https://doi.org/10.15388/vu.thesis.792
https://orcid.org/0000-0002-1741-1231

VILNIUS UNIVERSITY

Justinas Bacevičius

Cardiac Monitoring in Patients with Atrial Arrhythmias: Invention and Validation of a User-Friendly Wearable Device, Diagnostic Capability of an Artificial Intelligence Algorithm, and Detection of Pro-Arrhythmic Risk Markers in Long-Term Electrocardiograms

DOCTORAL DISSERTATION

Medical and Health Sciences,
Medicine (M 001)

VILNIUS 2025

The dissertation was prepared between 2020 and 2024 at the Clinic of Heart and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania.

Academic Supervisor – Prof. Dr. Audrius Aidietis (Vilnius University, Medical and Health Sciences Medicine, M 001).

This doctoral dissertation will be defended in a public/closed meeting of the Dissertation Defence Panel:
Chairman – Prof. Dr. Jelena Čelutkienė (Vilnius University, Medical and Health Sciences, Medicine, M 001)
Members:
Prof. Dr. Mélèze Hocini (University Hospital Institute LIRYC, Bordeaux Université, Medical and Health Sciences, Medicine, M 001)
Prof. Dr. Minvydas Kazys Ragulskis (Kaunas University of Technology, Natural Sciences, Mathematics, N 001)
Prof. Dr. Pranas Šerpytis (Vilnius University, Medical and Health Sciences, Medicine, M 001)
Prof. Dr. Jūratė Šipylaitė (Vilnius University, Medical and Health Sciences, Medicine, M 001)

The dissertation shall be defended at a public meeting of the Dissertation Defence Panel at 12:00 on 1st July 2025 in the Red auditorium of Vilnius University Hospital Santaros Klinikos and the Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania.
Address: Santariškių st. 2, the Red auditorium, 03101 Vilnius, Lithuania
Tel. +37052365307; e-mail: justinas.bacevicius@mf.vu.lt

The text of this dissertation can be accessed at the library of Vilnius University, as well as on the website of Vilnius University:
www.vu.lt/lt/naujienos/ivykiu-kalendorius

https://doi.org/10.15388/vu.thesis.792
https://orcid.org/0000-0002-1741-1231

VILNIAUS UNIVERSITETAS

Justinas Bacevičius

Širdies veiklos monitoravimas pacientams su priešširdinėmis aritmijomis: naudotojui draugiško nešiojamojo prietaiso išradimas ir validavimas, diagnostinis dirbtinio intelekto algoritmo pajėgumas bei aritmijos rizikos markerių aptikimas ilgalaikėse elektrokardiogramose

DAKTARO DISERTACIJA

Medicinos ir sveikatos mokslai,
Medicina (M 001)

VILNIUS 2025

Disertacija rengta 2020–2024 metais Vilniaus universiteto Medicinos fakulteto Klinikinės medicinos instituto Širdies ir kraujagyslių ligų klinikoje.

Mokslinis vadovas – prof. dr. Audrius Aidietis (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina, M001).

Gynimo taryba:
Pirmininkė – prof. dr. Jelena Čelutkienė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina, M001)

Nariai:
prof. dr. Mélèze Hocini (Universitetinės ligoninės institutas LIRYC, Bordo universitetas, Prancūzija, medicinos ir sveikatos mokslai, medicina, M 001)
prof. dr. Minvydas Kazys Ragulskis (Kauno technologijos universitetas, gamtos mokslai, matematika, N 001)
prof. dr. Pranas Šerpytis (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina, M001)
prof. dr. Jūratė Šipylaitė (Vilniaus universitetas, medicinos ir sveikatos mokslai, medicina, M001)

Disertacija ginama viešame Gynimo tarybos posėdyje 2025 m. liepos mėn. 1 d. 12:00 val. Vilniaus universiteto ligoninės Santaros klinikose ir Vilniaus universiteto, Medicinos fakulteto, Klinikinės medicinos instituto, Širdies ir kraujagyslių ligų klinikoje, Raudonojoje auditorijoje.
Adresas: Santariškių g. 2, Raudonoji auditorija, 03101 Vilnius, Lietuva, tel. +37052365307; el. paštas justinas.bacevicius@mf.vu.lt.

Disertaciją galima peržiūrėti Vilniaus universiteto (VU) bibliotekoje ir VU interneto svetainėje adresu:
https://www.vu.lt/naujienos/ivykiu-kalendoriu

ABBREVIATIONS

AF	atrial fibrillation
AI	artificial intelligence
AIVR	accelerated idioventricular rhythm
AUC	area under the curve
ROC	receiver operating characteristic
AVB	atrioventricular block
CNN	convolutional neural network
DALYs	disability-adjusted life years
DOAC	direct oral anticoagulant
DRAI	DeepRhythm artificial intelligence model
EAA	earliest atrial activation
EAR	ectopic atrial rhythm
ECG	electrocardiogram
EHRA	European Heart Rhythm Association
EMA	European Medicines Agency
EPO	European Patent Office
ESC	European Society of Cardiology
ESVEA	excessive supraventricular ectopic activity
FDA	Food and Drug Administration
FN	false negatives
FP	false positives
HR	hazard ratio
IS	Istel HR 2000
IVR	idioventricular rhythm

JPO	Japan Patent Office
KM	Kardia Mobile 6L
LMWH	low molecular weight heparin
LR	likelihood ratio
MDR	Medical Device Regulation
NPV	negative predictive value
OAC	oral anticoagulant
OR	odds ratio
PACs	premature atrial contractions
PPV	positive predictive value
PPG	photoplethysmography
PSVT	paroxysmal supraventricular tachycardia
PVI	pulmonary vein isolation
PVCs	premature ventricular contractions
QTc	corrected QT interval
RA	right atrium
RR	relative risk
SR	sinus rhythm
SVC	superior vena cava
TIA	transient ischemic attack
TP	true positives
VT	ventricular tachycardia
WIPO	World Intellectual Property Organization

CONTENTS

ABBREVIATIONS 5

PRINCIPAL PUBLICATIONS OF THE THESIS 12

List of Patents and Jurisdictions 12

List of Principal Scientific Papers 14

1 INTRODUCTION 15

1.1 Background and Relevance of the Study 15

1.2 The Aim of the Study 16

1.3 The Objectives of the Study 16

1.4 Defense Statements of the Doctoral Thesis 17

1.5 Novelty and Practical Value 17

2 LITERATURE REVIEW 19

2.1 Multiple-Lead, Wire- and Patch-Free ECG Technology in Wearables for Detection of Atrial Arrhythmias 19

2.2 Automated Analysis of Single-Lead ECG in Smartwatches for Detecting Atrial Arrhythmias 19

2.3 Artificial Intelligence for Direct-to-Physician Ambulatory ECG Reporting 20

2.4 Role of PPG in Atrial Arrhythmia Detection and Large-Scale AF Screening 21

3 METHODS 24

3.1 Overall Design and Rationale of the Series of Papers 24

3.2 Inclusion and Exclusion Criteria 28

3.3 Flow of Participant Inclusion 29

3.4 Technical Description of the Devices, PPG-Based Algorithm, Wearable-Recorded ECG, and DeepRhythmAI Model 31

3.5 Analysis and Interpretation of ECG and PPG Data 37

4 RESULTS 42

4.1 Intellectual Property and Development Contributions: Patents, MDR Certification, and Commercialization of the Wearable Technology 42

4.1.1 Patents 42
4.1.2 MDR Certification 44
4.1.3 Commercialization 45
4.2 Contributions in Scientific Papers 45
4.3 Paper I: Validating the Device by Assessing Diagnostic Accuracy 46
4.3.1 Automated PPG-Based Algorithm of the Device for AF Detection 49
4.3.2 Six-Lead-ECG of the Device for AF Detection When Assessed by Independent Cardiologists 50
4.3.3 The Cohesive System of the PPG-Based Algorithm and the Six-Lead-ECG of the Device for AF Detection 51
4.3.4 Summary 52
4.4 Paper II: Comparison of Six-Lead ECG with Single-Lead ECG for AF Detection 53
4.4.1 Single-Lead ECG, Six-Lead ECG and PPG-Based Algorithm for AF Detection when Controlled by SR with PACs and PVCs 54
4.4.2 Single-Lead ECG, Six-Lead ECG, and PPG-Based Algorithm for AF Detection when Controlled by SR with Frequent PACs 57
4.4.3 Single-Lead ECG, Six-Lead ECG, and PPG-Based Algorithm for AF Detection when Controlled by SR with Frequent PVCs 58
4.4.4 Summary 58
4.5 Paper III: AI vs. Technicians' Detection of Arrhythmia in Direct-to-Physician Ambulatory ECG Reporting 58
4.5.1 Critical Arrhythmias 59
4.5.2 Noncritical Arrhythmias 63
4.5.3 Summary 65
4.6 Paper IV: ECG-Based Risk Markers and Predictive Modeling for AF in Long-Term Holter Monitoring 65
4.6.1 Prediction Model Discrimination 66
4.6.2 Characteristics of Patients with “High-” versus “Low-Risk” of AF 70
4.6.3 Summary 72

5 DISCUSSION 73

5.1 Diagnostic Challenges: Key Requirements Guiding the Development of a Wearable Device 73

5.2 Uniqueness of the Invented Wearable: Addressing the Key Diagnostic Requirements in the Development of a Wearable Device 74

5.3 Discussion of Paper I: Validating the Device by Assessing Diagnostic Accuracy 75

5.3.1 Impact of Premature Contractions on the PPG-Based Algorithm for AF Detection 75

5.3.2 Impact of Premature Contractions on the ECG of the Wearable for AF Detection 76

5.3.3 Impact of Premature Contractions on Automated ECG Algorithm for AF Detection 77

5.3.4 Limitations 77

5.4 Discussion of Paper II: Comparison of Six-Lead ECG with Single-Lead ECG for AF Detection 79

5.4.1 Major findings 79

5.4.2 Why Six is Smarter than One: Impact of Electrode Contact in Wearables and Relation to the Topographic Anatomy of Sinus Node 79

5.4.3 ECG Examples of False Negative, False Positive and Inconclusive Cases in Single-Lead vs. Six-Lead ECGs 80

5.4.4 Results of Other Wearable Devices with Six-Lead ECG for AF Detection 87

5.4.5 Limitations 87

5.5 Discussion of Paper III: AI vs. Technicians' Detection of Arrhythmia in Direct-to-Physician Ambulatory ECG Reporting 88

5.5.1 Major Findings 88

5.5.2 Comparison to Other Studies 88

5.5.3 Why AI Outperformed the Manual Analysis of Technicians 89

5.5.4 Limitations 90

5.6 Discussion of Paper IV: ECG-Based Risk Markers and Predictive Modeling for AF in Long-Term Holter Monitoring 91

5.6.1 Predicted Target Group for Long-Term Monitoring 91
5.6.2 ECG features for Predicting AF 91
5.6.3 Limitations 92
6 CONCLUDING REMARKS 92
7 THE FIRST LIFE SAVED BY THE INVENTED DEVICE: A CASE REPORT OF PRACTICAL APPLICATION 94
8 RECOMMENDED PRACTICAL APPLICATIONS OF THE INVENTED DEVICE 100
8.1 Use of TeltoHeart in Patients Without an Established Diagnosis of AF/ Bradyarrhythmia/ Tachyarrhythmia 100
8.2 Use of TeltoHeart in Patients With an Established Diagnosis of AF/ Bradyarrhythmia/ Tachyarrhythmia 102
8.3 Future Directions 103
9 SANTRAUKA 104
Santrumpos 104
9.1 Įvadas 106
9.1.1 Tyrimo kontekstas ir aktualumas 106
9.1.2 Tyrimo tikslas 107
9.1.3 Tyrimo uždaviniai 107
9.1.4 Disertacijos ginamieji teiginiai 108
9.1.5 Naujumas ir praktinė vertė 109
9.2 Metodika: bendras straipsnių serijos dizainas ir pagrindimas 110
9.3 Rezultatai 114
9.3.1 Intelektinė nuosavybė ir indėlis į vystymą: patentai, MDR sertifikavimas ir prietaiso komercializacija 114
9.3.2 Straipsnis I: įrenginio diagnostinio tikslumo validacija 114
9.3.3 Straipsnis II: šešių derivacijų EKG palyginimas su vienos derivacijos EKG nustatant prieširdžių virpėjimą 114
9.3.4 Straipsnis III: dirbtinio intelekto ir rankinio aritmijų nustatymo palyginimas ambulatorinėje EKG 115

9.3.5 Straipsnis IV: EKG rizikos žymenys ir prognostinis prieširdžių virpėjimo modeliavimas ilgalaikiame Holterio monitoravime 115
9.4 Išvados 116
10 REFERENCES 117
11 OTHER SCIENTIFIC PAPERS 127
12 PRESENTATIONS 2020-2025 128
13 BRIEF INFORMATION ABOUT THE AUTHOR 130
14 ACKNOWLEDGMENTS 131

PRINCIPAL PUBLICATIONS OF THE THESIS

The main findings of the doctoral dissertation were published in the following patents and scientific papers.

List of Patents and Jurisdictions

1. Wrist-worn wearable patent application:
   1.1. Lithuania (LT) Patent
   Title: Long-Term Non-Invasive System for Monitoring and Characterizing Atrial Arrhythmias in Patients with Post-Stroke Conditions
   International Application Number: Not Applicable
   PCT Number: Not Applicable
   Publication Number: LT6743A
   Database: State Patent Bureau of the Republic of Lithuania
   Website Link:
   https://search.vpb.lt/pdb/patent/dossier/2018%20550
   1.2. WIPO (World Intellectual Property Organization) Patent
   Title: Long-Term Non-Invasive System for Monitoring and Characterizing Atrial Arrhythmias in Patients with Post-Stroke Conditions
   International Application Number: PCT/IB2020/054099
   Number: WO/2020/104986A
   Publication Number: WO/2020/104986A
   Database: WIPO's PATENTSCOPE
   Website Link:
   https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2020104986
   1.3. European Patent Office (EPO) Patent
   Title: Long-Term Non-Invasive System for Monitoring and Characterizing Atrial Arrhythmias in Patients with Post-Stroke Conditions
   International Application Number: Not Applicable
   PCT Number: Not Applicable
   Publication Number: EP3883463 and EP19845615
   Database: European Patent Office
   Website Link:
   https://register.epo.org/application?number=EP19845615&tab=main
   1.4. United States Patent

Title: Long-Term Non-Invasive System for Monitoring and Characterizing Atrial Arrhythmias in Patients with Post-Stroke Conditions
International Application Number: Not Applicable
PCT Number: Not Applicable
Publication Number: US20220015683
Database: United States Patent and Trademark Office
Website Link:
https://patents.google.com/patent/US20220015683A1/en

1.5. Japan Patent

Title: デバイスによる心房不整脈のモニタリングおよびサーバによる特性評価の非侵襲的方法 (Non-Invasive Method for Monitoring Atrial Arrhythmias by Device and Characterizing by Server)
International Application Number: Not Applicable
PCT Number: Not Applicable
Publication Number: JP2022508124
Database: Japan Patent Office (JPO) - J-PlatPat
Website Link:
https://www.j-platpat.inpit.go.jp/c1800/PU/JP-2022-508124/6A8E92C3B8B875AC3FD6DF8A7D49372E24CCD2F0164F673EA7AD3D66B3019061/11/en

2. Additional patent application:

Title: Method for Establishing a Causality Score Between Atrial Fibrillation Triggers and Atrial Fibrillation Pattern
International Application Number: Not Applicable
PCT Number: Not Applicable
Publication Number: EP4105941
Database: European Patent Office
Website Link:
https://worldwide.espacenet.com/patent/search/family/076483185/publication/EP4105941A1?q=pn%3DEP4105941A1

List of Principal Scientific Papers

1. **Paper I**:

High Specificity Wearable Device With Photoplethysmography And Six-lead Electrocardiography For Atrial Fibrillation Detection Challenged By Frequent Premature Contractions: DoubleCheck-AF. Frontiers in Cardiovascular Medicine. 06 April 2022. IF 5.846 (2022). DOI: 10.3389/fcvm.2022.869730

2. **Paper II**:

Six-lead Electrocardiography Compared To Single-lead Electrocardiography And Photoplethysmography Of A Wrist-worn Device For Atrial Fibrillation Detection Controlled By Premature Atrial Or Ventricular Contractions: Six Is Smarter Than One. Front Cardiovasc Med. 2023 Jun 9;10:1160242. DOI: 10.3389/fcvm.2023.1160242.

3. **Paper III**:

Artificial Intelligence for Direct-to-physician Reporting of Ambulatory Electrocardiography. Johnson, L.S. et al. Nat Med (2025). IF 58.7. DOI: 10.1038/s41591-025-03516-x.

4. **Paper IV**:

Can 24 H Of Ambulatory ECG Be Used To Triage Patients To Extended Monitoring? Ann Noninvasive Electrocardiol. 2023 Oct 6:e13090. DOI: 10.1111/anec.13090.

1 INTRODUCTION

1.1 Background and Relevance of the Study

Atrial fibrillation (AF), the most prevalent cardiac arrhythmia globally, affects approximately 60 million individuals and contributes to over 8 million disability-adjusted life years (DALYs) (1). In terms of paroxysmal supraventricular tachycardia (PSVT), it affects about one in 300 people (2). The prevalence in the United States ranges from 1.26 million, excluding those with concomitant diagnoses of AF or atrial flutter, to 2.06 million when including these conditions. As the prevalence of AF continues to rise, a significant number of cases remain undiagnosed (3,4). This includes not only asymptomatic individuals but also those whose symptoms, often paroxysmal, are not captured by standard 12-lead electrocardiograms (ECG) or conventional methods like Holter monitoring. The presence of undiagnosed AF poses serious health risks. Therefore, prompt diagnosis and management of AF are essential (5).

The increasing availability of wearable technologies is improving the detection of AF and other arrhythmias in asymptomatic individuals and those with symptoms but no confirmed diagnosis (6). Typically, devices that use PPG are preferred for initial screening over pulse palpation. However, if PPG screening suggests AF, only an ECG-based method should be used to confirm the diagnosis of AF, and it is preferred over PPG-based devices (7). Furthermore, wearables are a recognized option by EHRA for intermittent postablation rhythm monitoring in clinical practice or research trials (8), potentially benefiting even frail or elderly patients through long-term digital health monitoring (9).

In real life, numerous potential barriers hinder the widespread adoption of digital health tools, including the unmet perspectives of users and healthcare professionals, developers and industry partners (10). Key barriers encompass the lack of integration into healthcare systems, MDR regulatory approval, cost-effectiveness, tailored clinical applications, patient expectations, data logistics, and cybersecurity concerns (11). These obstacles can significantly impact patients by delaying the detection and treatment of arrhythmias. For instance, in 40% of European countries, the primary method to exclude AF following a transient ischemic attack relies solely on conventional ECG, without the benefits of long-term cardiac monitoring (12).

Within the parameters of wearable technology, the quality of the ECG signal is a critical factor affecting the diagnostic accuracy for arrhythmia detection. Even in conventional multi-lead ECG Holter monitoring, providing

additional ECG channels leads to more accurate interpretations of arrhythmias when artifacts are present (13). Similarly, artifacts, noise, and other concomitant arrhythmias that produce irregular heart contractions, such as premature beats, pose the most common challenges for ECG-based AF detection in wearables (14). Most current smartwatches only record a lead-I-like ECG, which we are convinced leads to a high number of false positives, consuming substantial additional healthcare resources.

To address the aforementioned issues, this PhD research aimed to significantly advance the field of digital health. The author co-invented the first MDR CE-marked wrist-worn device that combines a PPG-based algorithm for AF screening with an intermittent, wire-free 6-lead ECG for AF confirmation (15–21). Furthermore, in addition to securing a patent, four papers were published during this PhD: two on the diagnostic performance of the device challenged with a large group of patients with premature beats, and two on AI and ECG-based risk stratification to address the hurdles of long-term monitoring.

1.2 The Aim of the Study

To invent and/or evaluate the diagnostic accuracy of novel medical tools for the detection and prediction of atrial fibrillation, incorporating a wearable electronic device with PPG and multi-lead ECG, software algorithms, and AI-based approaches.

1.3 The Objectives of the Study

The objectives of the study are:

1. To create the world's first wearable that offers a combination of continuous PPG for screening of AF together with the possibility of recording an intermittent 6-lead standard-limb-like ECG without any wires for rhythm confirmation by a physician (**Patent**, **MDR Certification**).
2. To validate the device by assessing the diagnostic performance of the PPG-based algorithm, wire-free, wearable-recorded six-lead ECGs and a system of both in short-term monitoring for suspecting and diagnosing AF, with a specific emphasis on evaluating the impact of frequent PVCs/PACs in the control group on specificity (**Paper I**).
3. To investigate whether a six-lead wearable-recorded ECG brings an additional benefit for AF detection compared to a single lead-I-like

ECG commonly used in most smartwatches and automatic PPG-based AF detector (**Paper II**).

4. To compare the diagnostic performance of the AI algorithm's arrhythmia detection with the conclusions of certified ECG technicians in long-term Holter ECGs (**Paper III**).
5. To find the risk markers of AF in a single-day Holter ECG dataset, which could stratify patients who would potentially benefit from long-term monitoring with wearable or other monitoring strategies (**paper IV**).

1.4 Defense Statements of the Doctoral Thesis

1. The first wearable technology to combine a PPG-based algorithm with a 6-lead ECG represents a significant innovation, meriting patent protection. There is substantial demand for a reliable diagnostic device among patients and healthcare institutions, leading to its successful commercialization, MDR certification, and implementation into clinical practice as a new CE-marked medical device (**Patent**, **MDR Certification**, **Commercialization**).
2. Despite the presence of frequent PVCs/PACs in the control group, physicians can detect and diagnose AF with high specificity during short-term monitoring using the device, which integrates a PPG-based algorithm and a wire-free, six-lead ECG into a cohesive system (**Paper I**).
3. A six-lead wearable-recorded ECG does bring a clear additional diagnostic benefit for AF detection compared to a single lead-I-like ECG commonly used in most smartwatches and automatic PPG-based AF detector (**Paper II**).
4. The AI algorithm's arrhythmia detection demonstrates superior diagnostic performance compared to that of certified ECG technicians in long-term Holter ECGs (**Paper III**).
5. ECG-based risk markers identified within the first 24 hours of single-day Holter monitoring (up to 30 days) can successfully predict the occurrence of AF between the following 2-30 days (**Paper IV**).

1.5 Novelty and Practical Value

The use of over-the-counter devices without MDR CE certification for medical purposes, akin to using drugs without prescriptions or relying on food supplements, falls outside the realm of evidence-based medicine. While these

devices may theoretically offer value in isolated diagnostic methods, they often lack critical elements such as open-access validation of accuracy, consideration of real-world diagnostic scenarios, a clearly defined target population, or seamless integration into the workflows of medical institutions.

The novelty of this research lies in addressing the aforementioned challenges by developing and validating a new diagnostic medical tool. This work encompasses the entire process, starting from the author's initial concept of recording a six-lead ECG without wires using a wrist-worn device, to building a prototype that combines a PPG-based algorithm with six-lead ECG functionality. Additionally, the research team explored the use of an AI algorithm for long-term ECG analysis to tackle big data challenges. They also investigated pro-arrhythmic risk markers in target patients undergoing long-term Holter monitoring, identifying individuals who could benefit from extended monitoring and early AF diagnosis.

A significant practical indirect outcome of this research is the commercialization and global mass production of a device now known as TeltoHeart. The device has received full recognition from the European Medicines Agency (EMA) with Medical Device Regulation (MDR) certification: Class I for the hardware component (the device itself) and Class IIa for the software system operating within the device and its remote platform. Furthermore, the author has identified clear target patient groups and proposed workflows for the practical implementation of TeltoHeart in long-term monitoring, aligning with the guidelines and consensus documents of EHRA and ESC.

2 LITERATURE REVIEW

2.1 Multiple-Lead, Wire- and Patch-Free ECG Technology in Wearables for Detection of Atrial Arrhythmias

Among wrist-worn wearables available on the market, no device that is CE-marked and/or FDA-approved combines a PPG-based algorithm with a six-lead ECG (22). Other watches or wristbands typically feature either an intermittent single-lead ECG, with or without a PPG-based algorithm, or solely a PPG-based algorithm for arrhythmia detection, as outlined in the review above. Therefore, a direct comparison between the invented wearable and these existing devices is not possible.

Currently, only two commercial wearable devices, Kardia Mobile 6L (KM) and Istel HR 2000 (IS), can record six-lead ECG without wires. Of note, both serve as event recorders, exclusively providing intermittent six-lead ECG for opportunistic AF screening, unlike the wrist-worn device in this PhD research, which also includes a PPG-based AF detector for continuous screening and the possibility to detect asymptomatic episodes of arrhythmia (23).

Krzowski et al. conducted a head-to-head comparison of KM and IS in 98 patients with manual interpretation by physicians (24). KM yielded a sensitivity of 88.1% and a specificity of 89.7% in diagnosing SR, while IS yielded a sensitivity of 91.5% and a specificity of 84.6%. For AF detection, KM's sensitivity was higher (86.4% vs. 77.3%), but their specificities were similar (97.4% vs. 98.7%). Notably, their control group only included patients with SR without premature contractions.

Scholten et al. found that KM's six-lead ECG outperformed single-lead ECGs from Withings and Apple Watch in sensitivity (98.9% vs. 95.4% and 96.2%) and specificity (96.7% vs. 94.9% and 94.4%) for AF detection (25). Their study also lacked a control group with premature contractions, only including patients with stable SR post-electrical cardioversion.

These findings affirm the diagnostic superiority of six-lead over single-lead ECG for AF detection. Of note, there is a gap in research concerning patients with SR and frequent premature contractions.

2.2 Automated Analysis of Single-Lead ECG in Smartwatches for Detecting Atrial Arrhythmias

Automated ECG analysis in wearables provides critical immediate feedback to users for detecting AF. However, as per EHRA guidelines, only a

board-certified physician can officially diagnose the condition (26). In a comparative study of wearables recording single-lead ECGs, the proportion of inconclusive tracings—where the algorithm could not determine the heart rhythm—was 18% for Apple Watch 6, 17% for Samsung Galaxy Watch 3, 24% for Withings Scan Watch, 21% for Fitbit Sense, and 26% for AliveCor KardiaMobile (27). Importantly, no control group of sinus rhythm with frequent premature contractions was included. Further research is necessary to determine if the automated analysis from the six-lead ECG of the invented device offers superior AF detection compared to the automated analysis of these single-lead ECGs.

When applying smartwatches for ambulatory monitoring, in addition to AF, the reason for feeling palpitations may also be paroxysmal supraventricular tachycardias, sinus tachycardia, among others. In a recent analysis involving the Move-ECG smartwatch (Withings, Issy-les-Moulineaux, France), remote monitoring was conducted for an average duration of 17 ± 14 weeks for patients experiencing paroxysmal symptoms (28). All diagnoses were made based on symptom-triggered ECG recordings, identifying conditions such as AF (n=6), sinus tachycardia (n=6), normal ECG (n=2), premature ventricular complexes (n=1), sinus bradycardia (n=1), and atrioventricular nodal reentrant tachycardia (n=1), with no diagnoses arising from routine weekly ECGs. The smartwatch's automated ECG analysis for detecting AF yielded a sensitivity of 80% and specificity of 75% when unclassified ECGs were considered false results; excluding unclassified ECGs, the sensitivity was 95% and specificity was 96%, illustrating their utility even in stressful palpitation-induced situations. Although all 17/31 patients were diagnosed with symptom-triggered ECG recordings, the routine recording of prophylactic ECGs is important for the learning curve and preserving these skills, particularly in older populations.

