and artificial intelligence.

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NEDERLANDSE SAMENVATTING

Het elektronisch patiëntendossier (EPD) heeft het verrichten van klinisch cardiovasculair onderzoek getransformeerd door continuïteit en toegankelijkheid van data te garanderen. Deze “echte wereld” data kunnen handmatig worden ontsloten in registraties of toegankelijk worden gemaakt via “big data” platforms, waarbij technieken zoals *text-mining* en *deep learning* worden toegepast. In dit proefschrift zijn zowel registratie data als big-data platforms gebruikt in cardiovasculair onderzoek naar met name dilaterende cardiomyopathie (DCM): een heterogeen ziektebeeld waarbij patiënten een significant risico hebben op levensbedreigende hartritmestoornissen en hartfalen.

Het eerste deel van dit proefschrift focust zich op de “echte wereld” data die ontsloten zijn in klinische registraties om de heterogeniteit van DCM te onderzoeken. In **Hoofdstuk 2** hebben we data van het harttransplantatie cohort van het Universitair Medisch Centrum Utrecht gebruikt, met als focus eindstadium hartfalen. In dit stuk beschreven wij de transitie van ischemisch hartfalen naar non-ischemisch hartfalen in de loop der jaren als primaire indicatie voor harttransplantaties. We bediscussiëren de verbeterende overleving van patiënten na harttransplantatie, mogelijkerwijs door verbeterde post-transplantatie-zorg. Van belang is het tekort van donorharten, wat leidt tot langere wachtlijsten. *Assist devices* zijn hierin cruciaal als *bridge-to-transplantation* behandeling, waarbij steeds recenter de therapie ook als *“destination therapy”* wordt ingezet.

DCM kent een complexe etiologie, waarbij genetische en omgevingsfactoren een rol spelen. In **Hoofdstuk 3** vergelijken we het fenotype, behandeling en uitkomsten van familiaire DCM met non-familiaire (sporadische) DCM in Europa. Opvallende observaties zijn verschillen tijdens presentatie, zoals een jongere leeftijd met bijbehorend milder ziektebeeld en een gunstiger cardiovasculair ziekteprofiel (bv. minder roken, minder hoge bloeddruk) bij patiënten met familiaire DCM. Logischerwijs worden patiënten met DCM vaker genetisch onderzocht met bijbehorende hogere vangst van pathogene varianten. We bespreken de mogelijkheid van cardiovasculaire risicofactoren voor een aanvullende focus van behandeling en bediscussiëren het relatief lage aantal genetische testen en heterogeniteit van de genetische panels in Europa als mogelijkheid om de genetische counseling te verbeteren.

Het significante risico van levensbedreigende ritmestoornissen bij patiënten met DCM heeft geleid tot een richtlijn indicatie (linkerventrikel ejectiefractie (LVEF)) <35%, NYHA-klasse II/III) voor het implanteren van een implanteerbare cardiale defibrillator (ICD). Een tekortkoming van deze richtlijn is dat deze slechts 1 criterium (LVEF) bevat, waarbij er mogelijke overbehandeling is van patiënten met slechte kamerfunctie of onderbehandeling is van patiënten met relatief behouden kamerfuncties. Dit zou kunnen worden opgelost door

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een voorspelmodel te maken voor ritmestoornissen waarin verschillende factoren worden meegenomen. Als eerste stap naar zo'n voorspelmodel hebben wij in **Hoofdstuk 4** een systematische review en meta-analyse verricht naar voorspellers van levensbedreigende ritmestoornissen bij patiënten met DCM. Uit de 55 geïncludeerde studies kwam een grof jaarlijks risico op levensbedreigende ritmestoornissen van ±4.5%. Uit de studie kwam naar voren dat jonge leeftijd, hoge bloeddruk, eerdere aanhoudende ritmestoornis, LVEF, linkerventrikel verwijding en de aanwezigheid van late gadolinium aankleuring op MRI-scan (littekenvorming in het hart) geassocieerd zijn met levensbedreigende ritmestoornissen. Bovendien is er bij bepaalde gen-afwijkingen een groter risico op ritmestoornissen, bijvoorbeeld bij pathogene varianten in Phospholamban, Lamin A/C en Filamine-C. Met deze resultaten hebben wij in **Hoofdstuk 5** binnen een internationaal cohort van Nederlandse, Franse, Duitse en Poolse patiënten met DCM een klinisch risicopredictiemodel ontworpen. In het cohort waren 1,393 patiënten geïncludeerd, met name mannen (68%) van gemiddeld ±50 jaar. Het model omvatte toegankelijke klinische variabelen zoals leeftijd, QRS-duur en LVEF. Vergeleken met de bestaande richtlijnen zou dit nieuwe model hetzelfde aantal patiënten beschermen met 12% minder implantaties. Bovendien publiceerden wij een model dat geen ICD-implantaties oplegt, maar een numeriek risico geeft op ritmestoornissen. Dit kan helpen bij gedeelde besluitvorming tussen arts en patiënt, bijvoorbeeld in het geval van een LVEF >35% maar wel de aanwezigheid van andere risicofactoren. Hoewel pathogene varianten in hoog-risico genen vaker zijn beschreven bij levensbedreigende ritmestoornissen, wordt genetisch onderzoek binnen de huidige richtlijnen nog niet aanbevolen bij alle patiënten met DCM, tenzij ze bekend zijn met ritme- of geleidingsstoornissen. Echter vanwege het risico op levensbedreigende ritmestoornissen betogen wij het verrichten van genetisch onderzoek bij alle patiënten met DCM.