2.3 Artificial Intelligence for Direct-to-Physician Ambulatory ECG Reporting

The role of artificial intelligence (AI) in medicine (29), including clinical electrophysiology, continues to grow, accompanied by recent standardization efforts in AI-related research reporting (30). A notable advancement is the first randomized controlled trial which showed a significant increase in freedom from documented atrial fibrillation (AF) among patients with persistent AF who underwent AI-guided catheter ablation in addition to conventional pulmonary vein isolation (PVI), achieving 88% success

compared to 70% with PVI alone at 12 months ($P < 0.0001$ for superiority) (31).

In ambulatory ECG monitoring, the daily production of a high volume of ECGs coincides with a global shortage of healthcare workers projected at 15 million, highlighting the need for efficient AI-guided ECG analysis (32). If AI could replace technician analysis and safely enable direct-to-physician reporting, it could significantly improve healthcare accessibility.

In prior research, a deep neural network analyzed 328 thirty-second ECG strips and achieved an average area under the receiver operating characteristic curve (AUC ROC) of 0.97, with the ground truth determined by consensus among three cardiologists and a mean inter-annotator agreement of 72.8% (33). In another study, this network analyzed 828 ten-second, 12-lead resting ECGs, yielding a mean AUC ROC of 0.983 (34). Based on the examples presented and to the best of our knowledge, there is a lack of comprehensive evaluation of AI-guided models for standalone use in direct-to-physician ECG reporting. Additionally, robust validation demands a large dataset of ambulatory ECGs and collaboration among multiple expert cardiologists to establish a dependable consensus ground truth when validating AI-based ECG analysis results.

2.4 Role of PPG in Atrial Arrhythmia Detection and Large-Scale AF Screening

The role of the PPG method is acknowledged in the latest European Society of Cardiology Council on Stroke and EHRA consensus document, where it is recognized that a PPG recording may be used to provide an adequate estimate of AF burden (35). The AF burden is a valuable quantitative measure of classifying intermittent AF (rather than just paroxysmal/ persistent AF) and justifying the results of AF treatment modalities (rather than just qualitative assessment of recurrence as yes/ no). The document is the first standardization of using AF burden in clinical practice, which may lead to further development of digital health technologies and deeper knowledge of using PPG in everyday practice (36,37). The knowledge on how to use PPG-based monitoring indeed plays an important role, as presented in a recent survey on physician preferences in using novel digital devices (38). Even in the second case with an asymptomatic high-risk-of-AF patient, where an intermittent event-recorder-type ECG arguably has a lower chance of detecting AF with no symptoms, the overall number of respondents who would start PPG-based monitoring remained as low as 9.8%. Of note, physicians experienced with PPG would rather use a PPG-based device compared to other physicians in this scenario (13.6% vs. 7.2%, $P = 0.026$), suggesting the role of experience.

Also, it may represent a lack of available wearables with both a PPG-based algorithm and a reliable multiple-lead ECG in one device.

To date, two large-scale trials screening for AF with the use of wrist-worn devices with PPG-based algorithms have been published. In the Apple Heart study, in a fraction of the participants who returned the ECG patches and completed the study in relation to those who received irregular rhythm notification (450/2161, 20.1%), the notification algorithm of the device had a positive predictive value of 84% (95% CI, 76% - 92%) for observing AF on the ECG simultaneously with a subsequent irregular pulse notification (39). The overall probability of receiving notifications of irregular pulse was relatively low (over 117 days of monitoring, 2161/419297, 0.52%). Nevertheless, among those patients, frequent premature contractions significantly lowered the specificity of PPG-based notifications for irregular rhythm detection. A substudy reported that 40% of participants who received an irregular pulse notification from the Apple Watch exhibited no AF on subsequent ECG patches and were found to have other types of arrhythmias, primarily atrial or ventricular ectopic beats (40).

In another large-scale trial—the Fitbit Heart Study—the irregular heart rhythm detection was lower (4728/455699, 1%) (41) despite a potentially slightly younger population (median age 47 [35–58] yrs. vs. mean age 41±13 yrs. in Apple Heart Study). Based on AF detection on subsequent analyzable ECG patch monitor, the positive predictive value of irregular heart rhythm detection was 98.2% (95% CI, 95.5%–99.5%). The algorithm achieved high specificity (98.4%), minimizing false-positive detections primarily by a requirement of at least 30 minutes of an irregular pulse to detect AF, and by operating only during sedentary periods. This, however, significantly lowers the chance of detecting AF with durations shorter than 30 minutes. Among the reasons for lower sensitivity (67.6%), the most common was that AF occurred during the daytime when fewer periods of inactivity were available for the algorithm (56/110 of false-negative episodes) (41). This illustrates why detection of AF during periods of active motion remains a challenge and, thus, such algorithms are adapted to obligatory function only during sedentary periods.

Similarly, the negative effect of motion on the quality of the PPG signal has also been reported by other research groups in most daily activities, but it has a reasonably good quality for analysis during sleep (42). This is also relevant for PPG-based heart rate estimation with more accurate results during the nighttime than daytime (97% vs. 91 %, $P<0.001$) and during low mobility compared to high mobility (96% vs. 92%, $P<0.001$) (43).

More randomized controlled trials are needed to provide evidence with enhanced detection of treatment-relevant arrhythmias using PPG-based devices. For instance, a published paper demonstrating a certified PPG-based app on smartphone doubled the detection of treatment-relevant AF compared to usual care with odds ratios of 2.12 (95% confidence interval (CI), 1.19–3.76; P = 0.010) and 2.75 (95% CI, 1.42–5.34; P = 0.003) in the first phase and a cross-over in the second phase, respectively (44). However, just like in Apple Heart and Fitbit Heart studies, additional ECG monitoring with a separate ECG patch or ECG event recorder is usually later provided for final diagnosis establishment. In the opinion of this PhD research author, the approach of having a PPG-based algorithm for screening and multiple ECG-based confirmation already all-in-one device could save logistical resources, be more comfortable to the patient, and result in a more time-efficient workflow. This needs to be investigated in future studies.

3 METHODS

3.1 Overall Design and Rationale of the Series of Papers

This dissertation follows a cohesive methodological approach across the patent and four consecutive interrelated papers (**Table 1**):

- This invention (**Patent**) was originally conceptualized by the author to record a six-lead ECG from the wrist without wires and was developed in collaboration with the Biomedical Engineering Institute at Kaunas University of Technology (KTU).
- **Paper I** (doi: 10.3389/fcvm.2022.869730) was a prospective case-control validation study in Vilnius (Lithuania). It tested a novel wire-free, wrist-worn device integrating PPG and six-lead ECG technology, assessing whether the device could accurately detect atrial fibrillation (AF) even in the presence of frequent premature beats.
- **Paper II** (doi: 10.3389/fcvm.2023.1160242), also prospective and conducted in Vilnius, compared the diagnostic benefit of six-lead ECG with that of a single-lead ECG and the PPG-based algorithm.
- **Paper III** (doi: 10.1038/s41591-025-03516-x) was an AI validation study leveraging a large-scale ambulatory ECG dataset from the United States, comparing a deep-learning model with board-certified technician annotations for arrhythmia detection.
- **Paper IV** (doi: 10.1111/anec.13090), a retrospective case-control study using 24-hour Holter data from the United States, identified ECG-based risk markers predictive of AF during the subsequent 2–30 days.

Collectively, these papers span from the initial invention and validation of a new device to large-scale AI analysis and practical implementation considerations for AF monitoring.

Table 1. Patents and Study Design Characteristics of the Published Papers

	Paper I	**Paper II**	**Paper III**	**Paper IV**	**Patents**
Patent registration databases	NA	NA	NA	NA	Wearable device: 1) State Patent Bureau of the Republic of Lithuania (17) 2) WIPO (19) 3) EPO (18) 4) US Patent and Trademark Office (20) 5) JPO (21) Additional patent: 1) EPO (45)
Study design	Prospective case-control validation study	Prospective case-control	AI validation study of the patient cohort	Retrospective case-control	NA
Main inclusion site	Vilnius, Lithuania	Vilnius, Lithuania	United States of America	United States of America	NA
Study population	Inpatient and outpatient adults, aged ≥18 yrs.	Inpatient and outpatient adults, aged ≥18 yrs.	Outpatient adults, aged ≥18 yrs.	Outpatient adults, aged ≥18 yrs.	NA
Population size	344 patients in final analysis	249 patients in final analysis	14.606 patients	18.220 patients	NA
Aim	To evaluate whether the PPG-based algorithm, 6-lead ECG, and a system of both can accurately differentiate between AF and SR when challenged by a substantial group of patients with PVCs/PACs.	To investigate the potential diagnostic benefit of six-lead ECG compared to single-lead ECG and PPG-based algorithm for AF detection of the wrist-worn device.	To compare DeepRhythmAI-only analysis to technician analysis for detection of arrhtyhmia in ambulatory ECG. Panel beat-by-beat annotations by 17 teams of 3 expert cardiologists provided the ground truth for comparison.	To determine whether 24 h ECG data can predict AF detection on extended cardiac monitoring of the following 2-30 days.	NA

	Paper I	Paper II	Paper III	Paper IV	Patents
Length of monitoring	1) 2-3 min of ECG 2) 2-30 min of PPG	1) 2-3 min of ECG 2) 2-30 min of PPG	14 days	Up to 31 days	NA
Devices used for monitoring	a) Investigational wrist-worn device (prototype of TeltoHeart) b) a reference ECG Holter monitor (eMotion Faros, Kuopio, Finland).	a) Investigational wrist-worn device (prototype of TeltoHeart) b) a reference ECG Holter monitor (eMotion Faros, Kuopio, Finland)	PocketECG Holter ECG device (MEDICALgorithmics, Warsaw, Poland)	PocketECG Holter ECG device (MEDICALgorithmics, Warsaw, Poland).	NA
Investigational group	Patients with a current ECG-based diagnosis of AF.	Patients with a current ECG-based diagnosis of AF.	ECG recordings of random arrhythmic episodes including critical arrhythmias: atrial fibrillation ≥30s, ventricular tachycardia ≥10s + ≥120 bpm, supraventricular tachycardia ≥30s, 3rd degree AV-block, asystole ≥3.5s	"High-risk" patients defined as predicted AF risk ≥10% (matched on age in 5-year strata, sex, and recording duration).	NA
Control group (-s)	Patients with a current ECG-based diagnosis of: a) stable SR b) SR with frequent PVCs/PACs (≥ one ectopic beat in 2 min).	Patients with a current ECG-based diagnosis of SR with frequent PVCs/PACs (≥ one ectopic beat in 2 min).	NA	"Low-risk" patients defined as predicted AF risk <5% (matched on age in 5-year strata, sex, and recording duration).	NA
Number of ECG leads used in monitoring	a) 6-lead ECG with no wires (wrist-worn device) b) 3-lead ECG with wires (Holter reference)	a) 6-lead ECG with no wires (wrist-worn device) b) single-lead ECG with no wires (wrist-worn device)	2-channel ECG using three electrodes with wires, one of which serves as a ground (Holter device).	2-channel ECG using three electrodes with wires, one of which serves as a ground (Holter device).	NA

	Paper I	Paper II	Paper III	Paper IV	Patents
		c) 3-lead ECG with wires (Holter reference)			
Outcomes	Accuracy of AF detection	Accuracy of AF detection	False negative reporting of critical arrhythmia events and general accuracy of arrhythmia detection by AI network	Occurrence of AF episodes ≥30 s on days 2–30	NA
Statistical analysis	Sensitivity, specificity, accuracy, positive and negative likelihood ratio; independent sample Student's T-test/ Mann-Whitney U test; chi-square test/ a two-tailed Fisher's exact test; Cramer's V test.	Sensitivity, specificity, accuracy, positive and negative likelihood ratio; independent sample Student's T-test/ Mann-Whitney U test; chi-square test/ a two-tailed Fisher's exact test; Cramer's V test; Cohen's kappa.	Sensitivity, specificity, accuracy, positive and negative predictive value, F1 score; absolute rates of true and false positives and negatives.	Lasso model to predict AF episodes; high-risk and low-risk groups compared using conditional logistic regression analysis; ROC statistics. Prediction model 'ECG-only' included only ECG markers, while 'full model' added age and sex as well.	NA

3.2 Inclusion and Exclusion Criteria

For **Papers I** and **II**, patients were recruited from both inpatient and outpatient wards of the Cardiology Department at Vilnius University Hospital Santaros Klinikos, irrespective of the time of day. All participants provided written informed consent prior to enrolment. The trial was approved by a regional bioethics committee (registration No. 158200-18/7-1052-557) and is registered at ClinicalTrials.gov (NCT04281927).

In Paper I, eligible participants were adults aged 18 to 99 years with an ECG-based diagnosis of atrial fibrillation (AF), stable sinus rhythm (SR), or SR with frequent premature ventricular or atrial contractions (PVCs/PACs, defined as at least one ectopic beat every 2 minutes). Exclusion criteria included subjects with a regular pulse wave despite AF (e.g., paced ventricular beats), individuals with other arrhythmias, and those who refused or were unable to provide informed consent. In Paper II, the same exclusion criteria were applied, with the additional exclusion of patients with stable SR. Notably, **Paper II** is a substudy of **Paper I**, dedicated to comparing the accuracy of wearable-recorded six-lead ECG versus single-lead ECG for AF diagnosis.

In **Paper III** and **Paper IV** a pre-recorded dataset from the United States was used for either prospective AI analysis in comparison to the analysis of technicians (Paper III) or retrospective analysis to predict the occurrence of AF (Paper IV).

In **Paper III** monitoring indications were provided through the device for 14,596 patients. The most common monitoring indications were palpitations, syncope, dizziness, and examination of paroxysmal or unspecified AF. Other indications were transient ischemic attack, dyspnea, tachycardia, bradycardia, atrial flutter, premature ventricular complexes, persistent AF, stroke and other.

In **Paper IV**, the study included patients in the United States who had undergone ambulatory ECG monitoring for a duration of 2 to 30 full days in 2017. The index day was defined as the first complete day of recording. Exclusion criteria included cases with atrial fibrillation (AF) or atrial flutter observed on the index day and subjects older than 100 years. A separate analysis was conducted on a subgroup of patients who were monitored due to indications of stroke or transient ischemic attack (TIA).

3.3 Flow of Participant Inclusion

Attached below are the flowcharts or written information about the patient inclusion.

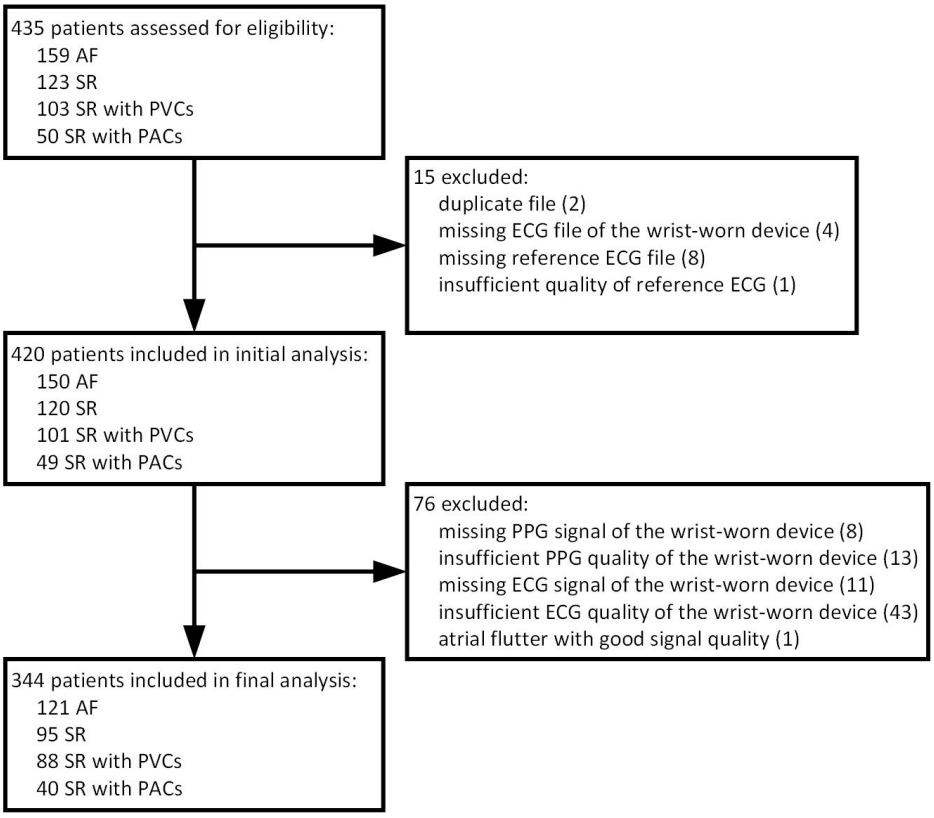

Figure 1. Flow chart of patients in **Paper I** (DoubleCheck-AF). AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; ECG, electrocardiography; PPG, photoplethysmography.

In **Paper II** from the database of DoubleCheck-AF (**Paper I**) 249 adults were enrolled in AF group (n = 121) or control group of SR with frequent premature ventricular (PVCs) or atrial (PACs) contractions (n = 128) (**Figure 2**).

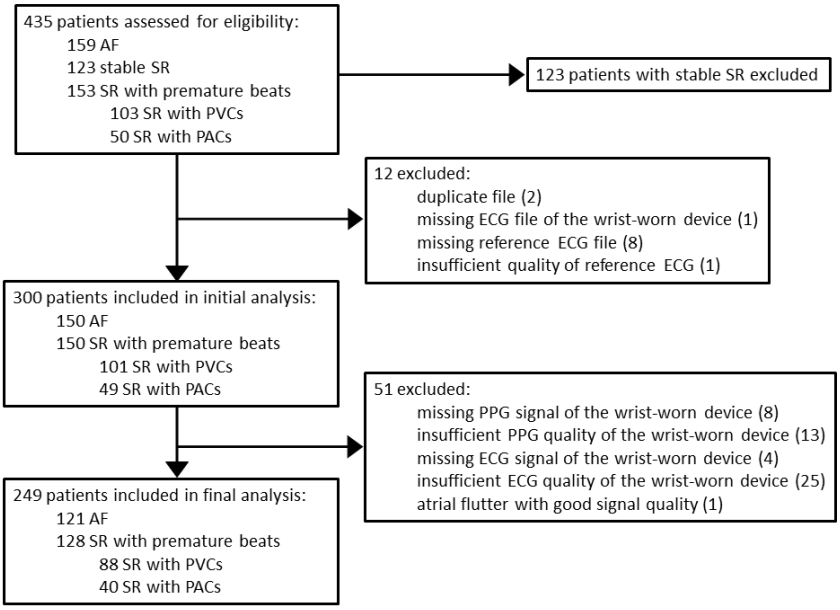

Figure 2. Flowchart of patients. AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; ECG, electrocardiography; PPG, photoplethysmography.

In **paper III** the study population consisted of 14,606 patients (mean age = 65.5 ± 10 years, 42.8% males), who were monitored for a mean of 14 ± 10 days (**Figure 3**).

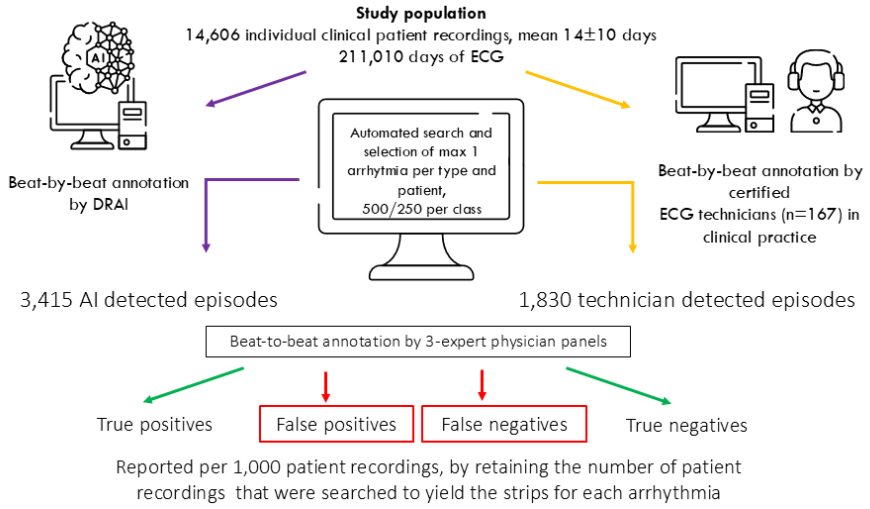

Figure 3. Flowchart and Analysis of Paper III. Courtesy MD PhD Linda Johnson, Lund University and MEDICALgorithmics.

In **paper IV** the study population was derived from patients who had recorded an ambulatory ECG with a duration of 2–30 full days of registration in the United States in 2017 (n = 19,947). Patients with AF or atrial flutter on the index day were excluded (n = 1719) as were subjects aged >100 years (n = 8). The final study population consisted of 18,220 patients and was randomly divided into equally sized training and testing datasets (n = 9110 each).

3.4 Technical Description of the Devices, PPG-Based Algorithm, Wearable-Recorded ECG, and DeepRhythmAI Model

In **paper I** and **II** cardiac rhythm monitoring was conducted using the investigational wrist-worn device, the description of which is cited here from previous publications (15,16). It is capable of providing continuous PPG-based AF monitoring and recording an intermittent, on-demand, six-lead ECG without any wires (**Figure 4**). Simultaneously, a reference ECG was registered using a medically-certified Holter monitor (Bittium Faros, Bittium, Finland).

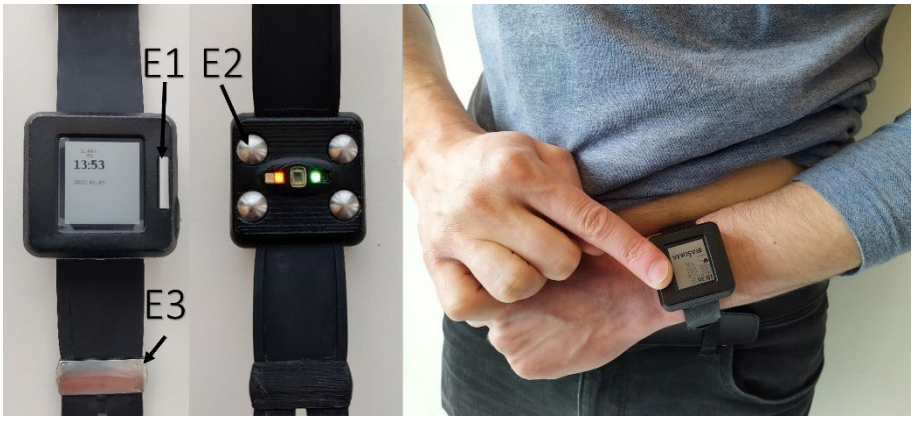

Figure 4. Prototype of the wearable device (left panel); acquisition of a 6-lead ECG without any wires (right panel).

The PPG signals are analyzed using an embedded AF detector (23), whose structure is inspired by the rhythm-based detector used for ECG signals (46). The sensor employs a green light-emitting diode, although it is also capable of recording red and infrared light channels, and uses a photodetector to continuously measure changes in blood flow. The algorithm relies on the analysis of peak-to-peak intervals using 4-8-beat long sliding window. It has several solutions to reduce the false alarm rate, including filtering of ectopic beats, bigeminy suppression, sinus arrhythmia suppression and continuous signal quality assessment. The sampling rate of the PPG signal is 100 Hz, the amplitude resolution is 18 bits, and the bandwidth is 0–50 Hz. The algorithm for AF detection is flexible with respect to the briefest

duration of possible AF episode (46). In this study, the algorithm was tuned to detect as short AF episodes as 30 seconds, accounting to the clinical definition of the minimal duration of paroxysmal AF. Therefore, the PPG-based algorithm triggers the AF alarm after an average duration of 30 seconds in AF if the condition of sufficient signal quality index is met (**Figure 5**) (23). It should be noted that the duration from the onset of AF to the alarm may vary depending on the heart rate irregularity. That is, the alarm can be triggered as soon as after 5 seconds in case of highly irregular AF, but no later than after 1 minute in case of AF with very low irregularity of heartbeats. Once the PPG-based algorithm detects a possible AF episode, it triggers a vibration alarm for the user.

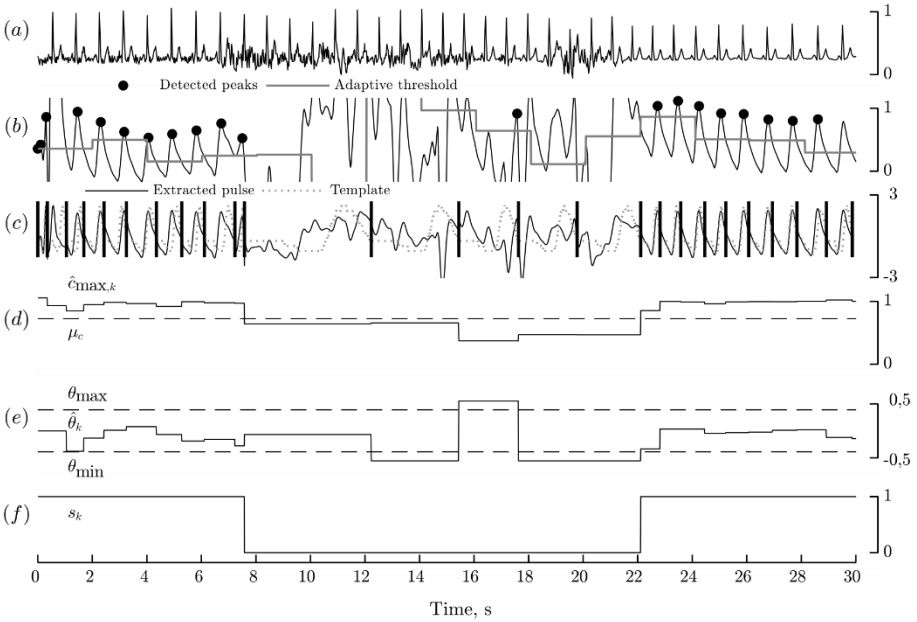

Figure 5. Illustration of signal quality assessment: synchronously wearable-recorded (a) ECG signal (displayed for reference) and, (b) PPG signal, (c) template matching (vertical lines show the boundaries of the extracted PPG pulses), (d) maximum correlation $\hat{c}_{max,\,k}$ between the extracted pulse and the template, (e) corresponding correlation lag $\hat{\theta}_k$, and (f) resulting SQI $_{Sk}$. Signal quality is assessed by comparing the lowest correlation value within a window of four to eight beats to a fixed threshold of 0.7. If this minimum value falls below 0.7, the PPG segment is classified as poor quality. Lag denotes the temporal shift in samples at which the template achieves optimal alignment with the extracted pulse. Courtesy PhD Andrius Sološenko.

Following the alarm notification, a wearable 6-lead ECG is acquired (**Figure 6**). During our study, even if no notification occurred in at least 1 minute of wearing it, an ECG was recorded as well to confirm the rhythm and investigate the method.

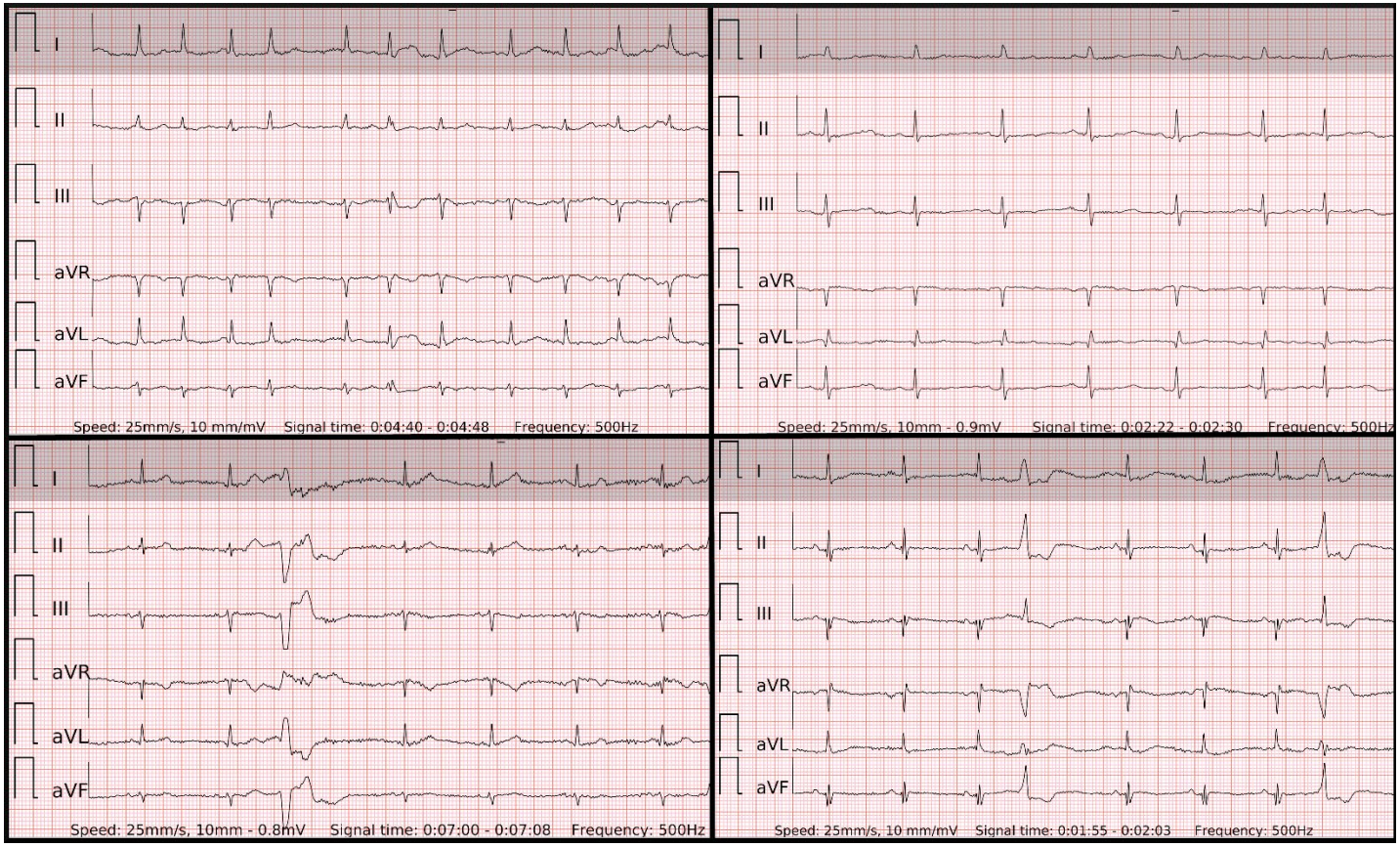

Figure 6. The 6-lead ECGs recorded by the wearable device with the examples of atrial fibrillation (top left panel); SR with frequent premature atrial contractions (top right panel); SR with frequent premature ventricular contractions with superior axis (lower left panel); SR with frequent premature ventricular contractions with inferior axis (lower right panel).

The recorded ECG leads resemble standard Einthoven-like limb leads and are measured through contact with three skin electrodes. Two electrodes are located on the outer surface: one atop the device enclosure, touched by the right index finger, and another on the bracelet, positioned against the left upper abdomen. The third electrode, situated on the inner surface adjacent to the PPG sensor, makes contact with the left wrist (**Figure 4**). Additional three ECG leads (Goldberger augmented limb leads aVR, aVL, and aVF) were calculated from Einthoven leads I, II, and III. The sampling rate of the ECG is 500 Hz, the amplitude resolution is 24bit, and the bandwidth is 0–130 Hz.

In **papers III** and **IV**, the devices used are commercially available and are summarized in **Table 1**. In **paper III**, the Deep Rhythm AI algorithm was used, the description of which is cited in the following five paragraphs from a previous publication (47).

The DeepRhythmAI model (v3.1; Medicalgorithmics) utilizes a mixed network architecture that incorporates both convolutional neural networks and transformers with custom-built components to perform QRS and noise detection, beat classification, and rhythm identification (48–51). The main network components for QRS detection and rhythm classification were pre-trained on 1,716,141 five-minute-long ECG strips and subsequently fine-tuned on 60,549 ECG strips that were each less than 30 seconds long. An overview of this comprehensive algorithm is provided in **Figure 7**, which includes preprocessing steps such as channel selection, signal amplitude scaling, and resampling at 300 Hz. In addition to initial CNN-based detection of QRS complexes, the predictions of DeepRhythmAI are based on all parts of the raw ECG signal using 7 different transformer models. This incorporates, e.g., P-waves, PR intervals, and any other parameters. The output from the deep learning model includes predictions on the presence of QRS complexes and signal readability (48), which are then integrated into an ensemble of models for final analysis.

The QRS complex detector employs a sophisticated design featuring custom residual modules inspired by MobileNetV2 (51). Each module consists of a sequence of three one-dimensional convolutional layers: a pointwise convolution that expands the feature dimensions, a convolutional layer with a 3-length kernel and variable dilation rates for detailed feature extraction, and a final pointwise convolution that restores the feature dimensions to their original size. The dilation rate in each module doubles during the first half of the model and decreases to one by the output layer. These processed features are then converted into probabilities of QRS complex presence and signal readability through a final linear layer. The

system applies thresholding and morphological operations to accurately identify QRS positions and highlight nondiagnostic ranges.

The signal-detail architecture is centered around transformer encoder layers that process the ECG signals, which are segmented into patches. Each patch is embedded by a linear layer before being processed by the transformer layers, with the resulting outputs generating logits for each QRS complex class from only those patches containing QRS complexes. This precise approach ensures focused and accurate rhythm detection. A dedicated asystole filter module mirrors the wide-context model's structure but is specially trained with unique hyperparameters and datasets suited for asystole detection.

For training, the same dataset was used across the QRS complex and noise detectors, as well as the main components of the heartbeat classification ensemble, which includes three wide-context models and three signal-detail models (**Figure 7**). Data augmentation techniques tailored to each task, such as generating noise artifacts or synthesizing heartbeats with rare features, were implemented to enhance the diversity of the training dataset and prevent overfitting. Additionally, a classifier specializing in asystole events was developed using a wide-context analysis architecture fed with a carefully selected mix of 11,670 strips with asystole or sinus arrest and 20,292 strips with noise or electrode dysfunction. The latter is typically caused by poor contact of adhesive ECG electrodes and is a well-recognized source of false-positive asystole detections or artefacts. The ensemble model output is adjusted by the asystole filter model output when necessary, providing refined probabilities for each QRS complex class.

The ECG recordings analyzed in this study had never been previously presented to the DeepRhythmAI model or any related AI model. As part of the study protocol, the entire raw ECG signal data was analyzed using the DeepRhythmAI model to perform detection and detailed beat-to-beat classification of all heartbeats.

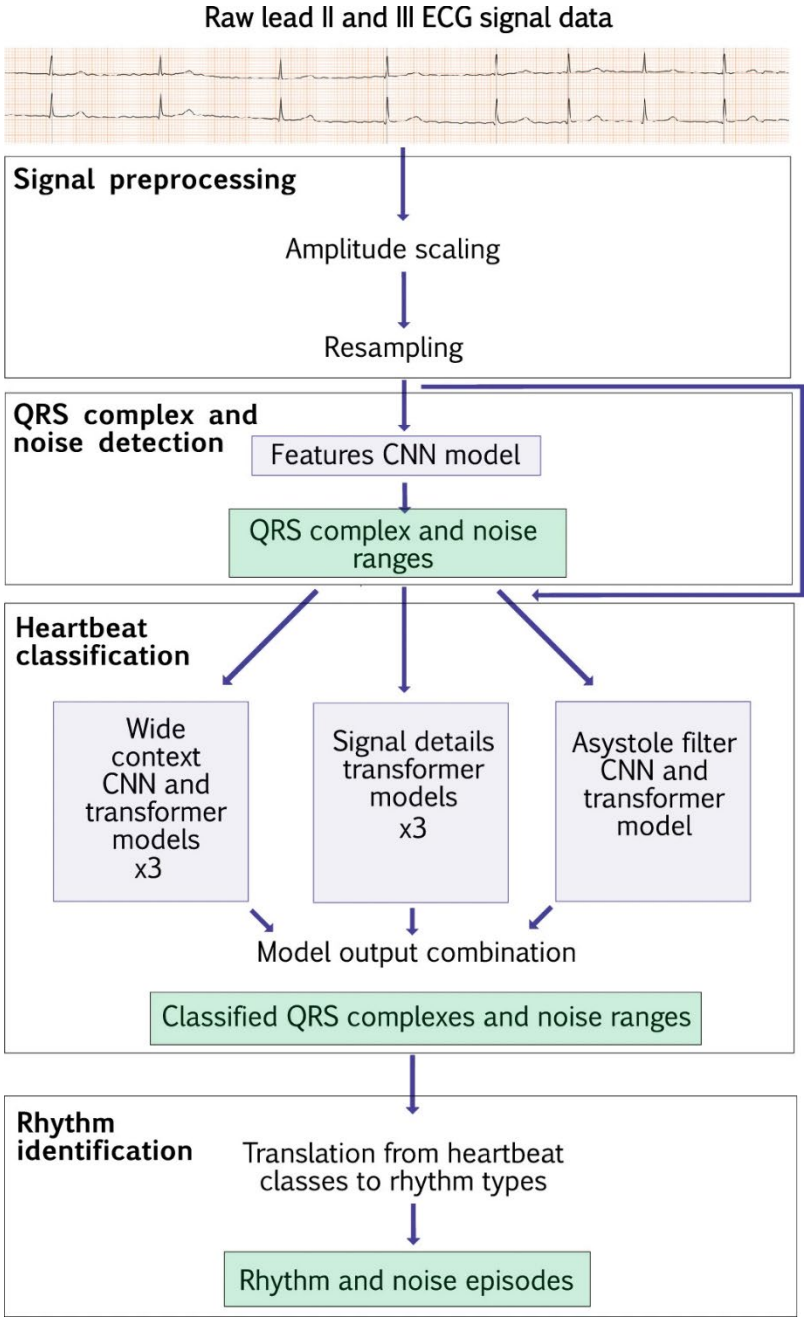

Figure 7. Schematic overview of the DeepRhythmAI model. The raw ECG signal, in timestamp + mV format, is preprocessed and analyzed by a CNN classifier that detects QRS complexes and identifies noisy segments. The output feeds into a network of seven models that analyze the data in two contexts: a wide context, assessing heart rate trends and beat morphology, and a narrow context, focusing on signal details. Three deep neural networks,

combining CNN and transformer layers, handle the wide context. The narrow context is addressed by three transformer models, tailored for 1D multichannel ECG signals based on Vision Transformer principles. An asystole filter, aligned with the wide context architecture but optimized for asystole detection, can override and replace other outputs when asystoles are detected or average them otherwise. Courtesy MD PhD Linda Johnson, Lund University and MEDICALgorithmics.

3.5 Analysis and Interpretation of ECG and PPG Data

In **papers I** and **II** two independent diagnosis-blinded cardiologists classified all ECG tracings as 'AF', 'SR' or 'Cannot be concluded'. In case of disagreement, a third diagnosis-blinded cardiologist was consulted. Reference ECG, six-lead ECG (**papers I** and **II**) and single-lead ECG (**paper II**) from each patient were evaluated. In **Paper II**, to ensure that episodes of arrhythmia appeared equivalent in a single-lead ECG, the six-lead wearable-recorded ECG was trimmed to the width of a lead-I-like ECG (marked in grey in **Figure 6**). Consequently, the accuracy comparisons between both methods at the preprocessing stage were not confounded by differences in recording complexity, as the exact same arrhythmia episodes—captured simultaneously—were used for both six-lead and single-lead ECG evaluations.

In **Papers I** and **II**, the diagnostic measures for both PPG-based and wearable ECG-based AF detection methods were calculated separately. Additionally, in **paper I** these methods were evaluated jointly as a 'double-check' system for detecting AF. In this latter strategy, an embedded PPG-based detector continuously monitors for AF episodes. If AF is suspected and the patient is alerted, only then is a matched wearable 6-lead ECG included in further data analysis for confirmation of diagnosis, mirroring the device's intended real-life operation. While this approach does not address false negatives from the PPG algorithm, i.e., sensitivity, it significantly helps reduce the number of false positives, thereby improving specificity.

All participants used the wearable device to record at least two minutes each of PPG and six-lead standard-limb-like ECG (**Table 1**). Additionally, each subject was simultaneously monitored with a validated ECG Holter monitor (eMotion Faros, Kuopio, Finland), which recorded a continuous three-lead ECG. The Holter monitor's ECG served as a gold standard for cardiologists to verify heart rhythms and provide a reliable reference for comparing the PPG-based algorithm and the wearable six-lead ECG of the device under study.

In **Paper III** ECGs underwent three separate interpretations: initially by technicians, subsequently by an AI system, and finally, the ground truth was established by expert cardiologists.

For the technician analysis, patients were referred by 1,079 different physicians across 166 clinics. The recordings were then analyzed in clinical practice at an independent diagnostic testing facility by one of 167 certified ECG technicians, each licensed in the U.S. following two years of specialized education. These technicians utilized a features-based algorithm that employed adaptive beat morphology template generation and comparison, ensuring that each QRS complex in the recording was annotated beat-by-beat by the technician. The work of ECG technicians was comprehensive, encompassing a thorough review of the entire ECG recording and the confirmation of all detected events by the algorithm, including pauses, asystoles, bradycardia events, missed heartbeats, and both 2nd and 3rd degree AV blocks, as well as all ventricular and supraventricular arrhythmias and episodes identified as atrial fibrillation. During this process, artefacts and issues with electrode functionality were corrected. Technicians also examined all sections of the recording flagged for 'patient triggered symptoms' and analyzed the data at the moments of the fastest, slowest, and average minutely heart rates. They utilized specialized software that facilitated manual inspections of heart rate trends for irregularities, allowed filtering of beats by heart rate, and enabled grouping of beats by morphology. Following the review, selected episodes were compiled into reports for physicians.

From an unselected patient population (n=14,606) an algorithm randomly searched for the presence of arrhythmic events within each rhythm class, selecting 34-second strips containing these events (**Figure 8**). Beyond just critical and noncritical rhythm classes, sinus rhythm, sinus bradycardia, and unreadable signals due to noise or electrode dysfunction were included. This inclusion aimed to assess the AI model's performance across these conditions and to provide physician annotators with a varied sample set, obscuring which strips contained critical arrhythmias. Ultimately, 5,245 strips were selected; of these, 2,240 contained critical arrhythmias. However, due to errors in uploading, ten strips were lost, resulting in a final count of 5,235 strips, with 2,236 containing critical arrhythmias.

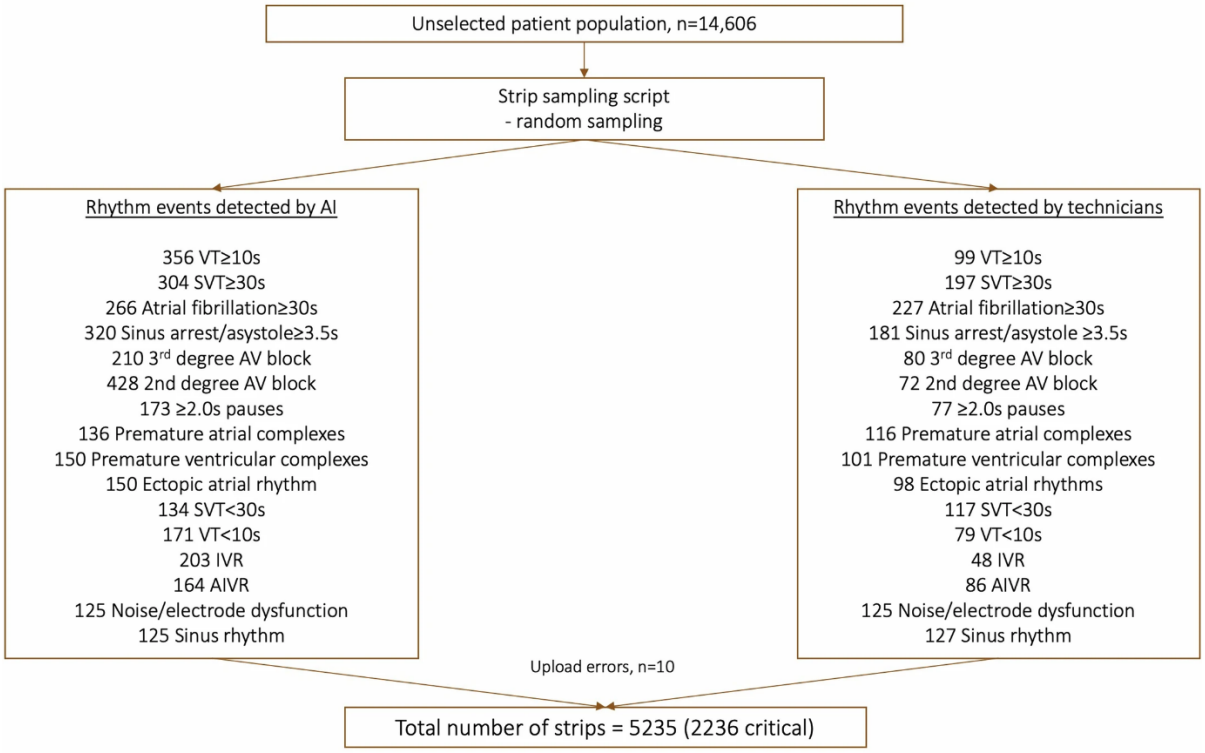

Figure 8. Strip Selection. VT = Ventricular tachycardia; AF = Atrial fibrillation; SVT = Supraventricular tachycardia; AIVR= Accelerated idioventricular rhythm; IVR = Idioventricular rhythm; EAR = Ectopic atrial rhythm. Courtesy MD PhD Linda Johnson, Lund University and MEDICALgorithmics.

Following the initial technician/AI analysis, all 34-second strips were meticulously annotated beat-to-beat by 17 panels, each consisting of three expert annotators to provide the ground truth for comparison. These panels included at least two board-certified cardiologists and were supplemented by either board-certified clinical physiologists (n = 2) or final-year cardiology residents. The physicians on the panels independently performed the annotations, blinded to the criteria used for strip selection. Strips were randomly distributed among the panels and presented in random order, with annotations being made using a custom-built software platform. Each strip was annotated beat-by-beat by the physicians, and any discrepancies at the beat level were resolved through consensus by a panel of three experts. The resulting gold-standard annotations were then compared to the beat-to-beat annotations made by the AI model and technicians based on prespecified acceptance criteria. Arrhythmic events were considered concordant with the panel annotations if there was ≥80% overlap in beat type and duration for all sustained tachyarrhythmias, and 90% overlap in duration for asystole events and pauses. For second- or third-degree AV block, the presence of any such event within the strip was deemed a concordant annotation. Single ectopic atrial and ventricular beats were deemed concordant within ±45 samples (150 ms). Noise annotations were deemed concordant if they matched at least 80% of the panel annotation in duration. Thus, minor discrepancies between the AI/technician annotations and the consensus panel annotations, on the beat-to-beat level, were permissible, such as a low number of supraventricular beats or beats with unknown types within AF episodes.

In **Paper IV**, as referenced here from a previous publication (52), all arrhythmias were detected using a deep learning algorithm, which performed beat-to-beat labeling of the entire recording for up to 31 days and included manual verification. Atrial fibrillation (AF) was defined as ≥30 seconds of irregular rhythm without discernible P-waves. Premature atrial complexes (PACs) were identified as premature complexes (QRS duration <120 ms) with incomplete compensatory pauses, while wide complex PACs due to aberrant conduction were specifically categorized. Premature ventricular complexes (PVCs) were defined as premature wide complexes with complete compensatory pauses. For both PACs and PVCs, prematurity was determined by a beat preceded by a rate interval that was >20 beats per minute faster than the preceding normal-to-normal interval.

A Lasso model with cross-validation and penalized coefficients was derived in a random 50% of the cohort (the training dataset) with AF as outcome. For inclusion, we specified a total of 28 predictors: age, sex, and ECG-derived variables including mean, minimum, and maximum heart rate during sinus rhythm; the lowest heart rate during bradycardia; the rate and

pattern of occurrence of PACs and PVCs as singles, couplets, triplets, SVTs, and VTs, as well as heart rate during couplets, triplets, and SVT, AIVR, or VT events. Arrhythmia frequencies were derived from total diagnostic signal time. In order to account for possible nonlinear relationship and highly skewed data, heart rate variables and variables describing the frequency of PAC and PVC occurrence were stratified according to deciles; the resulting strata were entered into the model as continuous variables. This model was denoted the "full model." For comparison, we also derived an "'ECG-only' model" based only on ECG-derived variables, without age and sex.

Since the Lasso model is a parsimonious model based on goodness of fit, the selected variables may not include all clinically relevant 24-h ECG risk markers. We therefore wanted to analyze differences in the 24-h ECG pattern among patients with a high risk of AF compared to patients with a low risk of AF. In order to do so, we performed a nested case–control study where "high-risk" patients, defined as predicted AF risk ≥10% were matched on age in 5-year intervals, sex, and recording duration, to "low-risk" patients, defined as predicted AF risk <5%. The resulting matches were then compared to each other using conditional logistic regression analysis adjusted for age, sex, and recording duration.

The statistical analysis measures from all papers are summarized in **Table 1**.

4 RESULTS

4.1 Intellectual Property and Development Contributions: Patents, MDR Certification, and Commercialization of the Wearable Technology

4.1.1 Patents

The major author's intellectual property contribution was the original creation of an idea in 2015-2016 to record a six-lead standard-limb-like ECG without any wires for diagnosis confirmation. This method was then co-developed into a practical application with the Bioengineering Institute of Kaunas University of Technology, led by Vaidotas Marozas and Andrius Petrenas, who were essential in transforming the concept into a tangible device. In addition, this device incorporates a PPG-based algorithm for AF detection, further enhancing the long-term monitoring and detection of asymptomatic arrhythmias. Moreover, the author made significant contributions through his practical observations, which included but were not limited to optimizing the placement of electrodes on the device and ensuring their correct positioning on the patient's skin to address potential issues. He focused on configuring the most user-friendly arrangement of the Einthoven-triangle-like electrode configuration on the skin, identifying the most optimal anatomical locations for electrode placement, and investigating how variations in electrode localization affect ECG signals and other aspects.

This innovative work led to the creation of the world's first wearable device that offers both continuous PPG for screening of AF and the capability to record intermittent, six-lead standard-limb-like ECG without wires for rhythm confirmation by a physician. The initial patent was filed as a national patent in Lithuania before the start of this PhD on November 22, 2018 (Priority Data) (17), co-authored by JB and colleagues, led by Andrius Petrenas. Subsequently, the patent was extended internationally on November 21, 2019, under WIPO (19) with the PCT Number: WO/2020/104986A, and has since been successfully published by the United States Patent and Trademark Office (20), Japan Patent Office (JPO) (21), and European Patent Office (EPO) (18).

The main patent, titled 'A Long-Term Non-Invasive System for Monitoring and Characterizing Atrial Arrhythmias in Patients with Post-Stroke Conditions,' is currently registered with five patent offices. The essential claims extracted from the patent are as follows:

1. Claim #1: A system for detection and long-term monitoring of atrial arrhythmias as well as for time distribution characterisation of atrial

arrhythmia's episodes in a patient non-invasive way, comprising the following components:

- a portable patient coupled device,
- a patient's smart device,
- a physician's smart device,
- a server intended for data transferring between the devices, data storage, processing, visualisation and report development.

2. Claim #5: A method for heart arrhythmia monitoring and characterisation according to claim 1, characterized in that, the a long-term arrhythmia monitoring is carried in non-invasive way, in which the continuous analysis of photoplethysmography signal is used to detect pulse irregularities, as well as a short-term electrocardiography, recorded by simultaneously touching with a finger the portable device (I lead), chest, abdomen or leg (modified I, II, III, aVR, aVL, aVF leads), which is used to reduce the number of false alarms.

The embodiments for system implementation are demonstrated below in **Figure 9** and **Figure 10**.

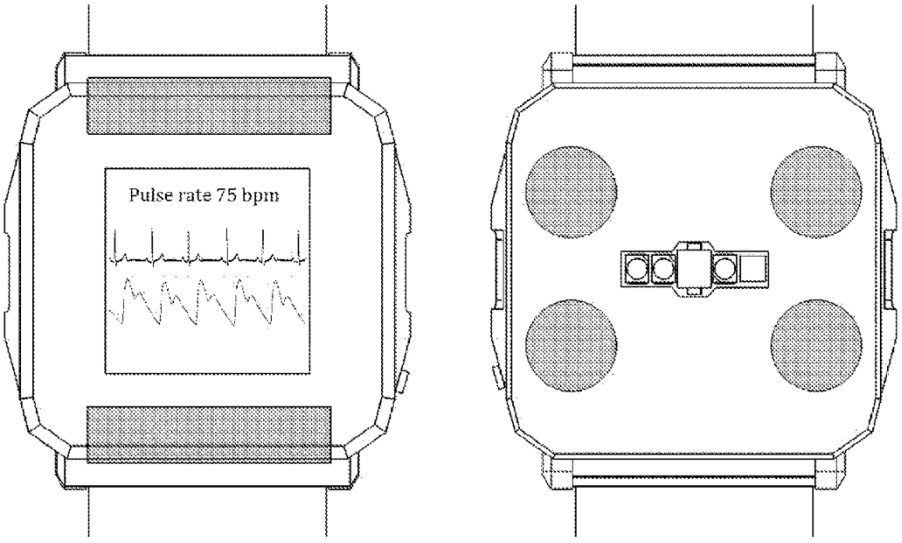

Figure 9. The view of the main components of the patient-coupled device.