In het volgende deel van het proefschrift ligt de focus op big data voor klinisch onderzoek waarbij gebruik wordt gemaakt van technieken als *text-mining* en *deep learning*. In **Hoofdstuk 6** beschrijven we het ontwerp van het UNRAVEL research data platform en de biobank. Dit platform extraheert zowel gestructureerde als ongestructureerde data uit het EPD in chronologische sequentie, zoals elektrocardiogrammen (ECG) en vrije tekst van bijvoorbeeld ontslagbrieven. Integratie van deze data in een research data platform ondersteunt efficiëntere collectie van data. Daarnaast kan restmateriaal, bijvoorbeeld na harttransplantatie, worden gebruikt, is bloedafname onderdeel van de biobank en zijn alle protocollen gedeeld via www.unravelrdp.nl.

Gestandaardiseerde terminologie voor diagnosen en risicofactoren is cruciaal voor epidemiologische studies. Hiervoor wordt vaak de *International Classification of Disease (ICD-10)* gebruikt, waarbij ontslagbrieven manueel worden geannoteerd met een ICD-10 code. In **Hoofdstuk 7** hebben wij een *natural language processing* pipeline ontworpen die klinische ontslagbrieven automatisch annoteert met een ICD-10 code, zoals atriumfibrilleren (I48) en DCM (I42.0). Deze modellen presteerden het beste als er gebruik werd gemaakt van gehele brieven. We beargumenteren de implementatie van deze technieken om de administratielast in de zorg te verlichten en bediscussiëren verder gebruik als research applicatie. Een andere techniek betreft het gebruik van simpelere text-mining methoden. In **Hoofdstuk 8** beschrijven wij het gebruik van een *Boolean Retrieval* algoritme voor het identificeren van patiënten met onverklaarde linkerventrikel hypertrofie voor vroege behandeling en familiescreening. In de discussie gaan wij in op het gebruik van computeralgoritmen voor patiëntidentificatie met bijbehorende infrastructuur en klinische implicaties.

Het gebruik van al gestructureerde grote datasets van het research data platform geeft ruimte voor deep learning methoden. Eerder beschreven wij bepaalde ECG kenmerken die geassocieerd zijn met levensbedreigende aritmieën, waarbij handmatige interpretatie een beperking is van deze techniek. Door Deep Neural Networks (DNN) te gebruiken kunnen we complexe patronen in ECG's herkennen zonder dat daar handmatige interpretatie aan te pas komt. Deze modellen zijn echter beperkt te interpreten, wat klinische implementatie bemoeilijkt. In **Hoofdstuk 9** hebben wij een inherent *explainable* DNN (waarbij voorspellers inzichtelijk kunnen worden gemaakt) ontworpen om levensbedreigende ritmestoornissen bij patiënten DCM te voorspellen. Wij zagen dat het netwerk inderdaad accurate voorspellingen kan doen op basis van P-golf afwijkingen. Deze bevinding opent de weg om hoog-risico patiënten beter te kunnen identificeren en het elektrofysiologische mechanisme van P-golf afwijkingen en plotse hartdood beter te begrijpen.

In het laatste hoofdstuk van deze thesis (**Hoofdstuk 10**) bediscussieer ik toekomstperspectieven voor diagnose en risicovoorspelling bij DCM met behulp van big data en kunstmatige intelligentie.

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CV

Arjan Sammani was born on 15 December 1992 in Tehran, Iran to Mehrdad Sammani and Gila Segerloo. In 1994, his family emigrated to the Netherlands where he first grew up in Sassenheim, and later Nijmegen as a bilinguist (Dutch and Persian), accompanied by a younger sister (Ima Sammani). In 2010, he graduated from the Kandinsky College Nijmegen following the International Baccalaureate English VWO whilst obtaining his *Diplôme d'Etudes en Langue Française*. Arjan moved to Utrecht in 2010 for Biomedical Sciences and after one year he pursued a career in medicine.

During his studies, Arjan was actively involved at research at the department of Cardiology. He followed the Honours Programme during his master's and was awarded with the Alexandre Suerman MD/Ph.D. stipend in 2018, enabling him to fund his own Ph.D. program under the supervision of Professor F.W. Asselbergs, Professor D.L. Oberski and his co-promotors Dr. A.S.J.M. te Riele and Dr. A.F. Baas. His research focussed on using electronic health record data for cardiovascular research, with special attention for cardiomyopathies, which culminated in his Ph.D. During his time as a Ph.D. student, he followed summer schools for statistical programming and data visualisation and was awarded with a *CVON eDETECT Young Talent Award* to obtain his postgraduate degree in health data analytics at University College London in his first two years. In his third year, Arjan followed a nine-month valorisation program at UtrechtInc to close the gap between science and implementation. During his Ph.D., he received several grants, which were used to develop text-mining algorithms in clinical discharge letters and the development of deep learning algorithms on electrocardiograms for cardiomyopathy risk prediction.