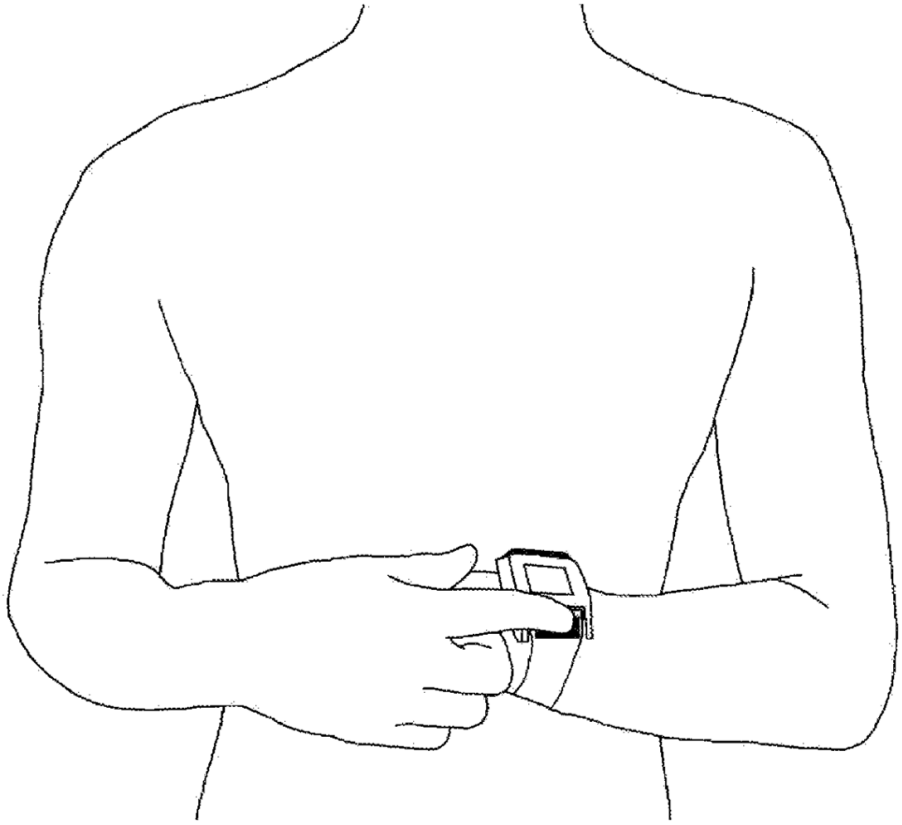

Figure 10. Presents one of the options of the device use, designed to record a 6-lead electrocardiogram not utilising the sticky electrodes (17).

Additionally, the author has contributed to another patent entitled 'Method for Establishing a Causality Score Between Atrial Fibrillation Triggers and Atrial Fibrillation Pattern,' which details a methodological approach for determining the relationship or causality between specific triggers of atrial fibrillation and the resulting patterns of the condition (45).

4.1.2 MDR Certification

From the inception of the device concept, designed to record PPG and 6-lead ECG, there was a deliberate strategy to position it as a professional medical device, distinguishing it from many consumer-grade lifestyle wearables available over the counter. Accordingly, the device underwent **MDR certification** and other certifications (53). The commercial version, now branded as Teltoheart, has successfully completed a comprehensive certification process. It has achieved **Class I CE marking** for the hardware

and **Class IIa CE marking** for the software and remote cloud platform. Throughout this process, the author of this PhD thesis played a pivotal role as the main clinical advisor.

4.1.3 Commercialization

Regarding the successful **commercialization** of the invention, the author has been significantly involved in the Research & Development department at Teltonika Telemedic. Specifically, leading the MDR certification process has been a key aspect of the work, contributing substantially to the device's global sales within the medical device and Internet of Things industries. Due to significant demand for a CE-marked PPG-based device capable of recording a multiple-lead ECG without wires, as of April 2025, TeltoHeart has been adopted by over 30 clinics worldwide, becoming an integral part of their treatment services. Each day, numerous physicians rely on data from TeltoHeart to make clinical decisions. Currently, the device is sold in 30 countries across 5 continents, with major buyers highlighted in **Figure 11**.

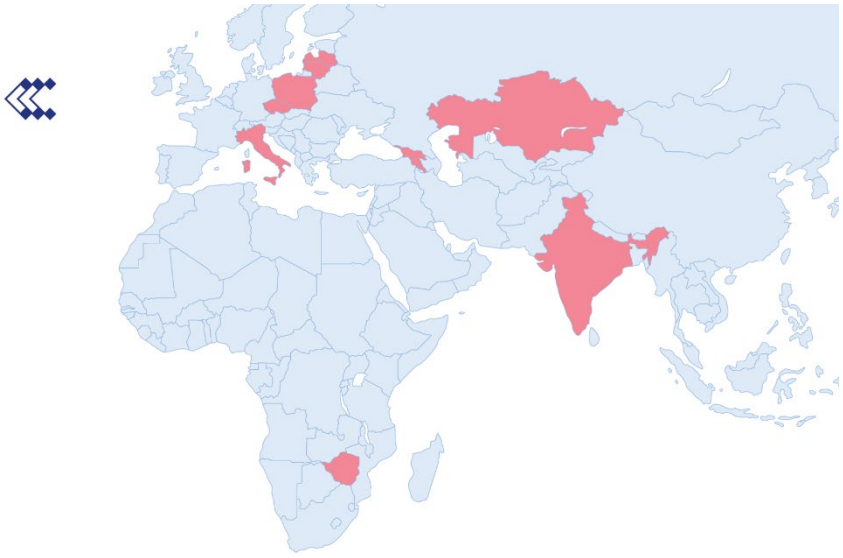

Figure 11. Global sales map of TeltoHeart as of April 2025, highlighting major buyers. Courtesy of Teltonika Telemedic.

4.2 Contributions in Scientific Papers

The author of this PhD thesis served as the principal investigator in **Paper I** and **Paper II**, with main responsibilities including study design and execution. These studies represented the first comprehensive clinical

investigations of the invented device in patients with heart rhythm disorders. The author was also directly involved in patient-related tasks such as recruitment and inclusion, conducted the majority of the statistical analyses, drafted both manuscripts, and contributed to their critical revision.

In **Paper III**, the author coordinated the Lithuanian panel of three cardiologists during the annotation process, completed full annotation of presented ECG recordings, and participated in the critical revision of the manuscript, resulting in co-authorship of the final scientific publication.

In **Paper IV**, the author contributed to the critical revision of the manuscript, which led to co-authorship of the published paper.

4.3 Paper I: Validating the Device by Assessing Diagnostic Accuracy

All three diagnostic methods of the invented device were tested not only against a control group with stable sinus rhythm (SR) but also against a control group with SR that exhibited frequent premature beats. The latter group consisted of 128 individuals with dominant PVCs (n = 88) or PACs (n = 40) (**Table 2**). The results in this chapter are cited from the previous publication (15).

Table 2. Baseline characteristics

Characteristic	AF (n=121)	Stable SR (n=95)	SR with frequent premature contractions (n=128)
Age (yrs.), mean ± SD	65.6 ± 11.2	64.0 ± 13.8	67.3 ± 14.2
Male, n (%)	64 (52.9)	55 (57.9)	69 (53.9)
Paroxysmal: Persistent: Permanent AF	101:14:6	NA	NA
Type and frequency of premature contractions			
Dominant PVC: Dominant PAC type	NA	NA	88:40
Cases with frequent runs of ≥3 PACs/ PVCs, n (%)	0 (0)	0 (0)	12 (9.4)
Cases with frequent bigeminy/ trigeminy episodes, n (%)	0 (0)	0 (0)	31 (24.2)
PVCs, median beats/min (IQR)	< 0.5	<0.5	6.7 (16.4-2.6)
PACs, median beats/min (IQR)	<0.5	<0.5	5.5 (14.6-2.9)
Total, median beats/min (IQR)	<0.5	<0.5	6.2 (16.1-2.8)

Characteristic	AF (n=121)	Stable SR (n=95)	SR with frequent premature contractions (n=128)
$CHADS_2VASc$ risk score (categorical)			
0-1, n (%)	37 (30.6)	4 (18.2)[a]	1 (3.2)[b]
2-4, n (%)	64 (52.9)	14 (63.6)[a]	21 (67.7)[b]
≥5, n (%)	20 (16.5)	4 (18.2)[a]	9 (29)[b]
$CHADS_2VASc$ risk score (quantitative), mean ± SD	2.7 ± 1.7	3.1 ± 1.4[a]	3.8 ± 1.7[b]
HAS-BLED score, mean ± SD	0.9 ± 0.8	0.8 ± 0.6[a]	1.4 ± 1.0[b]
OAC, n (%)	91 (75.2)	19 (20)	23 (18)
DOAC, n (%)	67 (55.4)	15 (15.8)	15 (11.7)
Warfarin, n (%)	23 (19)	4 (4.2)	8 (6.3)
LMWH, n (%)	1 (0.8)	0 (0)	0 (0)

[a]Calculated for patients with a history of AF, thus the denominator is 22. [b]Calculated for patients with a history of AF, thus the denominator is 31. AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; OAC, oral anticoagulant; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; IQR, interquartile range.

To meet a threshold for a sufficient frequency of at least one extrasystole per 2 min, a Holter ECG of validated device was thoroughly examined. The real burden of PVCs/PACs exceeded the threshold to a large extent and comprised a median of 6.2 (16.1–2.8) premature beats per minute. Importantly, almost a quarter of this group (31/128, 24.2%) had episodes of bigeminy or trigeminy and almost a one-tenth (12/128, 9.4%) had runs of ≥3 PACs/PVCs which were often irregular (**Figure 12**). The mentioned arrhythmogenicity parameters reflect the significant pressure we have put on both the PPG algorithm and the ECG of the device to differentiate between SR and AF.

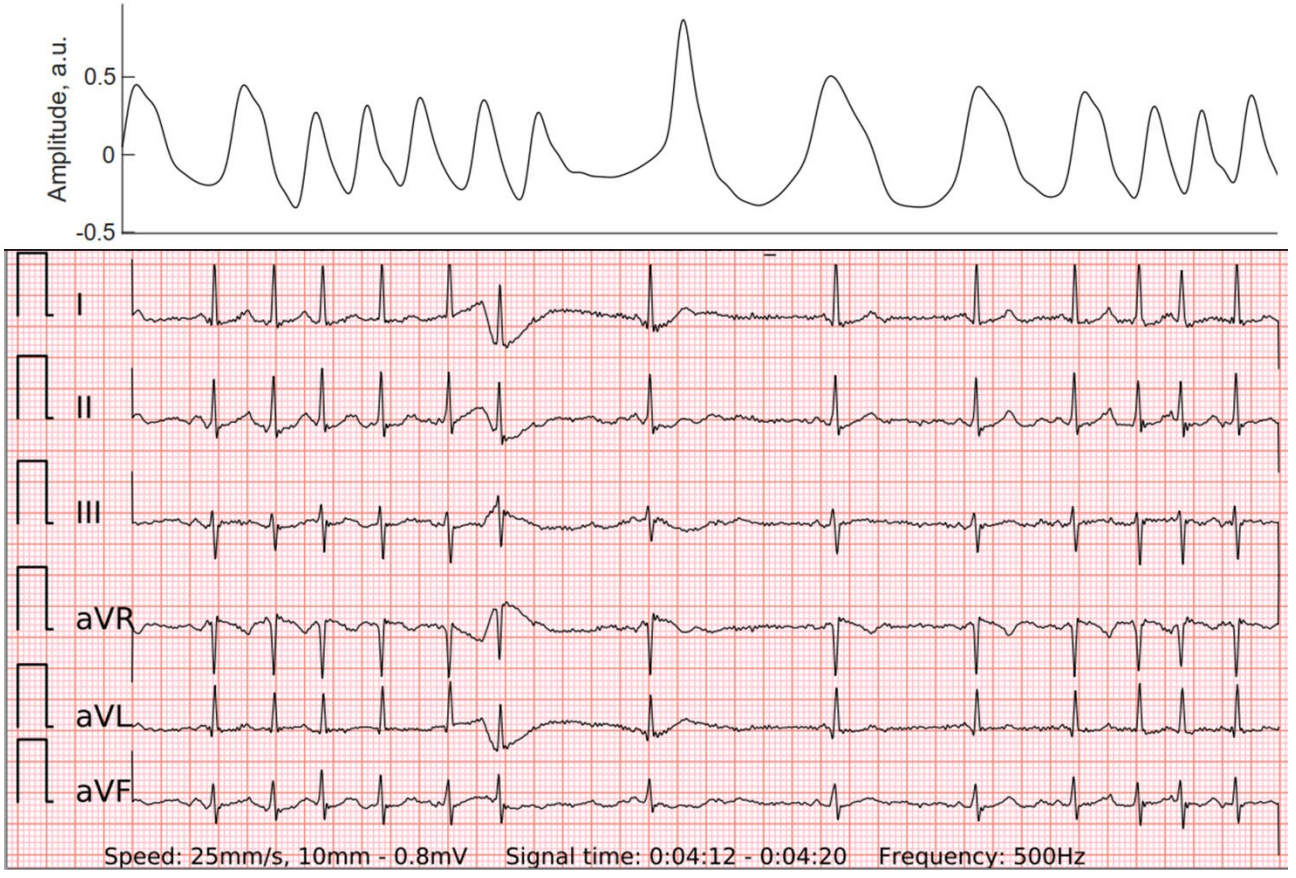

Figure 12. PPG (top panel) and wearable 6-lead ECG (lower panel) of the atrial run, which may also be called “micro-AF”. By definition, it is a sudden onset of irregular tachycardia with episodes of ≥5 consecutive supraventricular beats and total absence of P-waves, lasting less than 30 s (54).

4.3.1 Automated PPG-Based Algorithm of the Device for AF Detection

The total duration of the PPG recordings of 344 individuals was 8933.8 min, averaging 26.0 ± 29.9 min per patient. The PPG-based detector embedded in the wrist-worn device analyzed the rhythm and successfully detected AF with an overall accuracy of 99.9% when AF was compared to the stable SR group (**Table 3**). In addition, if we included patients with frequent PVCs/PACs into the control group, it resulted in seven false-positive cases (three due to frequent PVCs and four due to frequent PACs) compared to none in stable SR group ($P < 0.001$). Consequently, the overall accuracy dropped to 96.8%.

Table 3. Diagnostic measures of automated PPG-based algorithm for AF detection

Measure	AF vs. stable SR group (n=216)	AF vs. both SR groups including frequent PVCs/PACs (n=344)
Sensitivity (%), (95% CI)	94.2 (88.4-97.6)	94.2 (88.4-97.6)
Specificity (%), (95% CI)	100 (96.2-100)	96.9 (93.6-98.7)
Accuracy (%), (95% CI)	99.9 (98.2-100)	96.8 (94.4-98.4)
LR (+), (95% CI)	-	30.01 (14.46-62.31)
LR (-), (95% CI)	0.06 (0.03-0.12)	0.06 (0.03-0.12)

AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; LR (+), positive likelihood ratio; LR (-), negative likelihood ratio.

As anticipated, the median of premature beats per minute in our false-positive cases of the PPG-based algorithm reached 13.2 (IQR 41.2–10), ($n = 7$) and tended to be higher compared to the burden of ectopy in the rest of cases in the group of SR with frequent PVCs/PACs, which comprised 5.6 (IQR 16–2.5), ($n = 121$) ($P = 0.053$) (**Figure 13**). In contrast, among false-positive cases subgroup none of the patients had bigeminy/trigeminy episodes (0 of 7, $P = 0.124$) and only a minority had frequent runs of ≥3 PACs/PVCs (2 of 7, $P = 0.073$).

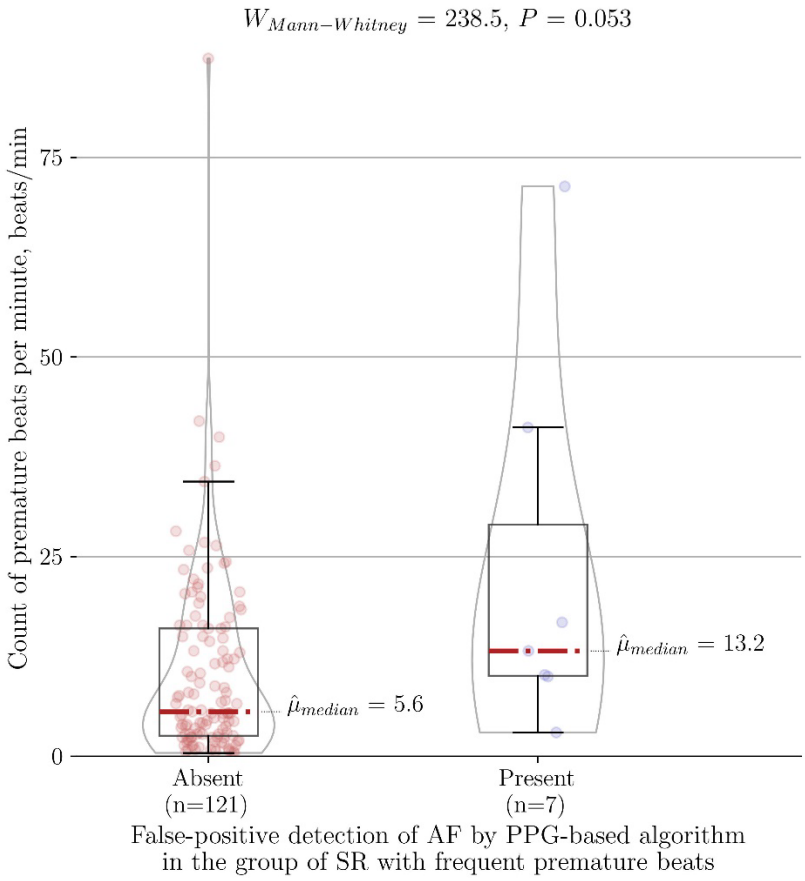

Figure 13. Association between count of premature beats per minute and type I error of the PPG-based algorithm for AF detection in the control group of SR with frequent premature beats (n = 128). PPG, photoplethysmography; AF, atrial fibrillation; SR, sinus rhythm.

4.3.2 Six-Lead-ECG of the Device for AF Detection When Assessed by Independent Cardiologists

When three diagnosis-blinded cardiologists assessed wearable ECG recordings (n=344), three of them were classified as 'Cannot be concluded' (n=3). The rest of the tracings (n=341) yielded a sensitivity of 99.2%, a specificity of 100% and an accuracy of 100% when comparing the AF group vs. the stable SR group (**Table 4**). Extending the control group with all SR patients including frequent PVCs/PACs led to a sensitivity of 99.2%, a specificity of 99.1% and an accuracy of 99.1%. Similarly to PPG-based AF detection results, the group of SR with frequent premature contractions here added two false-positive cases and thus slightly decreased the specificity.

However, the difference of type I error due to inclusion of patients with frequent PVCs/PACs was not significant compared to the stable SR group (P = 0.065).

Table 4. Diagnostic measures of the 6-lead ECG of the device for the detection of AF

Measure	AF vs. stable SR group (n=214)	AF vs. both SR groups including frequent PVCs/PACs (n=341)
Sensitivity (%), (95% CI)	99.2 (95.4-100)	99.2 (95.4-100)
Specificity (%), (95% CI)	100 (96.2-100)	99.1 (96.8-99.9)
Accuracy (%), (95% CI)	100 (-)	99.1 (97.4-99.8)
LR (+), (95% CI)	-	110.07 (27.70-437.41)
LR (-), (95% CI)	0.01 (0.00-0.06)	0.01 (0.00-0.06)

AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; LR (+), positive likelihood ratio; LR (-), negative likelihood ratio.

4.3.3 The Cohesive System of the PPG-Based Algorithm and the Six-Lead-ECG of the Device for AF Detection

The model of integrated 'double-check' system with both methods together, as described in the measurements section, yielded a sensitivity of 94.2%, a specificity of 100% and an accuracy of 99.9% when differentiating between AF vs. stable SR (**Table 5**). Furthermore, comparing AF vs. all patients with SR including frequent PVCs/PACs led to a sensitivity of 94.2%, a specificity of 99.6% and an accuracy of 99.5%. Of seven initially false-positive cases by the PPG-based algorithm, the diagnosis-blinded cardiologists were able to correct the diagnosis to SR in six of them (P = 0.012). The system of both methods demonstrated a high Cramer's V association (0.949, P < 0.001) (**Figure 14**).

Table 5. Diagnostic measures of the system combining monitoring with an automated PPG-based algorithm together with the 6-lead wearable ECG confirmation

Measure	AF vs. stable SR group (n=216)	AF vs. both SR groups including frequent PVCs/PACs (n=344)
Sensitivity (%), (95% CI)	94.2 (88.4-97.6)	94.2 (88.4-97.6)
Specificity (%), (95% CI)	100 (96.2-100)	99.6 (97.5-100)
Accuracy (%), (95% CI)	99.9 (98.2-100)	99.5 (98.0-100)
LR (+), (95% CI)	-	210.10 (29.71-1485.76)
LR (-), (95% CI)	0.06 (0.03-0.12)	0.06 (0.03-0.12)

AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; LR (+), positive likelihood ratio; LR (-), negative likelihood ratio.

4.3.4 Summary

To summarize, the system of both PPG-based algorithm and six-lead ECG yielded a sensitivity of 94.2% and a specificity of 99.6%. A separate method of manual six-lead ECG interpretation yielded a sensitivity of 99.2% and a specificity of 99.1% (**Paper I**).

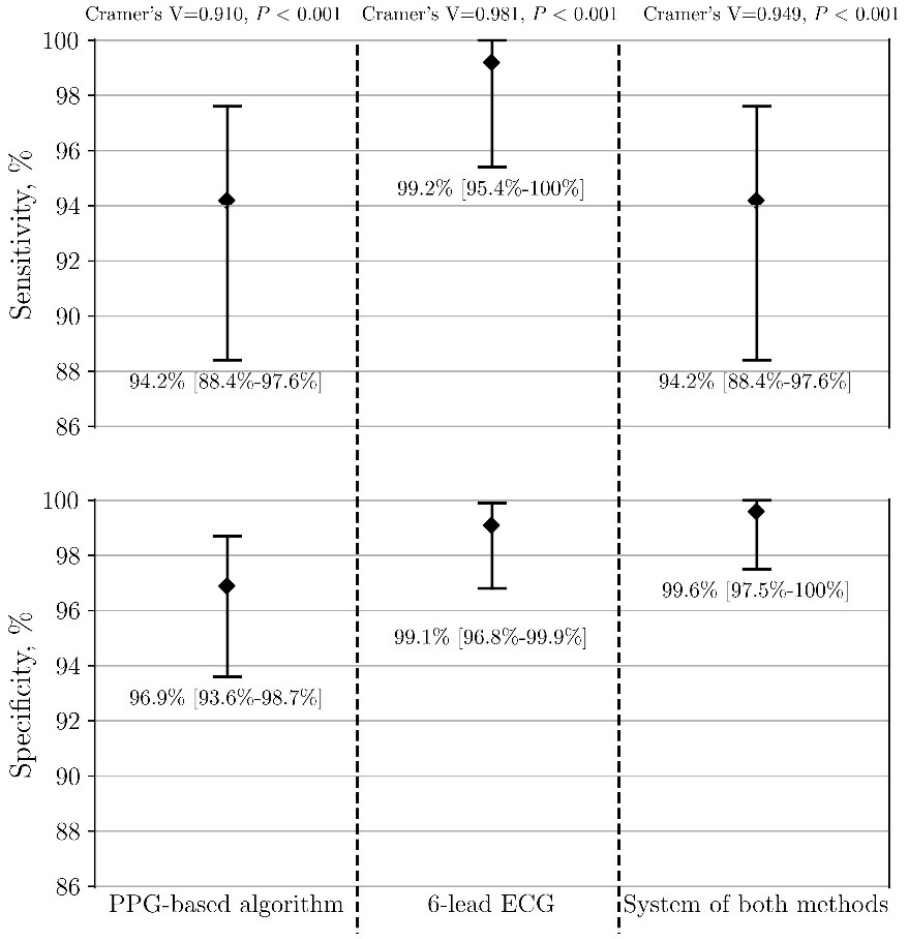

Figure 14. Performance of PPG-based algorithm, 6-lead ECG and the system of both methods to detect AF (n = 341). The group of AF is compared to both control SR groups, including patients with frequent PVCs/PACs. PPG, photoplethysmography; ECG, electrocardiography; AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction.

Despite the presence of frequent PVCs/PACs in the control group, physicians can detect and diagnose AF with high specificity during short-term monitoring using the device, which integrates a PPG-based algorithm and a wire-free, six-lead ECG into a cohesive system.

4.4 Paper II: Comparison of Six-Lead ECG with Single-Lead ECG for AF Detection

A crucial aspect of comparing the diagnostic methods involved challenging the device's performance with a significant presence of premature beats in the control groups. In the control subgroup of SR with PACs and PVCs, the median burden of premature beats per minute was recorded at 5.5 beats/min (IQR 3, 13.9) and 6.7 beats/min (IQR 2.7, 16.4), respectively (**Table 6**). Patients with frequent PVCs were more likely to exhibit bigeminy/trigeminy (31.8%, 28/88) and less likely to present with runs of ≥3 beats (5.7%, 5/88), compared to patients with frequent PACs, who showed rates of 7.5% (3/40) for bigeminy/trigeminy and 17.5% (7/40) for runs of ≥3 beats. These findings highlight not just the occurrence of discrete single premature beats but also the patterns of grouped extrasystoles or very frequent bigeminy/trigeminy episodes, contributing to significant irregularity.

In the group of AF the median duration of an ECG and the median number of six-lead or single-lead ECG recordings per patient was 166.5 s (130, 222.5) and 1 recording (1, 1), respectively.

In the control group of frequent PACs/PVCs the median duration of an ECG and the median number of six-lead or single-lead ECG recordings per patient was 156 s (125.5, 209.8) and 1 recording (1, 2), respectively.

Accordingly, the duration of PPG signal per patient was 1,358 seconds (892, 2,206) in patients with AF and 1,113 seconds (915.8, 1,718.8) in patients with frequent premature beats.

Table 6. Baseline characteristics

Characteristic	AF (n=121)	SR with frequent premature contractions (n=128)	
		SR with frequent PACs (n=40)	SR with frequent PVCs (n=88)
Age (yrs.), mean ± SD	65.6 ± 11.2	70.9 ± 11.6	65.7 ± 15.0
Male, n (%)	64 (52.9)	20 (50)	49 (55.7)
Paroxysmal: Persistent: Permanent AF	101:14:6	NA	NA
Type and frequency of premature contractions			

Characteristic	AF (n=121)	SR with frequent premature contractions (n=128)	
		SR with frequent PACs (n=40)	SR with frequent PVCs (n=88)
Cases with frequent runs of ≥3 PACs/ PVCs, n (%)	0 (0)	7 (17.5)	5 (5.7)
Cases with frequent bigeminy/ trigeminy episodes, n (%)	0 (0)	3 (7.5)	28 (31.8)
PACs, median beats/min (IQR)	< 0.5	5.4 (2.6, 12.8)	<0.5
PVCs, median beats/min (IQR)	<0.5	<0.5	5.6 (2.4, 16.4)
Total, median beats/min (IQR)	<0.5	5.5 (3, 13.9)	6.7 (2.7, 16.4)
$CHADS_2VASc$ risk score (categorical)			
0-1, n (%)	37 (30.6)	1 (7.1)[a]	0 (0)[b]
2-4, n (%)	64 (52.9)	8 (57.1)[a]	13 (76.5)[b]
≥5, n (%)	20 (16.5)	5 (35.7)[a]	4 (23.5)[b]
$CHADS_2VASc$ risk score (quantitative), mean ± SD	2.7 ± 1.7	4 ± 2.1[a]	3.6 ± 1.2[b]
HAS-BLED score, mean ± SD	0.9 ± 0.8	1 ± 0.7[a]	1.7 ± 1.2[b]
OAC, n (%)	91 (75.2)	10 (25)	13 (14.8)
DOAC, n (%)	67 (55.4)	6 (15)	9 (10.2)
Warfarin, n (%)	23 (19)	4 (10)	4 (4.5)
LMWH, n (%)	1 (0.8)	0 (0)	0 (0)

[a]Calculated for patients with a history of AF, thus the denominator is 14. [b]Calculated for patients with a history of AF, thus the denominator is 17. AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; OAC, oral anticoagulant; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; IQR, interquartile range.

4.4.1 Single-Lead ECG, Six-Lead ECG and PPG-Based Algorithm for AF Detection when Controlled by SR with PACs and PVCs

When compared to the control group, AF detection based on six-lead ECG, single-lead ECG, and PPG-based detector yielded a sensitivity of 99.2% (95% CI: 95.4–100), 95.7% (95% CI: 90.3–98.6), and 94.2% (95% CI: 88.4–97.6), respectively (**Table 7**). Due to type I error, the specificity of the same diagnostic tools was 98.4% (95% CI: 94.4–99.8), 92.5% (95% CI: 86.2–96.5) and 94.5% (95% CI: 89.1–97.8), respectively. The six-lead ECG demonstrated the highest overall accuracy with 98.4% (95% CI: 89.1–97.8), followed by the PPG-based detector with 94.5% (95% CI: 90.9–97) and single-lead ECG with 92.5% (95% CI: 88.4–95.5).

Table 7. Diagnostic measures of the wrist-worn device for AF detection controlled by SR with PVCs/PACs

Measure	Single-lead ECG	Six-lead ECG	PPG-based detector
[a]Sensitivity, % (95% CI)	95.7 (90.3-98.6)	**99.2** (95.4-100)	94.2 (88.4-97.6)
[a]Specificity, % (95% CI)	92.5 (86.2-96.5)	**98.4** (94.4-99.8)	94.5 (89.1-97.8)
[a]Accuracy, % (95% CI)	92.5 (88.4-95.5)	**98.4** (96.0-99.6)	94.5 (90.9-97)
False positive cases, n (%)	**9/120 (7.5)**	2/127 (1.6)	7/128 (5.5)
False negative cases, n (%)	5/117 (4.3)	1/119 (0.8)	**7/121 (5.8)**
Cannot be concluded by a physician, n (%)	**12/249 (4.8)**	3/249 (1.2)	NA
Cramer's V, PACs subgroup	0.803, $P < 0.001$	**0.950**, $P < 0.001$	0.823, $P < 0.001$
[b]Inter-rater agreement, PACs subgroup	0.803, $P < 0.001$	**0.950**, $P < 0.001$	NA
Cramer's V, PVCs subgroup	0.918, $P < 0.001$	**0.990**, P < 0.001	0.903, P < 0.001
[b]Inter-rater agreement, PVCs subgroup	0.918, P < 0.001	**0.990**, P < 0.001	NA
AUC, PACs subgroup (95% CI)	0.898 (0.849-0.946)	**0.971** (0.948-0.994)	0.921 (0.881-0.962)
AUC, PVCs subgroup (95% CI)	0.961 (0.935-0.987)	**0.996** (0.988-1.00)	0.954 (0.926-0.982)
PACs/PVCs in false positive cases, median beats/min (IQR)	18.8 (11.6, 22.6)	**64.3** (41.2, 87.4)	13.2 (10, 41.2)

[a]Calculated for the overall control group of SR with PACs and PVCs. [b]Measured as Cohen's kappa. AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction; IQR, interquartile range. Both wearable-recorded ECGs were interpreted manually by diagnosis-blinded cardiologists. The PPG-based AF detector operated automatically.

False positive cases were more common for single-lead ECG (9/120, 7.5%) or tended to be more common for PPG-based detector (7/128, 5.5%) compared to six-lead ECG (2/127, 1.6%) ($P = 0.02$ and $P = 0.08$, respectively).

The higher number of premature beats per minute was the main factor associated with false positive cases in comparison to true negative cases for each diagnostic method, namely the single-lead ECG (18.80 vs. 5.40 beats/min, $P < 0.01$), the six-lead ECG (64.3 vs. 5.8 beats/min, $P = 0.018$) and the PPG-based detector (13.20 vs. 5.60 beats/min, $P = 0.05$) (**Figure 15**). Of note, six-lead ECG was the most robust tool as it required 3.4 times more premature beats to result in a false positive outcome compared to single-lead ECG and 4.9 times more premature beats compared to the PPG-based detector. A single-lead ECG (12/249) was more frequently labeled "Cannot be concluded" than six-lead ECG (3/249) ($P = 0.01$).

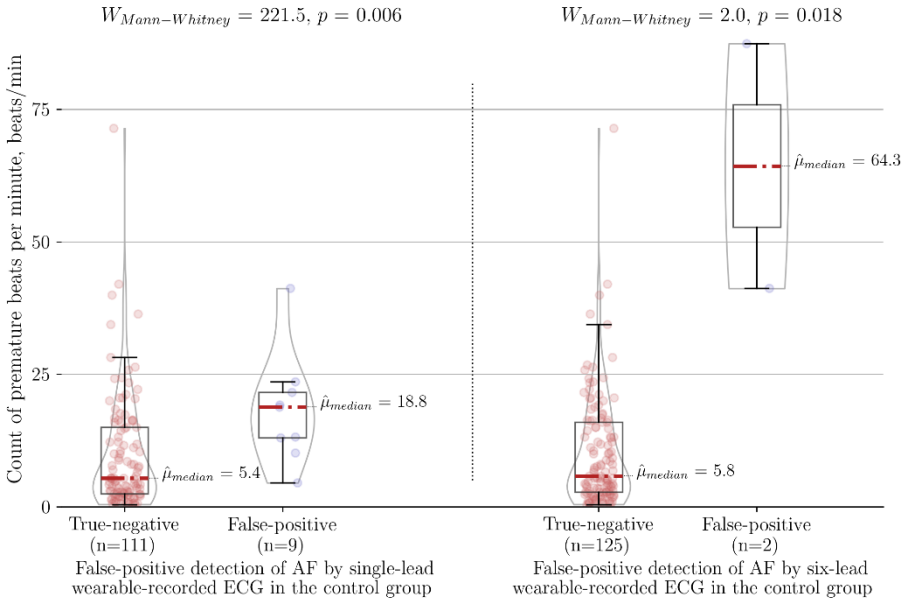

Figure 15. Association between count of premature beats per minute and type I error of the wearable-recorded single-lead ECG (left panel) vs. six-lead ECG (right panel) in the control group of SR with frequent premature beats. AF, atrial fibrillation.

There was no trend of AF with higher rates of beats per minute in false negative cases. The median beats per minute in false negative cases of PPG-based detector (7/121) was 92 bpm (58, 116). Accordingly, in a single false negative case of six-lead ECG (1/119) the median was 76 bpm and in 5 cases of single-lead ECG the median was 92 bpm (92, 94).

4.4.2 Single-Lead ECG, Six-Lead ECG, and PPG-Based Algorithm for AF Detection when Controlled by SR with Frequent PACs

When compared to the control subgroup of PACs, the specificity of AF detection by six-lead ECG, single-lead ECG, and PPG-based detector dropped to 95% (95% CI: 83.1–99.4), 83.8% (95% CI: 68–93.8), and 90% (95% CI: 76.3–97.2), respectively (**Figure 16**). Interestingly, further analysis of single-lead ECGs (AUC 0.898; Cramer's V association 0.803, $P < 0.001$; inter-rater agreement Cohen's kappa 0.803, $P < 0.001$) showed lower diagnostic value not only compared to six-lead ECG (AUC 0.971; Cramer's V association 0.950, $P < 0.001$; inter-rater agreement Cohen's kappa 0.950, $P < 0.001$), but also lower than PPG-based detection (AUC 0.921; Cramer's V association 0.823, $P < 0.001$).

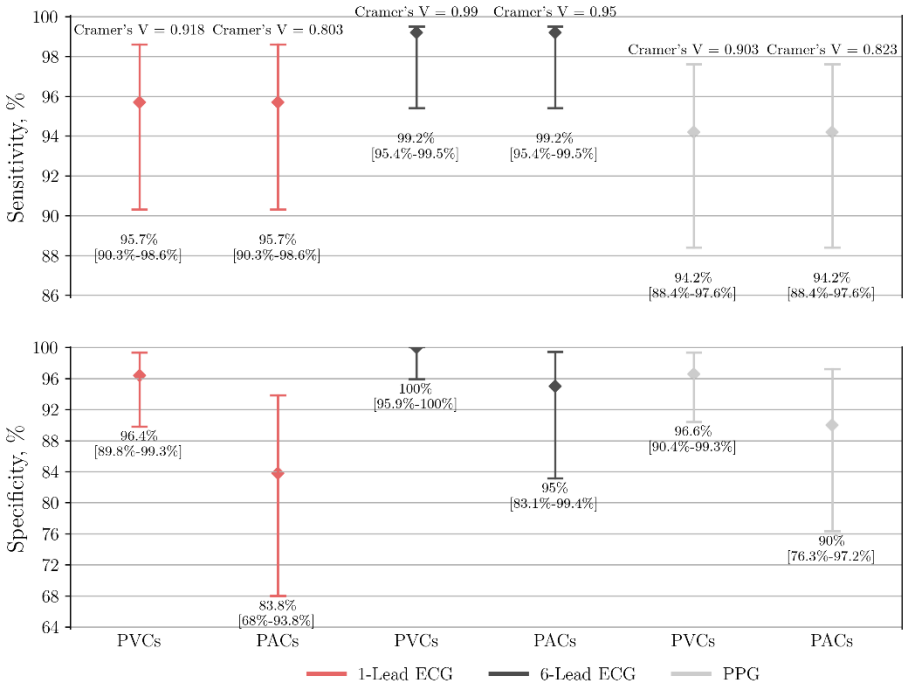

Figure 16. Performance of single-lead ECG ($n = 237$), six-lead ECG ($n = 246$) and the PPG-based algorithm ($n = 249$) to detect AF. The group of AF is compared to either a control subgroup of SR with frequent PVCs or PACs. PPG, photoplethysmography; ECG, electrocardiography; AF, atrial fibrillation; SR, sinus rhythm; PVC, premature ventricular contraction; PAC, premature atrial contraction.

4.4.3 Single-Lead ECG, Six-Lead ECG, and PPG-Based Algorithm for AF Detection when Controlled by SR with Frequent PVCs

When compared to the control subgroup of PVCs, the specificity of AF detection by six-lead ECG, single-lead ECG, and PPG-based detector yielded a specificity of 100% (95% CI: 95.9–100), 96.4% (95% CI: 89.8–99.3), and 96.6% (95% CI: 90.4–99.3), respectively (**Figure 16**). In this case the diagnostic value of single-lead ECG (AUC 0.961; Cramer's *V* association 0.918, $P < 0.001$; inter-rater agreement Cohen's kappa 0.918, $P < 0.001$) was lower compared to six-lead ECG (AUC 0.996; Cramer's *V* association 0.990, $P < 0.001$; inter-rater agreement Cohen's kappa 0.990, $P < 0.001$), but non-inferior to PPG-based detector (AUC 0.954; Cramer's *V* association 0.903, $P < 0.001$).

4.4.4 Summary

To summarize, single-lead ECG required 3.4 times fewer extrasystoles than six-lead ECG to result in a false positive outcome. A six-lead wearable-recorded ECG does bring a clear additional diagnostic benefit for AF detection compared to a single lead-I-like ECG commonly used in most smartwatches and automatic PPG-based AF detector (paper II).

4.5 Paper III: AI vs. Technicians' Detection of Arrhythmia in Direct-to-Physician Ambulatory ECG Reporting

The comparative analysis distinguished between two types of arrhythmias, namely, critical and non-critical.

1) Critical arrhythmias included:
- atrial fibrillation ≥30s,
- ventricular tachycardia ≥10s + ≥120 bpm,
- supraventricular tachycardia ≥30s,
- 3rd degree AV-block,
- asystole ≥3.5s.

2) The non-critical arrhythmias included:
- premature atrial complexes and premature ventricular complexes,
- second-degree AV block,
- pauses of 2.0–3.5 s,
- VT episodes <10 s,
- idioventricular/accelerated idioventricular rhythms,
- SVT episodes ≤30 s,
- ectopic atrial rhythm.

The most common monitoring indications were palpitations, syncope, dizziness and examination for AF (**Table 8**).

Table 8. Monitoring indications reported on device. Several answers per patient possible.

Indication	N	Age, mean±SD	% males
Palpitations	7026	61.7±17.3	36.3
Syncope/collapse	2231	68.5±16.7	43.7
Dizziness and giddiness	1500	69.0±14.9	45.7
Atrial fibrillation, paroxysmal	1481	71.7±10.7	49.6
Atrial fibrillation, unspecified	1222	71.3±11.7	51.6
Transient Ischemic Attack	1035	71.7±10.3	43.1
Dyspnea	946	66.8±15.2	39.1
Tachycardia	811	59.9±19.7	39.0
Bradycardia	890	70.2±15.3	55.1
Atrial flutter	651	68.6±12.2	56.5
Premature ventricular complexes	477	64.5±16.7	33.3
Persistent AF	382	62.1±17.2	49.0
Stroke	322	70.9±10.5	43.2
Other	222	61.0±19.6	41.4

Further described results are cited from the previously published **Paper III** (47).

4.5.1 Critical Arrhythmias

The AI model had superior sensitivity for the primary endpoint of false-negative findings (all instances of the arrhythmia missed for the full recording) of critical arrhythmia (98.6% (95% confidence interval (CI) = 97.7–99.4) versus 80.3% (95% CI = 77.3–83.3%) (**Table 9**). The AI model analysis had 3.2 false negatives per 1,000 patients, compared to 44.3 per 1,000 for technicians (**Figure 17**), resulting in a relative risk (RR) of a false-negative finding of critical arrhythmias of 14.1 (95% CI = 10.4–19.0) for technician analysis compared to DeepRhythmAI model analysis. **Table 10** reports these results for individual arrhythmias. The RR for false-negative findings over the full recording increased with increasing monitoring duration (RR = 7.8 (95% CI = 3.1–19.8) for 1–2 days of monitoring, RR = 9.1 (95% CI = 3.9–21.1) for 3–7 days of monitoring and RR = 17.9 (95% CI = 11.9–26.9) for ≥8 days of monitoring). Overall, the negative predictive value for critical arrhythmias was 99.9% (95% CI = 99.9–100%) for the AI model compared to 99.1% (95% CI = 98.9–99.2) for technicians, and the AI model had superior negative predictive values for all individual critical arrhythmia classes (**Table 9**). The AI model detection rates of true-positive VTs, SVTs, asystoles and third-degree AV blocks were substantially higher than the technicians, and the AI model detected numerically more AF events (**Figure 18**).

Table 9. Performance of DeepRhythmAI and ECG technicians compared to the consensus panel of cardiologists for critical arrhythmias.

	Accuracy (95% CI), %		True-positive rate/sensitivity, % (95% CI)		True-negative rate/specificity, % (95%CI)		PPV, % (95% CI)		NPV, % (95% CI)		F1 score, %	
	AI	Technician	AI	Technician	AI	Technician	AI	Technician	AI	Technician	AI	Technician
Overall average critical arrhythmias	98.1 (97.9–98.2)	98.4 (98.1–98.5)	**98.6 (97.7–99.4)**	80.3 (77.3–83.3)	98.1 (97.9–98.2)	**99.2 (99.0–99.3)**	71.3 (68.5–73.9)	**82.7 (79.4–85.6)**	**99.9 (99.9–100)**	99.1 (98.9–99.2)	82.7 (80.9–84.5)	81.5 (79.0–83.6)
VT ≥ 10 s	98.2 (98.1–98.3)	99.5 (99.4–99.6)	**98.0 (94.8–100)**	64.4 (54.9–73.8)	98.2 (98.1–98.3)	**99.8 (99.7–99.8)**	27.2 (22.8–32.3)	**67.7 (58.2–76.6)**	**99.98 (99.96–100)**	99.7 (99.6–99.8)	42.6 (37.1–48.6)	**66.0 (57.4–73.2)**
AF ≥ 30 s	97.2 (96.5–97.9)	97.4 (96.6–98.0)	**99.1 (97.7–100)**	90.5 (86.8–94.0)	96.9 (96.2–97.7)	**98.4 (97.8–98.9)**	82.3 (77.8–86.8)	88.9 (84.7–92.6)	**99.9 (99.7–100)**	98.6 (98.0–99.2)	90.0 (87.1–92.7)	89.7 (86.7–92.3)
SVT ≥ 30 s	97.4 (97.1–97.9)	96.1 (95.5–96.7)	**97.3 (94.9–99.1)**	62.9 (56.6–69.3)	97.4 (97.0–97.9)	98.1 (97.7–98.4)	70.6 (65.9–75.7)	65.8 (59.3–72.2)	**99.8 (99.7–99.9)**	97.8 (97.2–98.3)	**81.8 (78.3–75.2)**	64.3 (58.7–69.8)
Asystole ≥ 3.5 s	98.5 (98.2–98.7)	**99.2 (99.0–99.4)**	**100 (100–100)**	80.6 (75.0–86.0)	98.4 (98.2–98.6)	**99.8 (99.7–99.9)**	65.7 (60.5–70.4)	**91.2 (87.8–95.6)**	**100 (100–100)**	99.4 (99.2–99.6)	79.2 (75.4–82.6)	85.8 (82.1–89.5)
Third-degree AV block	99.3 (99.2–99.4)	99.5 (99.3–99.6)	**96.4 (92.5–99.2)**	52.6 (44.0–61.6)	99.3 (99.2–99.4)	**99.9 (99.8–99.9)**	51.2 (44.6–48.2)	**76.3 (67.1–85.4)**	**100 (99.9–100)**	99.6 (99.5–99.7)	66.9 (61.2–72.8)	62.2 (53.9–70.0)

1. The bold values denote nonoverlapping CIs between methods.
2. NPV, negative predictive value; PPV, positive predictive value.

Table 10. Relative risks of false-negative findings for technicians compared to artificial intelligence.

Critical arrhythmia	Relative risk	95% confidence intervals	P value
Any critical arrhythmia	14.1	10.4-19.0	<0.0001
AF≥30s	10.2	6.2-16.8	<0.0001
SVT≥30s	12.5	8.2-18.9	<0.0001
Asystole≥3.5s	82.0	11.0-589.0	<0.0001
3rd degree AV block	13.8	5.0-37.9	<0.0001
VT≥10s	18.5	4.5-76.7	<0.0001

AI analysis resulted in no false negatives for asystoles ≥3.5 seconds, results are calculated with the addition of 1 false negative for AI in this category. Two-sided P values were derived using Fischer's exact test. VT, ventricular tachycardia; AF, atrial fibrillation; SVT, supraventricular tachycardia.

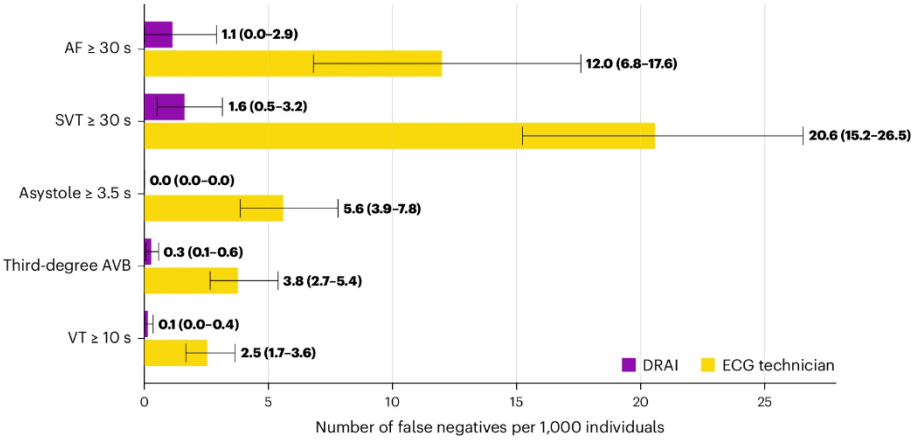

Figure 17. False-negative critical arrhythmias per 1,000 patients by AI and technician analysis. Error bars represent 95% CIs derived using bootstrapping. AVB, AV block.

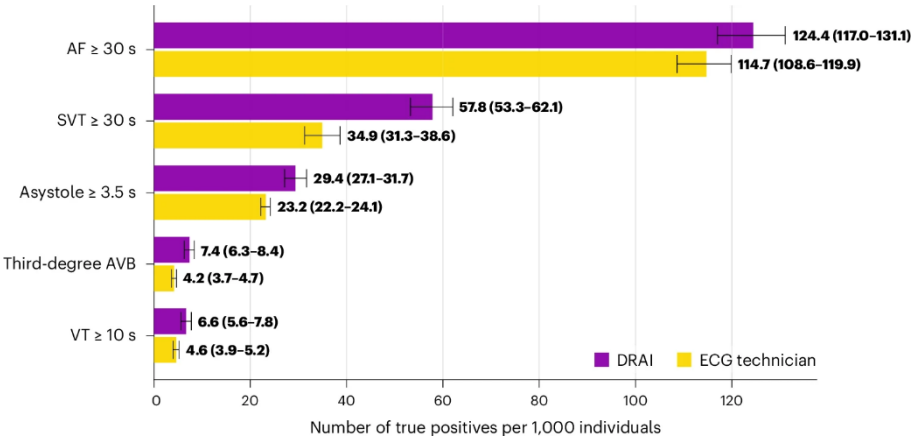

Figure 18. True-positive critical arrhythmias per 1,000 patients by AI and technician analysis. Error bars represent 95% CIs derived using bootstrapping.

DeepRhythmAI model analysis resulted in more false-positive findings of asystoles, third-degree AV block and ≥10 s VT (**Figure 19**). Panel classifications of patients for whom strips were extracted are reported in **Figure 20**.

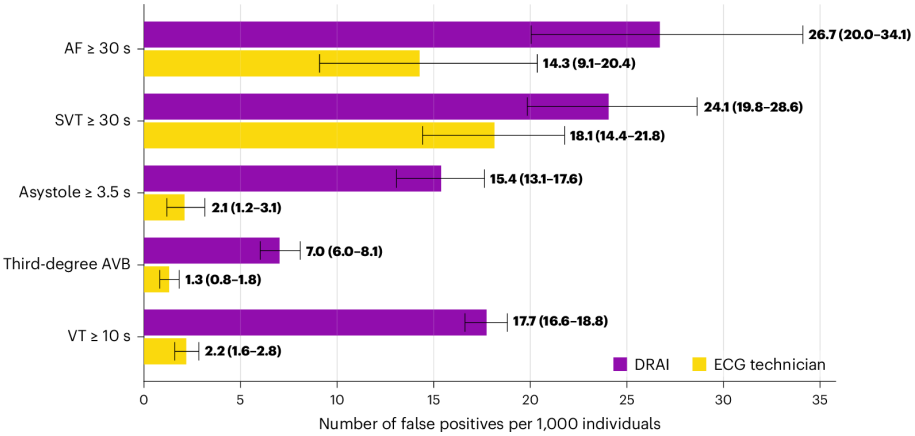

Figure 19. False-positive critical arrhythmias per 1,000 patients by AI and technician analysis. Error bars represent 95% CIs derived using bootstrapping.

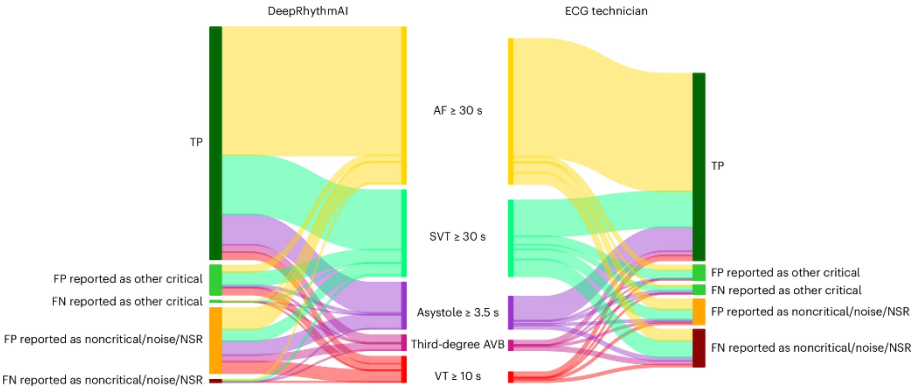

Figure 20. Diagnoses of patients with critical arrhythmias by DeepRhythmAI and ECG technicians. Sankey diagram showing arrhythmic event durations for critical arrhythmias as detected by each of the two methods. Cardiologist panel annotations are used to classify DeepRhythmAI and ECG technician annotations into TP, FP or FN. For FP and FN detections, we also report whether these were annotated by the cardiologist panels as another critical arrhythmia class or as a noncritical arrhythmia/noise or NSR. TP, true positives; FP, false positives; FN, false negatives; NSR, normal sinus rhythm.

Full confusion matrix statistics for individual critical arrhythmias for both the AI model and technicians compared to panel annotations are reported in **Table 9**. DeepRhythmAI model analysis was superior in terms of sensitivity but had lower specificity for ≥10 s VT, asystole and third-degree AV block. The AI model analysis had similar positive predictive value to technicians for AF and sustained SVTs but lower positive predictive values for sustained VT, third-degree AV block and asystoles. The overall F1 score, which is the harmonized mean of positive predictive value and sensitivity, was similar for the AI model and technicians. However, the F1 scores for AI were superior for sustained SVT, and the F1 score for technicians was better for VT.

4.5.2 Noncritical Arrhythmias

Results for noncritical arrhythmias are reported in **Table 11**. The AI model had superior sensitivity for all noncritical arrhythmias and a superior F1 score for pauses and idioventricular/accelerated idioventricular rhythms but lower specificity for all noncritical arrhythmias except SVT episodes <30 s and ectopic atrial rhythms.