During his final week at UCL in London, COVID-19 hit the Netherlands. After obtaining his postgraduate certificate, Arjan worked on the COHORT (COVID-19 inpatient wards) and started a foundation in October 2020 (Stichting Vaccinatieteam) support vaccination efforts and aid healthcare organisations in finding medical staff. Together with Feddo Kirkels and Lieke Numan they delivered syringes to general practitioners' offices that reduce vaccine waste significantly, leading to front page media coverage in the *Telegraaf* online newspaper.

Arjan will continue to pursue his career as a cardiology resident, starting at the Meander Medical Centre in Amersfoort.

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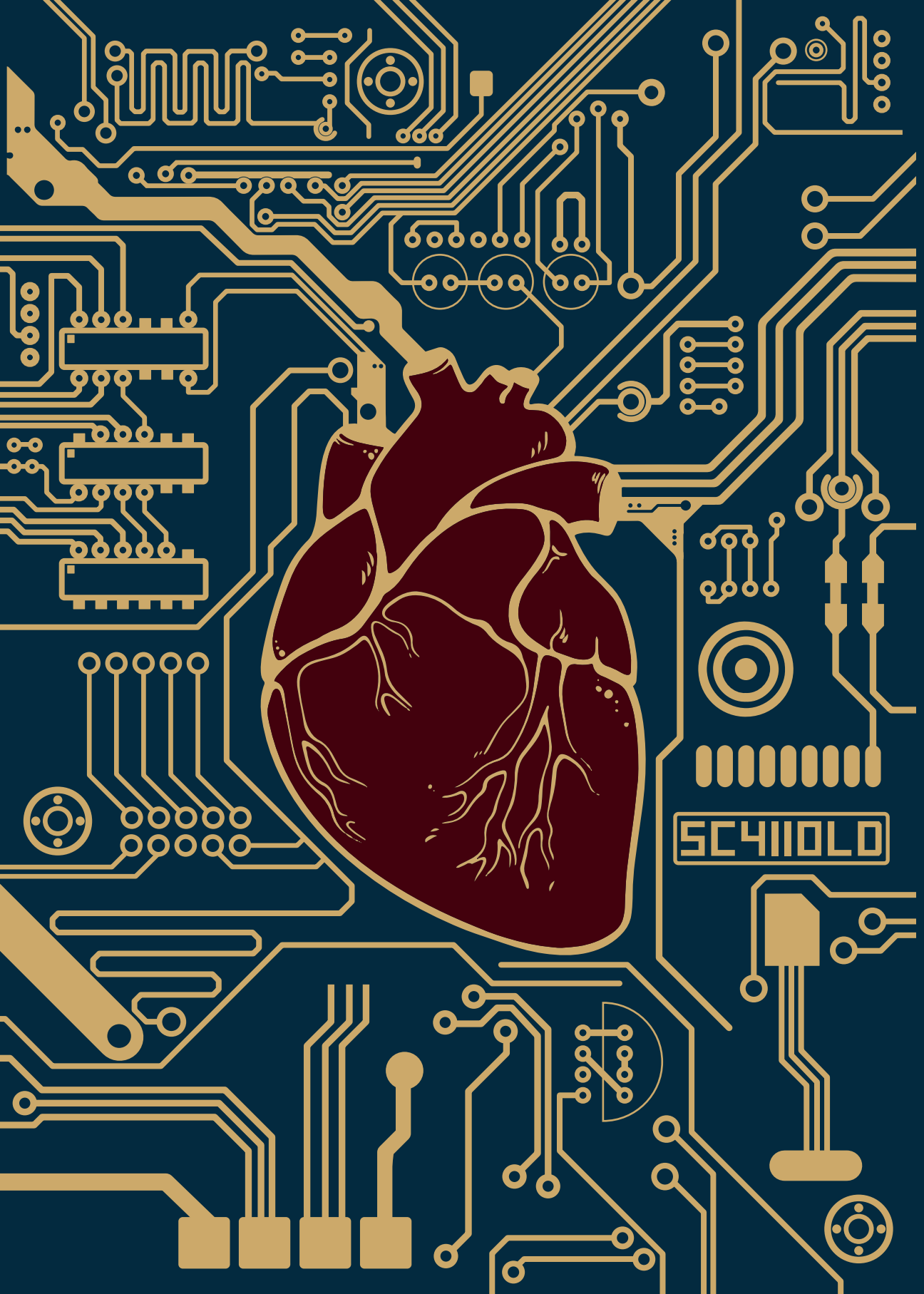
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