Table 11. Performance of DeepRhythmAI and ECG technicians compared to the consensus panel of cardiologists for noncritical arrhythmias

	Accuracy, % (95% CI)		Sensitivity, % (95% CI)		Specificity, % (95% CI)		PPV, % (95% CI)		NPV, % (95% CI)		F1 score, %	
	AI	Technician	AI	Technician	AI	Technician	AI	Technician	AI	Technician	AI	Technician
Second-degree AV block	92.3 (91.7–92.9)	**96.7 (95.7–97.4)**	**100 (100–100)**	38.6 (30.9–46.1)	91.9 (91.3–92.5)	**99.5 (99.3–99.7)**	41.9 (37.3–46.3)	**77.8 (68.9–87.0)**	**100 (100–100)**	97.1 (96.1–97.9)	59.1 (54.3–63.3)	51.6 (43.7–59.2)
2.0–3.5 s pauses	**95.0 (93.7–96.3)**	90.3 (87.4–92.5)	**97.8 (95.1–100.0)**	48.8 (40.1–57.7)	94.5 (93.0–96.0)	**97.8 (96.7–98.8)**	78.0 (71.9–84.3)	80.5 (70.4–89.3)	**99.5 (99.0–100.0)**	91.3 (88.1–93.6)	**86.8 (82.8–90.5)**	60.8 (52.0–68.0)
VT 3 beats, 10 s	81.9 (78.6–85.2)	84.7 (80.0–88.7)	**100.0 (100.0–100.0)**	58.3 (48.8–67.7)	75.8 (72.6–79.3)	**95.7 (93.6–97.8)**	58.5 (50.9–66.1)	**84.8 (76.8–92.4)**	**100.0 (100.0–100.0)**	84.7 (79.2–89.0)	73.8 (67.5–79.6)	69.1 (61.3–76.7)
AIVR	85.5 (82.6–88.4)	81.3 (77.2–84.8)	**100.0 (100.0–100.0)**	52.5 (42.4–62.0)	81.1 (78.1–84.3)	**90.1 (87.5–92.4)**	61.6 (53.8–69.2)	61.6 (50.6–71.1)	**100.0 (100.0–100.0)**	86.2 (81.5–90.2)	**76.2 (70.0–81.8)**	56.7 (47.3–64.6)
IVR	93.0 (92.0–94.1)	92.8 (90.4–94.6)	**100.0 (100.0–100.0)**	29.7 (22.1–38.2)	92.4 (91.4–93.5)	**98.9 (98.4–99.4)**	54.0 (47.5–61.1)	**72.9 (60.0–85.7)**	**100.0 (100.0–100.0)**	93.6 (91.0–95.4)	**70.1 (64.4–75.9)**	42.2 (32.9–51.1)
SVT 3 beats, 30s	79.1 (73.1–84.6)	76.9 (71.0–82.3)	**100.0 (100.0–100.0)**	90.3 (84.2–96.0)	55.8 (49.6–62.9)	62.9 (56.4–70.4)	71.6 (63.4–79.1)	71.8 (63.5–79.4)	**100.0 (100.0–100.0)**	86.2 (77.7–94.1)	83.5 (77.6–88.4)	80.0 (73.9–85.1)
EAR ≥ 3 beats	**83.0 (78.7–87.6)**	64.8 (59.4–70.2)	**99.1 (96.8–100.0)**	56.6 (45.9–67.4)	70.1 (65.0–75.9)	68.9 (64.7–73.2)	**72.7 (65.7–79.7)**	48.0 (38.0–58.0)	**99.0 (96.5–100.0)**	75.8 (68.7–82.2)	**83.8 (78.9–88.7)**	51.9 (43.0–60.5)

1. The bold values denote nonoverlapping CIs between methods.
2. AIVR, accelerated idioventricular rhythm; IVR, idioventricular rhythm; EAR, ectopic atrial rhythm.

4.5.3 Summary

To summarize, the diagnostic accuracy of the AI algorithm's arrhythmia detection outperforms the accuracy of certified ECG technicians' conclusions in long-term Holter ECGs (**Paper III**). The DeepRhythmAI model outperformed the technician analysis with an excellent negative predictive value of 99.9% (false negatives in 3.2/1,000 patient days) for critical arrhythmias compared to 99.1% (44.3/1,000 patient days). This substantial reduction in false-negative findings comes with a modest increase in false-positive findings (12/1,000 vs. 5/1,000 patient days, respectively).

4.6 Paper IV: ECG-Based Risk Markers and Predictive Modeling for AF in Long-Term Holter Monitoring

The results are cited from a previously published **Paper IV** (52). Study population characteristics are reported in **Table 12**. The mean (SD) monitoring duration was 18.6 (9.6) days overall and 23.5 (7.7) days among patients monitored for stroke/TIA. During follow-up, there were 1290 AF events (7.1%) after a median recording duration of 5 days (interquartile range (IQR) 2–11). Among patients monitored for stroke/TIA, there were 55 AF events (3.7%) after a median recording duration of 11 days (IQR 5–16). On the first monitoring day, 19.7% of the overall population had excessive supraventricular ectopic activity (ESVEA).

Table 12. Study population characteristics.

	Full population	Poststroke/TIA patients
Number	18,220	1492
Age, mean (SD)	64.4 (17.3)	71.1 (11.8)
Male sex	3862 (42.4%)	697 (46.7%)
Mean heart rate, mean (SD)	72.8 (11.3)	71.9 (10.1)
Maximum heart rate, mean (SD)	112.0 (20.9)	107.6 (16.9)
Minimum heart rate, mean (SD)	56.1 (9.4)	56.8 (9.1)
Total beats, mean (SD)	94,588 (21,007)	91,878 (21,246)
Total PACs, median (IQR)	54 (11, 315)	63.0 (16.0, 272.5)

	Full population	Poststroke/TIA patients
Single PACs, median (IQR)	41 (8, 238)	47 (13, 211)
PAC couplets, median (IQR)	1 (0, 6)	1 (0, 6)
PAC triplets, median (IQR)	0 (0, 2)	0 (0, 2)
SVTs ≥4 beats, median (IQR)	0 (0, 2)	1 (0, 2)
AIVR beats, median (IQR)	0 (0, 0)	0 (0, 0)
Total PVC count, median (IQR)	19 (2, 245)	29 (3, 238)
Single PVC count, median (IQR)	18 (1, 236)	28 (2, 230)
PVC couplets, median (IQR)	0 (0, 1)	0 (0, 1)
PVC triplets, median (IQR)	0 (0, 0)	0 (0, 0)
VT runs ≥4 beats, median (IQR)	0 (0, 0)	0 (0, 0)

AIVR, accelerated idioventricular rhythm; PAC, premature atrial complex; PVC, premature ventricular complex; SVT, supraventricular tachycardia.

4.6.1 Prediction Model Discrimination

Odds ratios (OR) and penalized coefficients for the full model and the ECG only model are reported in **Table 13**, along with the formula with which one can calculate the PocketECG risk score for AF using the β-coefficients in the table. The full model included eight covariates and the "ECG-only" model included seven. In the testing dataset, the main model and the "ECG-only" model both had good, and almost identical, discrimination, full model ROC statistic 0.7497 (95% CI 0.7336–0.7658), and "ECG-only" model ROC statistic 0.7497 (95% CI 0.7336–0.7659). The ROC curves for the logistic regression model in the testing dataset based on the predicted risk of outcome are presented in **Figure 21** and **Figure 22**. A model based only on age and sex had substantially poorer discrimination, ROC statistic 0.6542 (95% CI 0.6364–0.6720) (**Figure 23**), as did a model including age, sex, and ESVEA; ROC statistic 0.6990 (95% CI 0.6827–0.7152).

Table 13. Penalized odds ratios and coefficients for AF risk.

	Main model		"ECG-only" model	
	Odds ratio	β-coefficient	Odds ratio	β-coefficient
Age, per year	1.033	0.0324	–	–
Male sex	–	–	–	–
Mean heart rate, per bpm	–	–	–	–
Maximum heart rate, per bpm	0.734	−0.3091	0.726	−0.3200
Minimum heart rate, per bpm	–	–	–	–
Lowest rate during bradycardia, per bpm	–	–	–	–
Single PACs, per decile of population distribution[a]	1.514	0.4150	1.526	0.4226
Number of PAC couplets	–	–	–	–
Fastest rate during PAC couplet, per bpm	1.036	0.0351	1.040	0.0390
Number of PAC triplets	–	–	–	–
Fastest rate during PAC triplet, per bpm	1.179	0.1648	1.181	0.1664
Number of SVTs ≥4 beats	–	–	–	–
Longest duration of SVT, per beat	1.022	0.0221	1.022	0.0222
Fastest rate during SVT ≥4 beats, per bpm	–	–	–	–

	Main model		"ECG-only" model	
	Odds ratio	β-coefficient	Odds ratio	β-coefficient
Total number of AIVR events	–	–	–	–
Fastest rate during AIVR, per bpm	–	–	–	–
Longest duration of AIVR, per beat	–	–	–	–
Total PVC count, per 1 beat	–	–	–	–
Single PVC count, per 1 beat	–	–	–	–
Total number of PVC couplets	–	–	–	–
Fastest rate during PVC couplet, per bpm	1.040	0.0394	1.042	0.0411
Number of PVC triplets	–	–	–	–
Fastest rate during PVC triplet, per bpm	–	–	–	–
VT runs ≥4 beats	1.032	0.0315	1.032	0.0314
Fastest rate during VT run ≥4 beats, per bpm	–	–	–	–
Longest duration of VT run, per beat	–	–	–	–

Predicted risk for the models can be calculated as $P = e^{(\beta_0+\beta_1X_1+\beta_2X_2+\cdots+\beta_nX_n)}/(1 + e^{(\beta_0+\beta_1X_1+\beta_2X_2+\cdots+\beta_nX_n)})$. AIVR, accelerated idioventricular rhythm; bpm, beats per minute; PAC, premature atrial complex; PVC, premature ventricular complex; SVT, supraventricular tachycardia. [a] Decile cut points at 0, 1, 3, 7, 18, 50, 140, 406, and 1680.

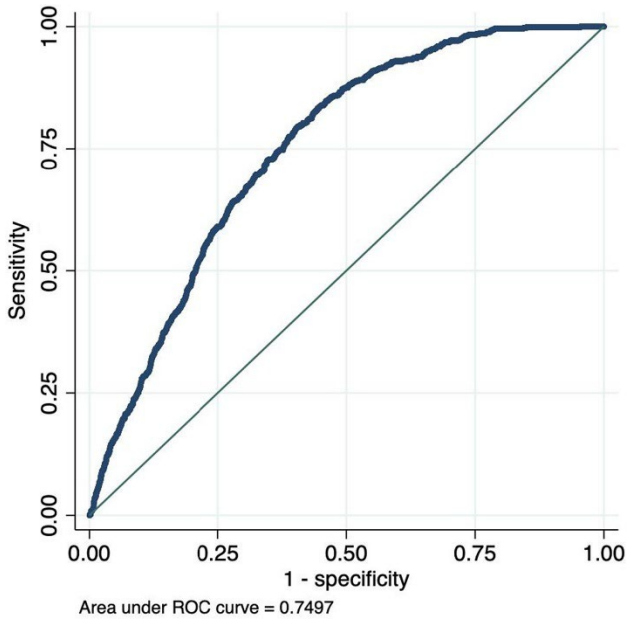

Figure 21. ROC curves for AF occurrence by predicted risk on 24hECG, full model.

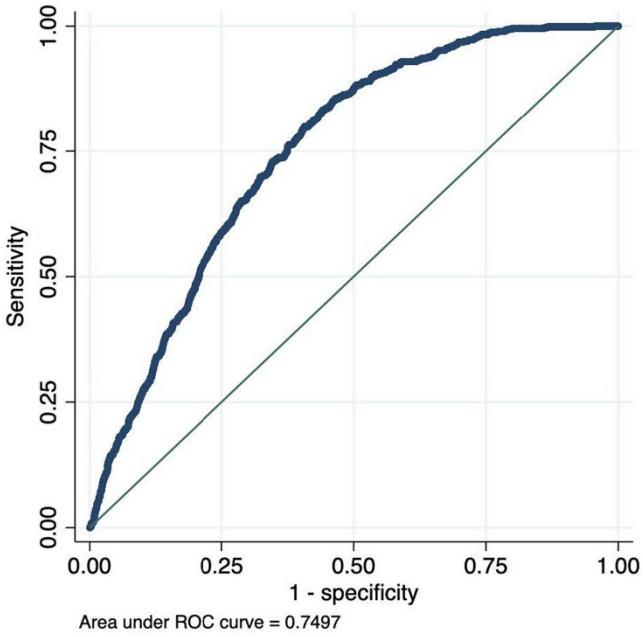

Figure 22. ROC curve for AF occurrence by predicted risk on 24hECG, "ECG-only" model.

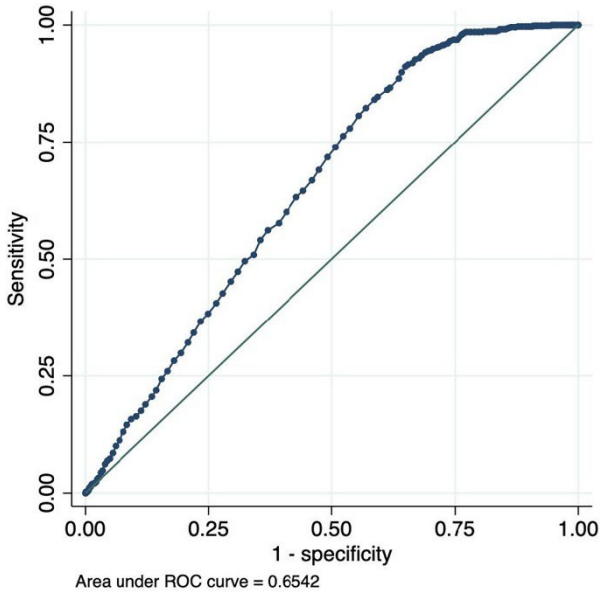

Figure 23. ROC curve for AF occurrence by predicted risk using age and sex only model.

The prevalence of observed AF in the testing dataset in 'ECG-only' model increased by quintile of predicted risk: 0.4% in Q1, 2.7% in Q2, 6.2% in Q3, 11.4% in Q4, and 15.9% in Q5. In Q1, the negative predictive value for AF in 'ECG-only' model was 99.6%.

4.6.2 Characteristics of Patients with "High-" versus "Low-Risk" of AF

A case–control study was conducted in which "high-risk" patients, defined as having a predicted AF risk ≥10%, were matched to "low-risk" patients, defined as having a predicted AF risk <5%, based on age (in 5-year intervals), sex, and recording duration. Using predicted probabilities of AF from the "ECG-only" model, a successful match was created between 2465 "high-risk" and "low-risk" pairs, with a similar gender distribution as the larger cohort and a mean age of 72 years (**Table 14**). Median (IQR) predicted probability of AF was 12.5% in the high-risk group and 3.8% in the "low-risk" group, while the observed rates of AF occurrence during mobile cardiac telemetry monitoring were five times more common in the "high-risk" group (15.4%) compared to 3.5%. The "high-risk" group differed substantially from the "low-risk" group as regards mean, maximum, and minimum heart rate, which were all significantly lower, as well as the occurrence of PACs, which were significantly more common. The median PAC count in the "high-risk" group was relatively low, at 1049 PACs per 24 h. In contrast, the median PAC count

in the “low-risk” group was 15. There were also substantial differences as regards the occurrence of PAC couplets, triplets, and runs of four beats or more, all of which were substantially more common among “high-risk” compared to “low-risk” patients. Finally, in “high-risk” patients, we also observed significantly higher heart rates during couplets and triplets of PACs compared to “low-risk” patients.

Table 14. Characteristics of patients with high versus low risk of AF during ≤30 days of monitoring, matched for age, sex, and recording duration.

	Low risk	High risk	*p*-Value
N	2465	2465	
Age, mean (SD)	71.5 (8.2)	71.6 (8.1)	Matching variable
Probability of AF, median (IQR)	3.8 (3.1–4.4)	12.5 (11.1–14.5)	
Observed AF outcome events, %	3.5%	15.4%	<.001
Male sex	1089 (44.2)	1089 (44.2)	Matching variable
Mean heart rate, mean (SD)	75.4 (9.8)	67.3 (10.0)	<.001
Max heart rate, mean (SD)	114.7 (16.7)	99.3 (14.8)	<.001
Minimum heart rate, mean (SD)	59.0 (9.0)	53.0 (8.6)	<.001
Total PACs, median (IQR)	15 (6, 30)	1049 (311, 3799)	<.001
Single PACs, median (IQR)	12 (5, 23)	839 (233, 3069)	<.001
Occurrence of any PAC couplet, *n* (%)	4.9	72.9	<.001
Number of PAC couplets, median (IQR)	0 (0, 1)	14 (5, 54)	<.001
Occurrence of any PAC triplet, *n* (%)	8.5	90.9	<.001
Number of PAC triplets, median (IQR)	0 (0, 0)	3 (1, 10)	<.001
Occurrence of any SVT ≥4 beats, *n* (%)	216 (8.7)	2254 (91.3)	<.001
SVTs ≥4 beats, median (IQR)	0 (0, 0)	3 (1, 8)	<.001
AIVR events, median (IQR)	0 (0, 0)	0 (0, 0)	.23
Total PVCs, median (IQR)	18 (2, 202)	88 (11, 566)	.96

	Low risk	High risk	*p*-Value
Single PVCs, median (IQR)	17 (2, 198)	84 (10, 548)	.60
Occurrence of any PVC couplet, *n* (%)	41.3	67.6	<.001
Number of PVC couplets, median (IQR)	0 (0, 0)	0 (0, 3)	.08
Occurrence of any PVC triplet, *n* (%)	47.8	69.4	<.001
Number of PVC triplets, median (IQR)	0 (0, 0)	0 (0, 0)	.01
Occurrence of any VT run ≥4 beats	79 (3.2)	218 (8.8)	<.001
Number of VT runs ≥4 beats, median (IQR)	0 (0, 0)	0 (0, 0)	.002
Fastest pair interval rate of PAC couplet, bpm mean (SD)	123 (22)	137 (26)	<.001
Fastest rate of PAC triplets, mean (SD)	116 (22)	130 (26)	<.001
Fastest rate of SVT runs, mean (SD)	127 (24)	132 (24)	.003
Fastest pair interval rate of PVC couplet, mean (SD)	136 (32)	135 (32)	.74
Fastest rate of PVC triplets, mean (SD)	125 (29)	122 (34)	.80
Fastest rate of VT runs, mean (SD)	129 (23)	134 (26)	.69

'High-risk' patients are defined as those with a predicted AF risk of ≥10%; 'low-risk' patients are defined as those with a predicted AF risk of <5%. AIVR, accelerated idioventricular rhythm; bpm, beats per minute; PAC, premature atrial complex; PVC, premature ventricular complex; SVT, supraventricular tachycardia.

4.6.3 Summary

To summarize, ECG-based risk markers identified within the first 24 hours of long-term Holter/ECG patch monitoring (up to 30 days) can successfully predict the occurrence of AF between the following 2-30 days (Paper IV). Reliable markers of the 'ECG-only' prediction model include the number of single PACs, the fastest rate during PAC couplets, the fastest rate during PAC triplets, the longest duration of SVT, the fastest rate during VT runs of ≥4 beats, and the maximum heart rate.

5 DISCUSSION

This PhD research series outlines a cohesive trajectory from the conceptualization of a novel device to its practical implementation in clinical workflow. The research can be categorized into two essential parts:

1. The technological invention and development of PPG- and multiple ECG-based diagnostic methods, aimed at meeting the needs of an ideal medical MDR-certified device for patients with arrhythmias (covered in the **Patent**, **MDR Certification**, **Paper I**, and **Paper II**),
2. The development of solutions for potential clinical implementation, by addressing big data challenges in telemedicine using AI (discussed in **Paper III**), exploring the potential target population for monitoring (analyzed in **Paper IV**), and providing recommended use case guidelines for clinical application (7.1 Recommended Practical Applications of TeltoHeart).

5.1 Diagnostic Challenges: Key Requirements Guiding the Development of a Wearable Device

The clinical challenges associated with monitoring arrhythmias using various available wearables have inspired technological solutions dedicated to addressing these issues, resulting in the creation of a CE-marked, user-friendly invention. This led to the specific combination of diagnostic parameters implemented in the novel wrist-worn device. Ideally, a diagnostic wearable should meet the following requirements:

1) It should be user-friendly and comfortable, allowing unobtrusive wear without wires or glued sticky patches, thus avoiding wire entanglements, electrode detachment, and discomfort to the patient.
2) It should enable long-term monitoring capable of detecting not only frequent episodes of arrhythmia but also rare and short episodes, crucial for identifying early stages of arrhythmia to prevent disease progression.
3) It should provide continuous monitoring to detect not only symptomatic but also asymptomatic arrhythmias.
4) It should offer the opportunity for the user to instantly record a reliable multiple-lead ECG for rhythm confirmation, allowing differentiation between frequent premature beats and AF, approximate localization of arrhythmia origin, and maintain the quality of at least one lead ECG even if one of three electrode contact on the skin is insufficient.

5) The ECG should be recorded from electrodes that are not closely spaced on the skin to avoid low voltage amplitudes and limitations in localizing the arrhythmia origin.
6) It should be non-invasive to eliminate the need for skin incisions, thereby reducing the risks of migration and infection, and minimizing the (in-)direct costs associated with the occupation of operation lab for implantation and the high price of invasive devices.
7) It should be recognized as a professional medical device by respected regulatory bodies such as the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). Consequently, it must undergo the certification process to comply with the Medical Device Regulation (MDR) or other relevant legislation. This ensures that the device meets high-quality standards.

5.2 Uniqueness of the Invented Wearable: Addressing the Key Diagnostic Requirements in the Development of a Wearable Device

In the author's view, the invention fulfills all the aforementioned requirements (Section 5.1, Requirements 1-7), having been granted **patents** and successfully achieved **Class I CE MDR** marking for the hardware, along with **Class IIa CE MDR** marking for the software and remote cloud platform.

Consequently, this innovation has led to the development of the world's first and only device that integrates the following features into a single, user-centric design:

1) User-Centric and Long-Term Monitoring Design: a **wrist-worn**, non-obtrusive, and non-invasive **MDR**-certified wearable device that is compatible with **long-term** monitoring,
2) **Continuous** Detection of **(A-)symptomatic** Arrhythmias: A continuous **PPG**-based algorithm capable of detecting both symptomatic and asymptomatic arrhythmias, including variations in heart rate such as tachycardia and bradycardia.
3) Reliable **6-Lead ECG** for Rhythm Confirmation: An instant six-lead, standard-limb-like, wire-free ECG that maintains **high specificity**, even in the presence of frequent premature beats.

In contrast, current wearable technologies generally exhibit the following limitations:

1) Limited Monitoring Options: Most devices offer **either** PPG **or** ECG capabilities but not both, with many lacking continuous monitoring features. Devices with only ECG capabilities often fail to detect

asymptomatic episodes as patients do not know precisely when to initiate an ECG recording.

2) Limited Diagnostic Specificity with only **Single-Lead** ECGs: almost all available wearables use single-lead ECGs (except Kardia6L), which are susceptible to artifacts and loss of ECG if one of two contacts are insufficient. Furthermore, the presence of premature beats often leads to significantly decreased diagnostic specificity in real-world applications.

The following published papers further test the accuracy of the device, highlight the importance of six-lead ECG compared to single-lead ECG, and address practical issues related to the implementation into the clinical practice like interpreting big data and the selection of target patients for long-term monitoring.

5.3 Discussion of Paper I: Validating the Device by Assessing Diagnostic Accuracy

In Paper I, significant emphasis was placed on the challenge posed by ectopic contractions—a factor that often lowers specificity and is frequently underestimated in the realistic evaluation of emerging digital Health technologies.

5.3.1 Impact of Premature Contractions on the PPG-Based Algorithm for AF Detection

PPG-based algorithms for AF detection are prevalent in wearables but lack comprehensive validation, especially for patients with frequent premature contractions. The routine selection of stable sinus rhythm (SR) for control groups fails to reflect the variability seen in everyday clinical settings, contributing to a reduced trust among physicians regarding the specificity of these devices. This skepticism is supported by a survey where 36% of respondents reported reimbursement denials for wearable diagnostics (55).

Our study addressed the issue by reporting a comprehensive analysis of premature contractions as beats per minute, cases with frequent runs of PACs/PVCs or bigeminy/trigeminy episodes. This rigorous approach revealed that frequent PVCs/PACs significantly lowered the specificity of the PPG-based AF detection algorithm, with all seven false-positives originating from this group. Interestingly, specific episodes like bigeminy/trigeminy or runs of ≥3 PACs/PVCs did not affect diagnostic accuracy, likely due to the

algorithm's bigeminy suppression capability, although a higher burden of premature beats per minute tended to increase type I errors (**Figure 13**).

Frequent premature contractions significantly lower the specificity of PPG-based notifications for irregular rhythm detection by Apple Watch. A substudy reported that 40% of participants who received an irregular pulse notification from the Apple Watch exhibited no AF on subsequent ECG patches and were found to have other types of arrhythmias, primarily atrial or ventricular ectopic beats (40). This observation is crucial for the application of PPG-based technologies in extensive population research, such as the Apple Heart Study (39) or the TeleCheck-AF project (56). Although intended for screening, these technologies can lead to adverse outcomes, including unnecessary medical interventions and increased patient anxiety, particularly in individuals with frequent PVCs/PACs.

In the realm of wearables using continuous PPG algorithms for AF screening, the importance of maintaining high specificity cannot be overstated. Continuous, long-term, unobtrusive monitoring significantly increases the likelihood of detecting arrhythmias, underscoring the necessity for these technologies to adhere to the medical principle of "first, do no harm."

5.3.2 Impact of Premature Contractions on the ECG of the Wearable for AF Detection

In our study, the influence of premature beats on ECG-based AF detection was minimal. The 6-lead ECG of the wearable effectively reduced Type I errors associated with the PPG algorithm. Notably, both false-positive cases involved complex tracings of sinus rhythm with multiple irregular runs of PACs, which might represent the early stages of atrial fibrillation or what the STROKESTOP study group at Karolinska Institute terms 'micro-AF'—a sudden onset of irregular tachycardia with episodes of ≥5 consecutive supraventricular beats and a total absence of P-waves, lasting less than 30 seconds (54). This condition has been linked to an increased risk of AF (HR 4.3; 95% CI 2.7–6.8) and mortality (HR 2.0; 95% CI 1.1–3.8) in a large-scale screening study involving 7,173 individuals (57). Additionally, a false-negative case in our study featured f-waves mimicking irregular P-waves, posing diagnostic challenges. Interestingly, short strips of reference Holter ECG corresponding to these two false-positive and one false-negative cases were also falsely recognized as AF and SR, respectively. Only after thorough examination of long reference Holter ECG tracings cardiologists were able to confirm the diagnosis of these challenging cases. It suggests that diagnostic

measures of a 6-lead-ECG of the wearable without any wires could be non-inferior to regular 3-lead Holter ECG recordings.

5.3.3 Impact of Premature Contractions on Automated ECG Algorithm for AF Detection

The impact of frequent PVCs/PACs on the accuracy of automated ECG algorithms is likewise important, especially in devices like implantable loop recorders known for prolonged monitoring and high compliance. Despite the mentioned advantages, these devices use only a single-lead ECG of closely spaced electrodes and often yield a significant number of false positives. A prospective study of 559 patients using implantable loop recorders for AF monitoring reported a false-positive rate of 46% (201/440) (58). False diagnoses of AF accounted for 50% of scheduled transmissions and 32% in alert transmissions, with premature ventricular or atrial ectopy being the leading cause (52%). Reviewing these false-positive transmissions and consulting with electrophysiologists typically required 30 to 45 minutes per case.

5.3.4 Limitations

The generalizability of this study may be limited by its specific population. According to a comprehensive review (59), the accuracy and cost-effectiveness of mHealth technologies for AF detection are influenced by various factors such as incidence rates, risk profiles, and types of AF. Notably, all participants in this study were White, and diverse skin pigmentation could affect the results of PPG-based AF detection. Additionally, the selection of predefined groups of patients with AF and SR might introduce bias. Patients with atrial flutter, who exhibit different pulse wave patterns, were not included in this study, though the wearable 6-lead ECG shows potential for future research in these cases (**Figure 24**). Some recordings were not analyzed for specified reasons (**Figure 1**), potentially leading to additional costs or clinic visits in real-life scenarios. Moreover, the findings are based on short-term, in-hospital recordings, and diagnostic performance may vary in outpatient settings. Specifically, the quality of PPG measurements tends to decrease during daily activities but remains adequate during sleep (42), suggesting that AF screening accuracy may be higher during nocturnal monitoring.

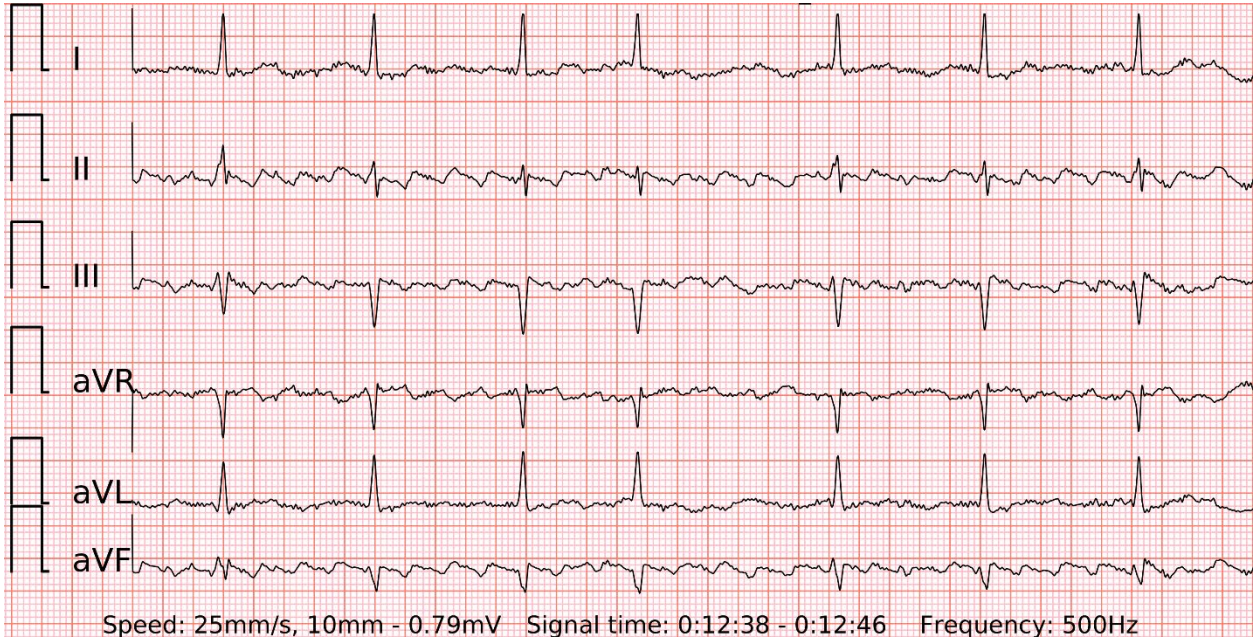

Figure 24. A 6-lead ECG of typical counterclockwise atrial flutter with variable atrioventricular conduction recorded by the wearable device.

5.4 Discussion of Paper II: Comparison of Six-Lead ECG with Single-Lead ECG for AF Detection

5.4.1 Major findings

The primary objective of this analysis is a direct comparison between single-lead and six-lead ECGs, as well as the automatic PPG-based AF detector, all within the same wearable device. Major findings are cited from **Paper II** (16) as follows: (1) comparing to any control subgroup of SR with premature beats (PACs or PVCs) the diagnostic value of six-lead ECG was significantly superior to single-lead ECG and PPG-based AF detector both regarding type I and type II errors. (2) The sensitivity of single-lead ECG was slightly higher compared to PPG-based detector in both control subgroups. (3) Single-lead ECG demonstrated lower specificity not only vs. six-lead ECG but also vs. PPG-based automatic AF detection when controlled by a subgroup of frequent PACs. (4) The specificity of single-lead ECG and PPG-based detector were equivalent when controlled by a subgroup of frequent PVCs. (5) The number of premature beats per minute was the main factor associated with false positive cases compared to true negative cases for all diagnostic tools. (6) Six-lead ECG was the most robust tool as it required 3.4 times more premature beats to result in a false positive outcome compared to single-lead ECG and 4.9 times more premature beats compared to the PPG-based detector. (7) Based on previous findings, the widespread use of single-lead ECGs recorded by smartwatches significantly increases the risk of type I error in populations with frequent premature contractions.

The choice of control group in this study, which included sinus rhythm (SR) with frequent premature contractions and excluded stable SR, contrasts sharply with most other mHealth studies (24,25,27,60). This decision was based by findings from the DoubleCheck-AF trial, which showed that stable SR does not adequately test the specificity of diagnostic tools (15).

5.4.2 Why Six is Smarter than One: Impact of Electrode Contact in Wearables and Relation to the Topographic Anatomy of Sinus Node

The original concept of Einthoven's triangle, which arises from the placement of three electrodes and was described by Prof. W. Einthoven, illustrates why certain ECG leads in modern mHealth technologies vary in signal quality (61). When recording a single-lead ECG, like lead-I in smartwatches, one poor contact on either arm can result in the loss of ECG signal or generate artifacts, complicating interpretation. Conversely, in a six-

lead ECG using three electrodes, one poor contact may affect only two leads, leaving the others intact. This redundancy is why a wearable-recorded six-lead ECG is more effective than a single-lead ECG at accurately distinguishing AF from SR with frequent premature beats.

Another factor contributing to the superior performance of six-lead ECG compared to single-lead ECG is the anatomical location of the sinus node in the right atrium (RA). Chen X. et al. (62) utilized 3D electroanatomical mapping to identify the earliest atrial activation (EAA), indicative of the sinus node exit site, in patients with AF undergoing superior vena cava (SVC) isolation. Most patients displayed EAA above the RA SVC junction, particularly prevalent in persistent AF cases (52.9% overall; 60.5% in persistent AF). This high positioning influences the P wave characteristics in ECG readings: in sinus rhythm, the P wave by definition presents with a larger amplitude in lead II than in lead I, which is less discernible in lead-I-like ECGs commonly used in smartwatches. This subtle difference in P wave amplitude, combined with common artifacts in wearable-recorded ECGs, partly explains why single-lead ECGs underperform relative to six-lead ECGs in detecting AF. Moreover, even if a smartwatch records a single-lead-II-like ECG (63,64), it arguably still cannot match the diagnostic accuracy of six-lead ECGs, which allow for cross-validation of P wave reproducibility across multiple leads, helping to distinguish genuine signals from the mimicking artifacts.

These hypotheses are partly validated by a study of 220 patients (25), in which manual interpretation of lead-II-like ECGs from Withings or Apple Watch showed a numerically higher correct classification rate (54%) compared to lead-I-like ECGs by Withings (28%, $P = 0.076$) or Apple Watch (33%, $P = 0.246$) for atrial flutter detection. Furthermore, Kardia 6L's six-lead ECG proved most effective, accurately diagnosing atrial flutter in 63% of cases ($P < 0.001$ versus Withings and Apple Watch). Notably, the study did not include a control group of SR patients with frequent PACs/PVCs.

5.4.3 ECG Examples of False Negative, False Positive and Inconclusive Cases in Single-Lead vs. Six-Lead ECGs

Ideally, even a single PQRST complex in single-lead ECGs might suffice to differentiate AF from SR with premature beats when there are no major artifacts (**Figure 6**). However, the real-world diagnostic accuracy often suffers due to lower signal quality, where artifacts are prevalent not just in wearable ECGs but also in traditional ambulatory ECG monitoring. El-Sherif et al. (13) found artifacts in 4.8% (48/1,000) and misinterpretations in 3.5% (35/1,000)

of ambulatory ECG recordings, often misclassifying movements as pseudo-ventricular tachycardia or pseudo-AF/atrial flutter.

In our study, six-lead ECG consistently outperformed single-lead ECG in terms of sensitivity. The ECG signal quality was predominantly compromised in isolated leads, such as lead-I-like. Single-lead ECGs occasionally showed repetitive artifacts at typical P wave locations, with regularly-irregular R-R intervals mimicking SR with PACs (**Figure 25**), leading to false negatives in AF detection, while six-lead ECGs more accurately identified true positive cases. Interestingly, there was no trend of increased heart rates in false negative cases; median beats per minute did not exceed 100 bpm.

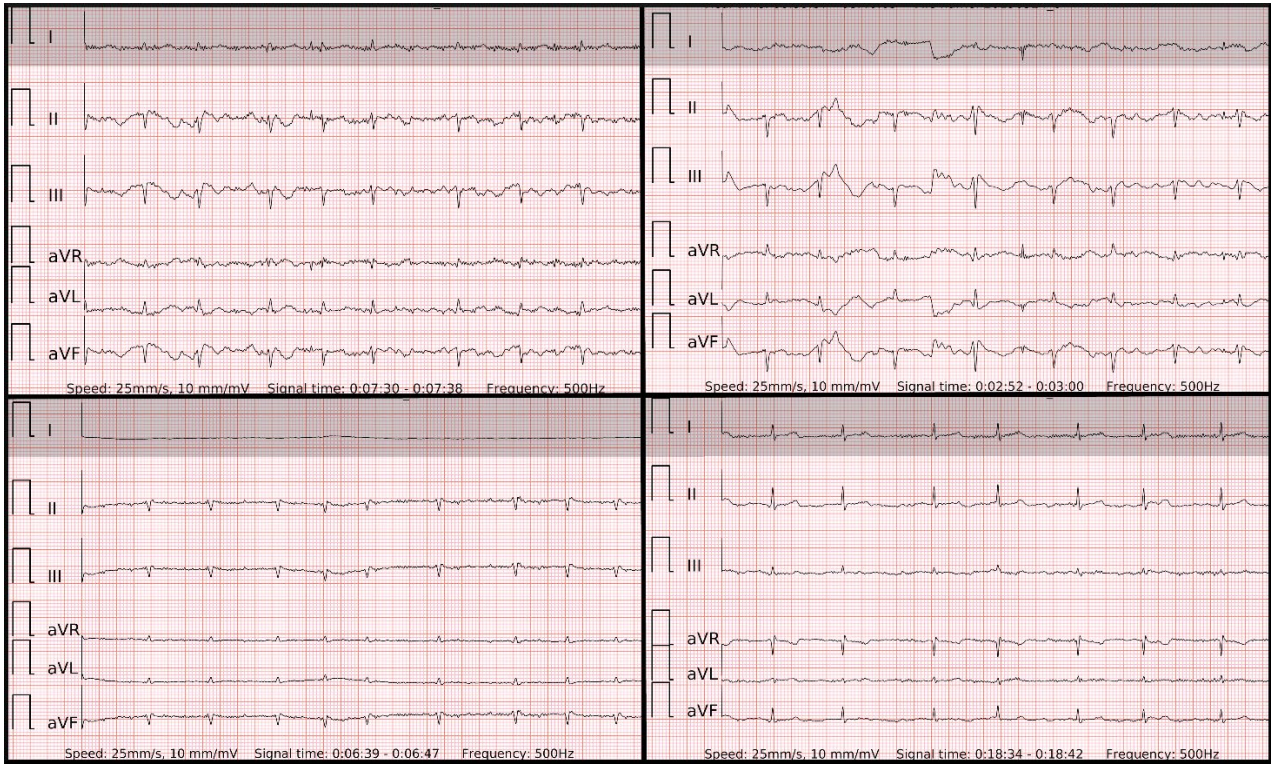

Figure 25. Problematic recordings of AF. False if interpreted by single lead-I-like ECGs (marked in gray) vs. correct if interpreted by six-lead ECGs. Top left panel: false negative due to artifacts mimicking P' of runs of PACs in single-lead ECG, true positive in six-lead ECG with no reproducible *P* waves; Top right panel: cannot be concluded due to low amplitudes in single-lead ECG, true positive in six-lead ECG; Lower left panel: cannot be concluded due to isoelectric signal in single-lead ECG, true positive in six-lead ECG with no reproducible *P* waves; Lower right panel: false negative due to artifacts mimicking P' of PACs and pseudo *regularly*-irregular R-R intervals in single-lead ECG, true positive in six-lead ECG with no reproducible *P* waves.

The specificity of the six-lead ECG surpassed that of the single-lead ECG due to several reasons. First, a likely poor electrode contact resulted in distorted signals on two leads of Einthoven's triangle, including the lead-I-like, while leaving the third lead unaffected. Second, the amplitude of P waves in lead-I-like appeared smaller than in lead-II-like ECGs. Consequently, the six-lead ECG more effectively prevented false positives compared to the single-lead ECG in control groups with frequent PACs (**Figure 26**) and PVCs (**Figure 27**). Additionally, in a few cases (2/127), runs of PACs caused false positives in both six-lead and single-lead ECGs, likely due to the low amplitude of abnormal P waves and irregular R-R intervals during rapid PAC bursts (**Figure 28**).

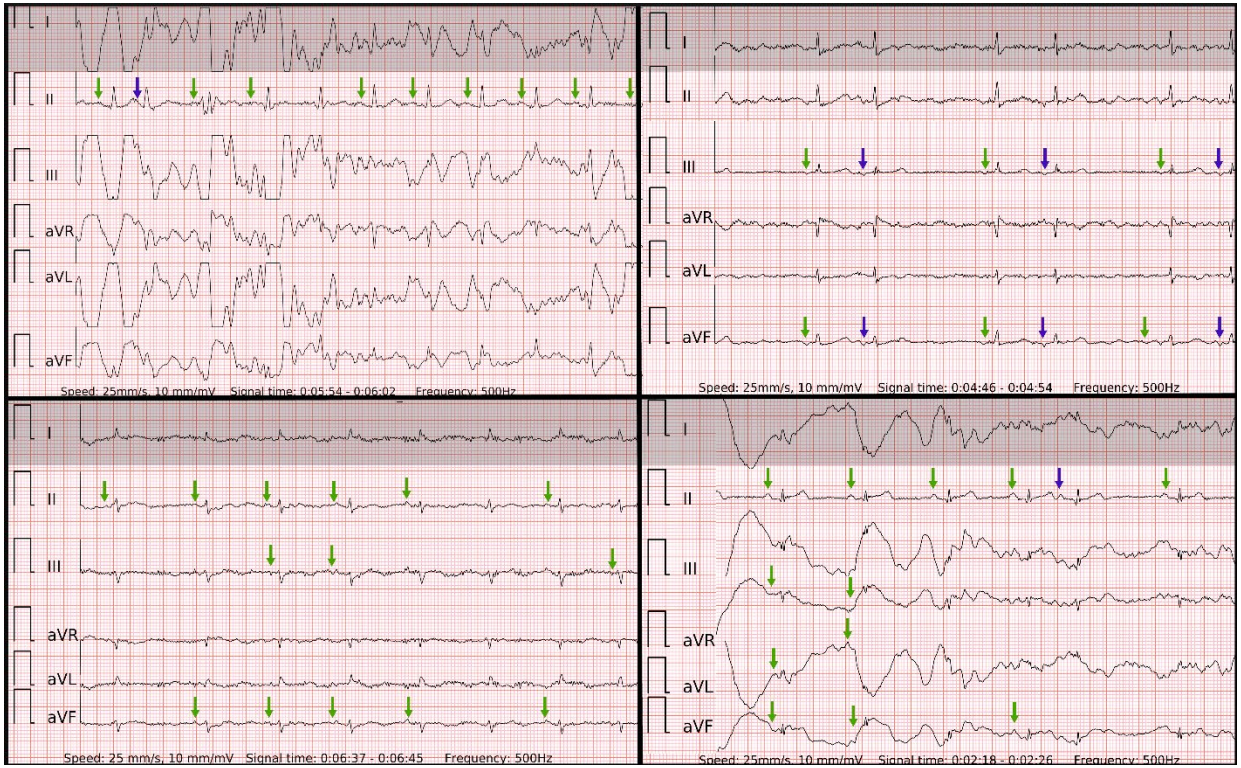

Figure 26. Problematic recordings of SR with PACs. False if interpreted by single lead-I-like ECGs (marked in gray) vs. correct if interpreted by six-lead ECGs. Top left panel: cannot be concluded due to artifacts in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows) and *P′* of PAC on the T wave (blue arrow); Top right panel: false positive due to artifacts masking small *P* waves and mimicking f waves in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows) and P' of PACs (blue arrows); Lower left panel: false positive due to artifacts masking small *P* waves and mimicking f waves in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows); Lower right panel: cannot be concluded due to artifacts in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows) and P' of PAC after the T wave (blue arrow).

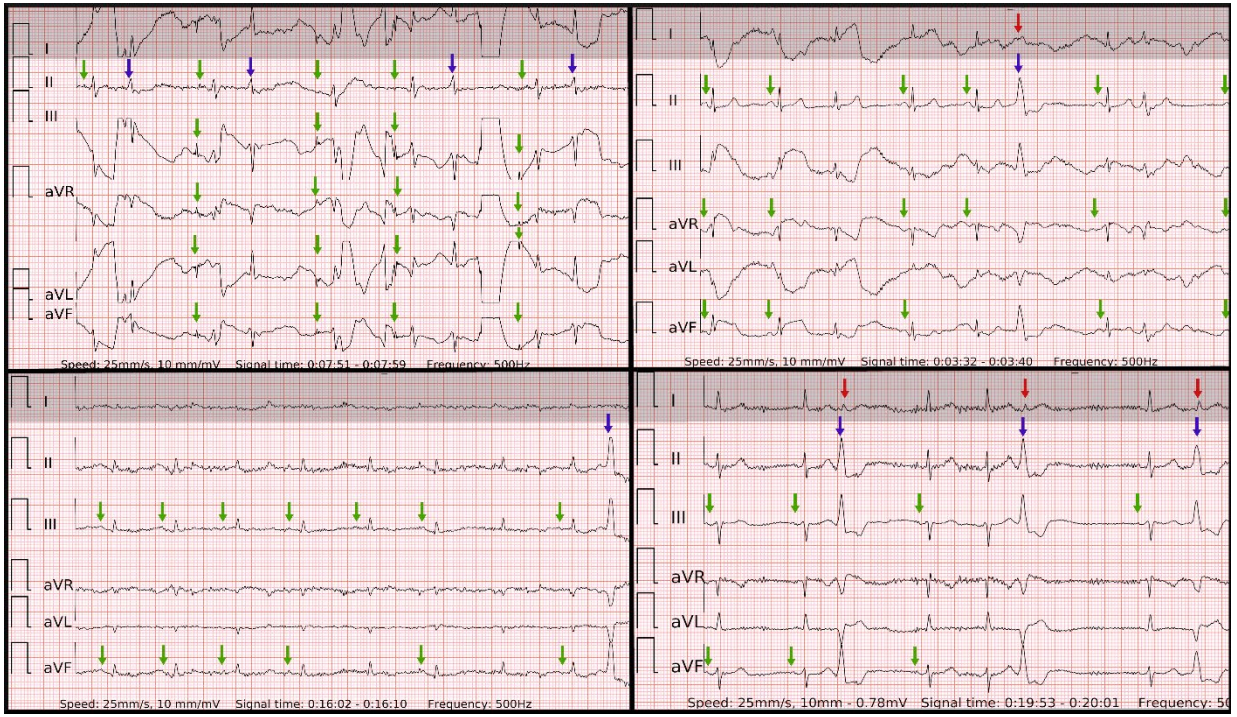

Figure 27. Problematic recordings of SR with PVCs. False if interpreted by single lead-I-like ECGs (marked in gray) vs. correct if interpreted by six-lead ECGs. Top left panel: cannot be concluded due to artifacts in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR with some artifacts (green arrows) and QRS of PVC or aberrancy (blue arrow); Top right panel: false positive due to artifacts masking small *P* waves and mimicking f waves as well as pseudo irregularly-irregular R-R intervals due to barely visible QRS of PVC (red arrow) in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows) and big QRS of PVC with inferior axis (blue arrow); Lower left panel: cannot be concluded due to artifacts and small amplitudes in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows) and QRS of PVC with inferior axis (blue arrow); Lower right panel: cannot be concluded due to artifacts and unclear irregularity type of R–R intervals due small QRS of PVCs (red arrows) in single-lead ECG, true negative in six-lead ECG with reproducible *P* waves of SR (green arrows), regularly-irregular R–R intervals and QRS of bigeminy/trigeminy PVCs with inferior axis (blue arrows).

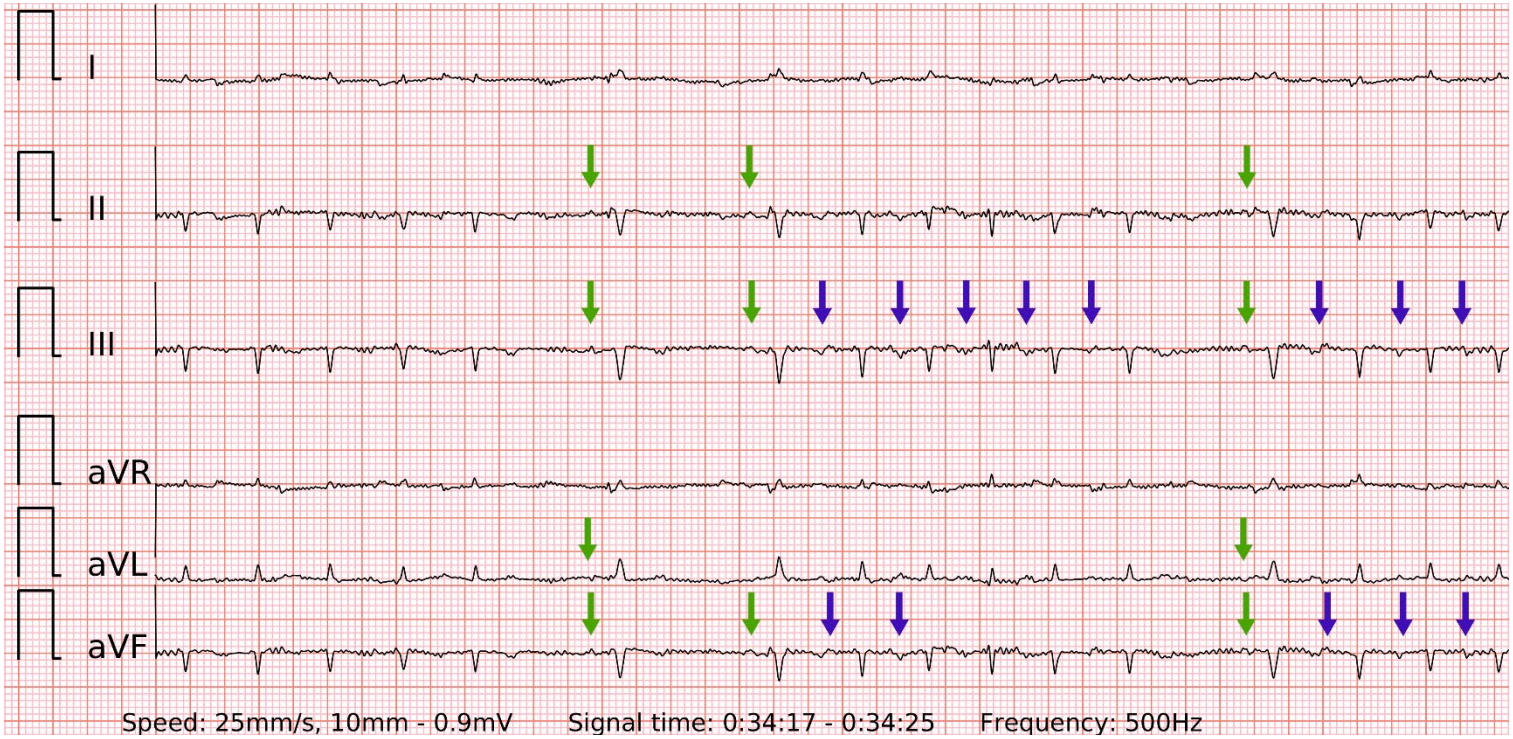

Figure 28. A problematic recording of SR with runs of PACs. A rare example of false positive in both single-lead and six-lead ECGs. Presumably due to the small amplitude of abnormal P' waves (blue arrows) and lightly irregular R-R intervals during fast bursts of runs of PACs. The *P* waves of SR are visible and reproducible (green arrows), but overwhelmed by the previous findings.

These ECG examples demonstrate that the six-lead ECG was the most resistant to frequent premature contractions and least likely to yield inconclusive results. Looking ahead, the six-lead ECG offers the added potential to reconstruct the axes of both QRS complexes and P waves. While beyond the current study's scope and without showing precordial leads, this capability could facilitate the localization of arrhythmias with rare clinical presentations, similar to existing ECG algorithms used for idiopathic ventricular tachycardia/PVC and atrial tachycardia (65–67).

5.4.4 Results of Other Wearable Devices with Six-Lead ECG for AF Detection

As comprehensively presented in the literature review (Section 2.1), only two commercially available devices—Kardia Mobile 6L and Istel HR 2000—are capable of recording a wire-free six-lead ECG. However, both function exclusively as event recorders, meaning they are not worn continuously on the body. Consequently, they lack any continuous monitoring for arrhythmia, such as a PPG-based algorithm, making asymptomatic episodes likely to remain undetected.

With that being said, the ability of Kardia Mobile 6L and Istel HR 2000 to detect AF still supports the superior diagnostic accuracy of six-lead ECGs compared to single-lead recordings (24,25). However, both studies included only a control group with stable sinus rhythm and did not account for patients with frequent premature contractions. This is a significant limitation, particularly when considering the real-world application of wearables for AF screening in individuals over 65 years of age, who are more likely to exhibit concomitant arrhythmias.

5.4.5 Limitations

Here the same limitations apply as in section 5.3.4. In addition, Paper II is a substudy of DoubleCheckAF (Paper I), which originally was not intended for recording a single-lead ECG. In order to display a single-lead ECG, the six-lead wearable-recorded ECG was trimmed to a width of lead-I-like ECG. However, there is also an advantage to it as the accuracy of both diagnostic tools was not influenced by any potential difference in the complexity of recording since it was exactly the same episode of arrhythmia.

5.5 Discussion of Paper III: AI vs. Technicians' Detection of Arrhythmia in Direct-to-Physician Ambulatory ECG Reporting

The analysis of big data is a critical concern in both wearable-recorded intermittent ECG and, especially, in continuous traditional ECG-based monitoring strategies, due to the substantial review burden and associated costs. According to findings in the following sections cited from **Paper III**, these challenges could be effectively mitigated by employing the DeepRhythmAI model.

5.5.1 Major Findings

This large, carefully adjudicated analysis demonstrates that the DeepRhythmAI model could safely replace technician interpretation of ambulatory ECG recordings, with an impressive sensitivity for critical arrhythmias and a modest increase of false-positive detections.

The DeepRhythmAI model:

1) had a negative predictive value for critical arrhythmias that exceeded 99.9%. Compared to technicians, it resulted in 17 times fewer patients with a missed diagnosis of a critical arrhythmia;

2) this was at a cost of 2.4 times more false-positive detections of critical arrhtyhmias, i.e. seven extra false-positive findings per 1,000 patient days of recording (12 (6–74) for AI vs. 5 (2–153) for technicians).

Considering that the DeepRhythmAI model performance exceeds the benchmarks of 99% negative predictive value and 70% positive predictive value that guidelines have recommended for accepting a single high-sensitive troponin to rule out major adverse cardiovascular events (68–72) we consider DeepRhythmAI model-only analysis to be safe for the analysis of ambulatory ECG data.

5.5.2 Comparison to Other Studies

The current study differs fundamentally from previous studies of AI for arrhythmia classification in that we evaluate the use of AI as the only reader for the majority of the health data, with physician confirmation only of AI model-selected episodes. This may be necessary for the management of the rising volume of ECG that will need to be accurately adjudicated without missing critical events. The sample size in terms of annotated strips in this study is 6–16 times larger than previous studies (33,34), and the patient population negative predictive value, absolute false-positive and false-

negative rates for AI-only analysis have never been reported before. These data are necessary to determine whether an AI can safely be used for direct-to-physician reporting and have not been shown in previous studies evaluating AI for arrhythmia diagnostics. Direct-to-physician reporting of ambulatory ECG results could unburden strained healthcare environments and result in an appropriate expansion of access, which should result in more equitable access to testing and subsequent care. We used a large, unselected clinical patient population to estimate how the use of the DeepRhythmAI model analysis instead of ECG technician analysis would affect the accurate detection and false-positive rates, using the beat-to-beat classification of a large and representative sample of arrhythmic events. Due to our sampling strategy, the measures of sensitivity that we report are not directly comparable to the sensitivity reported in selected rhythm strips in previous studies. We report as false negatives only patients in whom a diagnosis was missed for the full duration of the recording (that is, 14 ± 10 days of monitoring), arguably a more relevant evaluation metric. With this in mind, the AI model we evaluated had better sensitivity for all critical arrhythmias that were evaluated in both this study and a study assessing a deep neural network architecture for rhythm classification of single-lead ECGs (33), a study evaluating a convolutional neural network for rhythm classification of 12-lead ECGs (34) and a study comparing a deep neural network with physician over-reading of the full ECG to an electrophysiologist review of a traditional Holter system (73). While the technician sensitivity in this study is low, this finding is in line with previous studies that show a low average accuracy in ECG interpretation for technicians (74).

5.5.3 Why AI Outperformed the Manual Analysis of Technicians

The large difference in false-negative findings using the DeepRhythmAI model and technician analysis could be dependent on factors related to algorithms and factors related to causes of human error. The higher rate of technician false negatives is likely in part to be due to limitations of features-based algorithms compared to AI models, but because technician work also includes scanning the ECG manually and assessing heart rate trends, there could also be effects of time pressure, information overload (75,76) and other factors related to limits in human perception and memory (77,78), which do not affect AI models. Thus, with increasing data volume that will require analysis, the AI model increasingly outperforms technician interpretation, giving consistent annotations not subject to fatigue. Rhythm analysis by technicians depends on correctly identifying and retaining in memory a large

number of visual features; for example, a single capture beat in a wide complex tachycardia is pathognomonic for VT, but the human working memory has a fixed upper limit, and high information loads, such as in the analysis of ambulatory ECG recordings, can lead to reduced accuracy decision quality (75,77).

5.5.4 Limitations

Some limitations in study design should be considered. First of all, the technicians, but not the physician panels or the AI model, had access to clinical information such as monitoring indication, age and sex, which may have introduced a bias in favor of the technicians. At the same time, while the technicians were performing their analysis during paid clinical work hours, the cardiologist panels were performing their analysis as part of a research protocol, and therefore the panel annotations do not exactly represent a clinical workflow. Panel cardiologists may have been either more or less careful than they would have been with clinical patients, which could have introduced misclassification bias. We have not differentiated between second-degree AV block types 1 and 2, and we do not report subgroups by monitoring indication. Because monitoring indications were entered through the device, the absence of a reported indication should not be interpreted as a lack of that indication. The false-negative events in the study were patients in whom all episodes of arrhythmia were missed for the entire recording duration by one method, but at least one was detected by the other. While we consider this to be a robust method for false-negative estimation, it is possible that there are additional arrhythmic events that were undetected by both the AI model and technicians. If any arrhythmias were missed by both methods, this would imply a lower sensitivity and negative predictive value for both technicians and the AI model but not affect the results showing a superior sensitivity and negative predictive value for the AI model compared to technicians. It is also important to point out that, while the technicians were aided by a Food and Drug Administration-approved algorithm and also performed a manual review and reannotation of the data, their use of a different algorithm may have yielded different results. The underlying ECG data were recorded by a device providing leads II and III. However, the use of devices with nonstandard lead configurations and single-lead recording is becoming more prevalent. The results cannot be generalized to other AI algorithms, and the DeepRhythmAI model may have different performances on other signals, although, in view of the accuracy that the DeepRhythmAI model demonstrated in this study, the model could be tested on other ECG recording signals in the future. Finally, while we used an

unselected patient population and extracted a large representative sample of relevant arrhythmic episodes for evaluation, some evaluation metrics that we report, such as the negative predictive value, are dependent on the population prevalence of arrhythmia, which may differ between different populations and may change over time.

5.6 Discussion of Paper IV: ECG-Based Risk Markers and Predictive Modeling for AF in Long-Term Holter Monitoring

An essential application of wearables and other ambulatory ECG monitoring strategies is the primary detection of AF. As cited below from Paper IV we found an ECG-based target group identified through single-day Holter monitoring. These patients could potentially benefit from extended monitoring, incorporating the wearable technology developed in this PhD research or other monitoring modalities.

5.6.1 Predicted Target Group for Long-Term Monitoring

In "ECG-only" model a clear group of patients who are not likely to benefit from long-term monitoring are in the lowest quintile of predicted AF. In this group, AF was detected in approximately only one of 250 (7/1816, 0.4%) patients, yielding a negative predictive value of 99.6%. In addition, a useful comparison matched by gender and age between 2465 "high-risk" and "low-risk" pairs was done. The observed rates of AF occurrence during mobile cardiac telemetry monitoring were five times more common in the "high-risk" group (15.4%) compared to 3.5%, which suggests patients in "high-risk" group may benefit from long-term monitoring.

5.6.2 ECG features for Predicting AF

A previous study employing a machine learning approach to predict AF from shorter ambulatory monitoring did not demonstrate significantly improved ROC statistics (79). The current approach offers a distinct advantage due to its relative simplicity and clear linkage between ECG features and AF risk. Several ECG characteristics have been shown to predict the incidence of AF over extended follow-up periods. For instance, both PACs and supraventricular tachycardia episodes (SVTs) have been associated with future AF occurrences in both population-based and clinical settings (80–82). PACs originating from the pulmonary veins are particularly noted for triggering AF episodes (83). Furthermore, a low resting heart rate and mean heart rate during ambulatory ECG have also been linked to subsequent AF

(80,84). Our study not only confirms that these factors predict concurrent paroxysmal AF detectable through extended monitoring but the first to show that the pattern of occurrence of PACs and PVCs has clinical relevance: PAC couplets and triplets were notably more prevalent and exhibited a higher maximum heart rate in "high-risk" compared to "low-risk" patients, marking a novel finding. Additionally, the count of PACs, rate of couplets, triplets, and SVTs as well as the duration of SVTs were the only variables incorporated into the ECG-only model.

Including age and sex with ECG variables led to the selection of more variables, yet it did not enhance discrimination or calibration. This suggests that the influence of biological age on AF risk is largely captured by these basic ambulatory ECG variables. In short, a 24-hour ECG that suggests an elevated risk of AF typically shows a moderate increase in PACs and PVCs, presenting as rapid couplets, triplets, and SVTs, coupled with a low mean heart rate. Enhancements in predicting AF might be attainable through more comprehensive ECG data, such as p-wave indices, or by incorporating clinical data.

5.6.3 Limitations

A significant limitation of this study is the lack of access to clinical data for the participants. Thus, it is not possible to evaluate whether the ECG-based prediction remains effective across different levels of CHA_2DS_2-VASc (85), CHA_2DS_2-VA (26) or other risk scores (86,87). Also, limitations of a retrospective design apply.

6 CONCLUDING REMARKS

1. The first wearable wrist-worn device that combines a PPG-based algorithm with a 6-lead wire-free ECG has proven to be a significant innovation, having successfully achieved patent protection. This innovation has met with substantial demand from both patients and healthcare institutions, leading to its commercialization, MDR certification, and integration into clinical practice as a new CE-marked medical device (**Patent, MDR Certification, Commercialization**).
2. Despite the presence of frequent PVCs/PACs in the control group, physicians were able to effectively detect AF using the PPG-based algorithm and diagnose it using the six-lead, wire-free ECG with high specificity during short-term monitoring. The integrated system of

both methods demonstrated a specificity of 99.6% (95% CI 97.5-100) and an overall accuracy of 99.5% (95% CI 98.9-100) (**Paper I**).

3. A six-lead wearable-recorded ECG did bring an additional diagnostic benefit for AF detection as it was superior to a single lead-I-like ECG commonly used in most smartwatches and automatic PPG-based AF detector (**Paper II**). Six-lead ECG was the most robust tool as it required 3.4 times more premature beats to result in a false positive outcome compared to single-lead ECG and 4.9 times more premature beats compared to the PPG-based detector.
4. The DeepRhythmAI model outperformed the technician analysis with an excellent negative predictive value of 99.9% (false negatives in 3.2/1,000 patient days) for critical arrhythmias compared to 99.1% (44.3/1,000 patient days). This substantial reduction in false-negative findings comes with a modest increase in false-positive findings (12/1,000 vs. 5/1,000 patient days, respectively) (**Paper III**).
5. ECG-based risk markers identified within the first 24 hours of long-term Holter/ECG patch monitoring (up to 30 days) can successfully predict the occurrence of AF between the following 2-30 days (**Paper IV**). Reliable markers in the prediction model include the number of single PACs, the fastest rate during PAC couplets and triplets, the longest duration of SVT, VT runs of ≥4 beats, and the maximum heart rate.

7 THE FIRST LIFE SAVED BY THE INVENTED DEVICE: A CASE REPORT OF PRACTICAL APPLICATION

This section discusses a case study with all personal and medical data disclosed with the patient's consent. A 51-year-old male was admitted for the second time to the emergency department of Vilnius University Hospital Santaros Klinikos after suddenly losing consciousness while driving, possibly preceded by palpitations. However, the etiology remained unknown for the second time as all examinations—including an ECG showing sinus rhythm and laboratory tests such as high-sensitivity troponin I, electrolytes, and creatinine clearance—returned normal results.

On this occasion, the patient was enrolled in the TriggersAF trial (NCT05526170) and was set to undergo a 7-day outpatient monitoring regimen. He was equipped with a wrist-worn device for long-term screening to detect potential arrhythmias, among other protocol devices. The initial wire-free six-lead ECG revealed frequent ectopic atrial activity characterized by quadrigeminal to bigeminal beats displaying P' waves with an inferior rightward axis. As the 6-lead ECG allows for analysis in multiple channels, according to the P-wave algorithm (65) to predict the site of origin, there was a bifid positivity in lead II and positivity in lead I, in line with a possible location in the right pulmonary veins of the left atrium (**Figure 29**). Later, the patient experienced a sudden-onset arrhythmia, felt dizzy but did not lose consciousness, and was able to record a six-lead ECG. The PPG signal and the ECG captured rapid tachycardia at 152 bpm, with P-wave morphology consistent with the earlier ectopic beats (**Figure 29**).

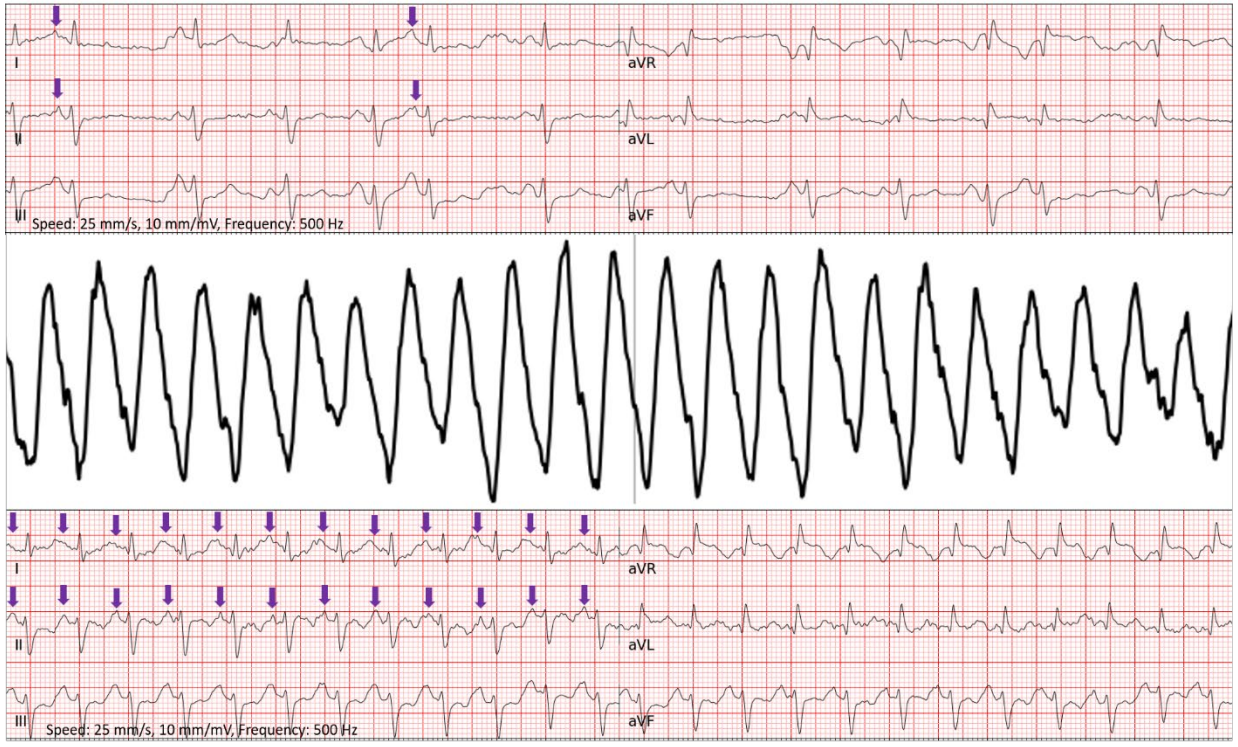

Figure 29. The six-lead ECG of the wearable initially detected atrial ectopic activity with the following P-waves (purple arrows): inferior rightward axis, bifid positivity in lead II with the second part bigger than the initial one, positivity in lead I, in line with a possible location in the right pulmonary veins of the left atrium (upper panel). The photoplethysmogram of the wearable during the tachycardia with sudden onset and 152 bpm (middle panel). The six-lead ECG of the wrist-worn device during the tachycardia displayed the same P-wave (purple arrows) morphology as in ectopic beats (lower panel).

Subsequently, the patient underwent invasive electrophysiological testing and 3D electroanatomic mapping using the Ensite system. We observed a clear difference in P'-wave of tachycardia (positive and bifid in II, positive in V1) compared to the normal P-wave of SR (positive in II, positive-negative in V1) (**Figure 30**). The high-density multipolar HD grid catheter localized the earliest activation to the right superior pulmonary vein in the left atrium (**Figure 31**). The clinical arrhythmia spontaneously and repeatedly induced and terminated itself without pacing and displayed a centrifugal activation map, prompting to the ectopic atrial tachycardia mechanism with TCL of 270-290 ms (206-222 bpm). Ablation with an irrigated radiofrequency catheter with 30W (TactiCath, Abbott) immediately terminated the arrhythmia at this site. In addition, a full antral isolation of the right-sided pulmonary veins was performed to prevent recurrence (**Figure 32**).

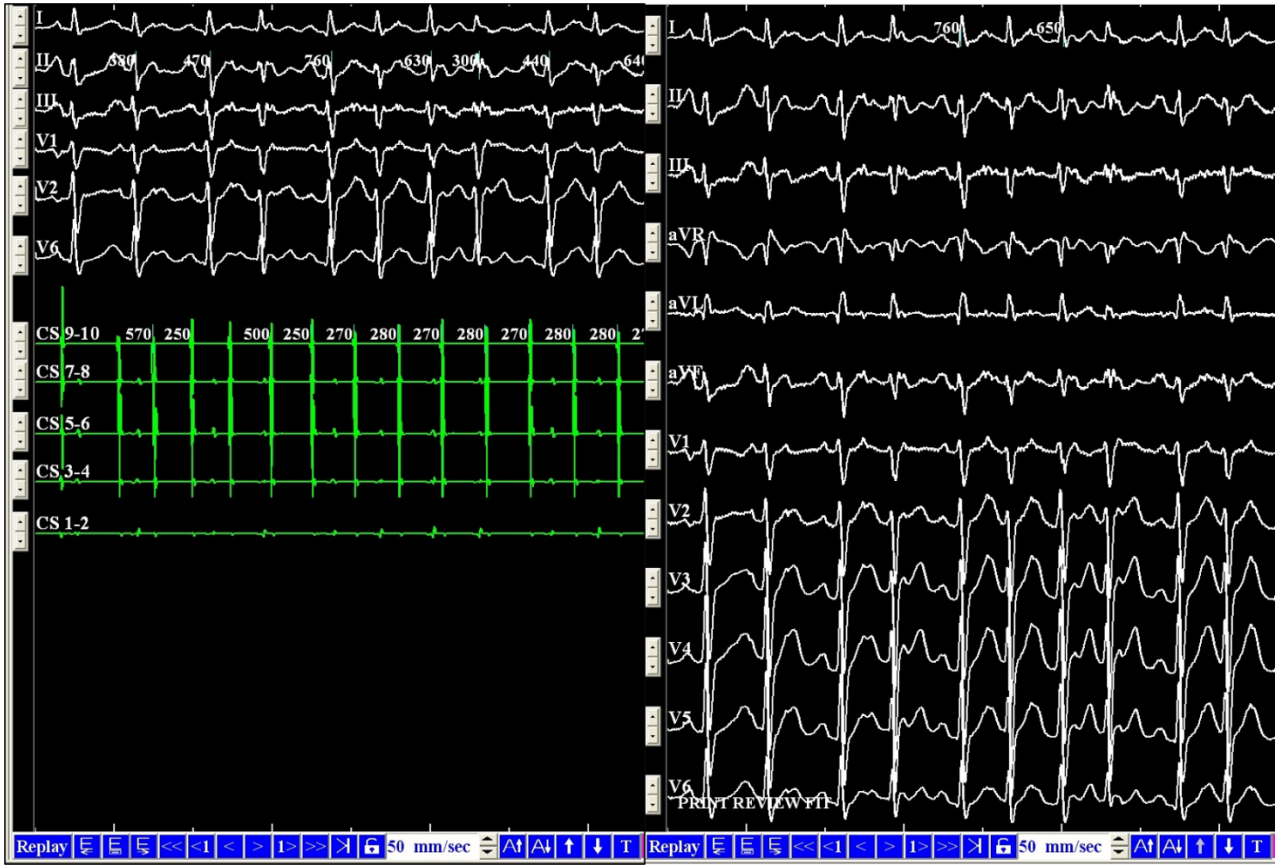

Figure 30. Invasive electrophysiological testing: 1) intracardiac signals revealed atrial salves with concentric CS activation, A:V ratio predominantly 1:1 and intermittently 2:1, and TCL of 270-290 ms; 2) simultaneous 12-lead ECG with differences of P-waves in SR (beat #1: pos.-neg. in V1-V2, pos. in II) compared to tachycardia (all other beats: pos. in V1-V2, bifid pos.in II).

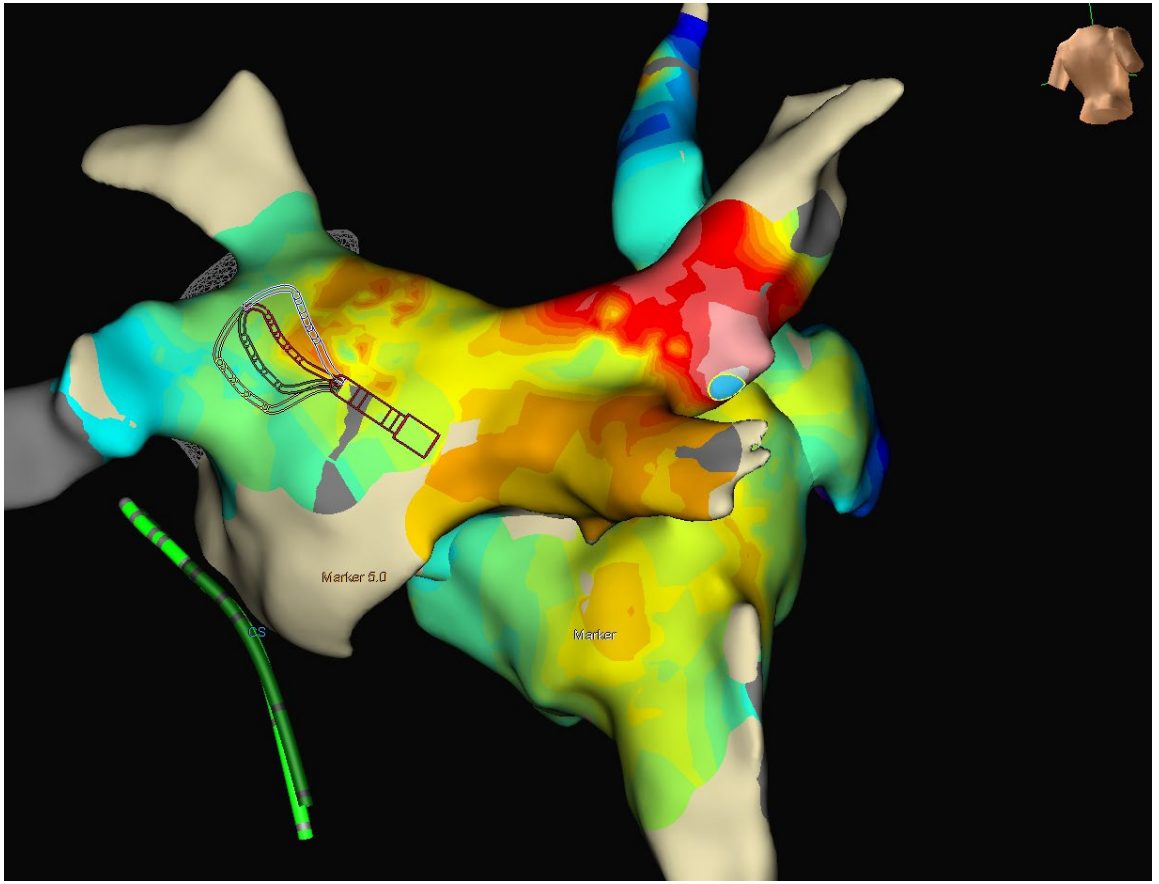

Figure 31. Activation map of arrhythmia displays a centrifugal propagation, characteristic for ectopic atrial tachycardia. The earliest activity is in the right superior pulmonary vein of left atrium in white colour (marked with light blue dot). The view is posterior and slightly tilted rightwards.

During annual follow-up calls, the patient consistently reported no recurrence of arrhythmia symptoms, palpitations, or loss of consciousness for over three years following the procedure. This success story, marking the first life saved by the invented device, demonstrates the value of novel wearable technology in enabling timely diagnosis of paroxysmal life-threatening arrhythmias, which subsequently leads to life-saving interventions with immediate and long-term effectiveness.

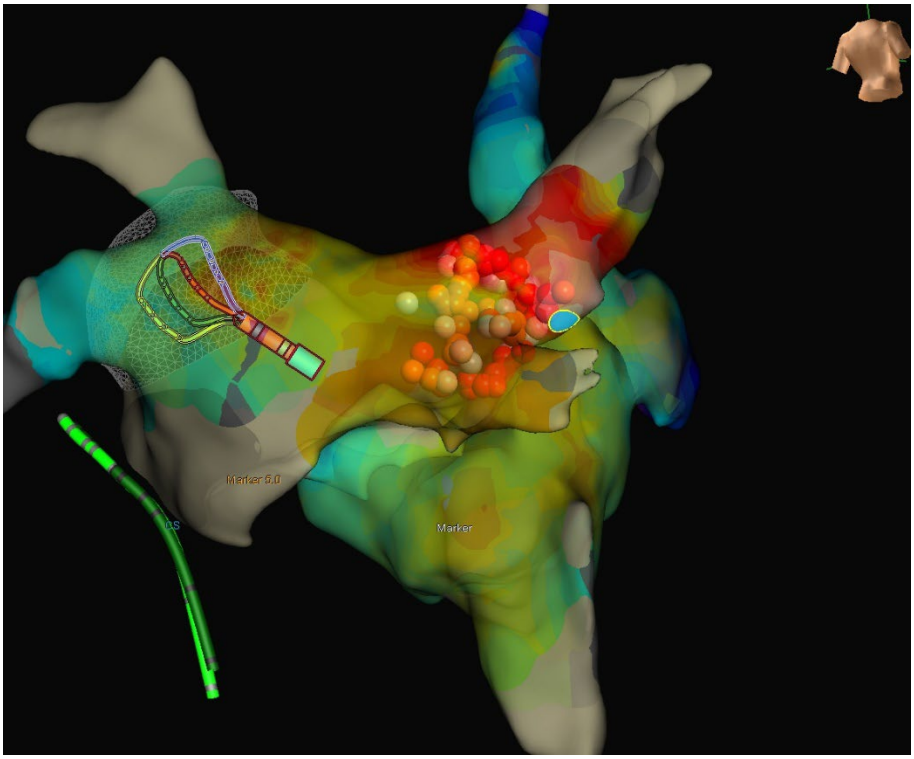

Figure 32. Ablation set: 1) a focal application on the source of arrhythmia origin inside the right superior pulmonary vein and 2) additional full antral isolation of the right-sided pulmonary veins to prevent recurrence.

8 RECOMMENDED PRACTICAL APPLICATIONS OF THE INVENTED DEVICE

Based on the insights from the EHRA consensus document (7) and practical findings from investigating 435 patients in the short-term DoubleCheck-AF trial (NCT04281927) (15,16) and 182 patients in the long-term TriggersAF trial (NCT05526170) (88), the author delineates practical applications for the commercialized version of the device, called TeltoHeart (Teltonika Telemedic, Vilnius, Lithuania).

Two major scenarios for the use of the device are identified: patients with no prior diagnosis of arrhythmia, for primary detection, and patients with a known arrhythmia diagnosis, for monitoring recurrence.

8.1 Use of TeltoHeart in Patients Without an Established Diagnosis of AF/ Bradyarrhythmia/ Tachyarrhythmia

a. By Symptom Frequency (**Figure 33**): According to the EHRA consensus, for patients experiencing symptoms less frequently than weekly, conventional Holter monitoring may not be cost-effective due to its limited ability to detect arrhythmias. A wearable-enabled long-term diagnostic approach is recommended for these cases.
b. By age and comorbidities (**Figure 34**): Differentiates between opportunistic versus systematic screening for AF, tailored to patient-specific risk profiles.
c. Post-Intervention/Surgery: Particularly applicable for procedures affecting the heart or potentially altering electrolyte balance (e.g., colorectal or cardiac surgery, TAVI). Consider TeltoHeart monitoring 6-12 months post-intervention if needed; otherwise, monitoring may not be necessary.

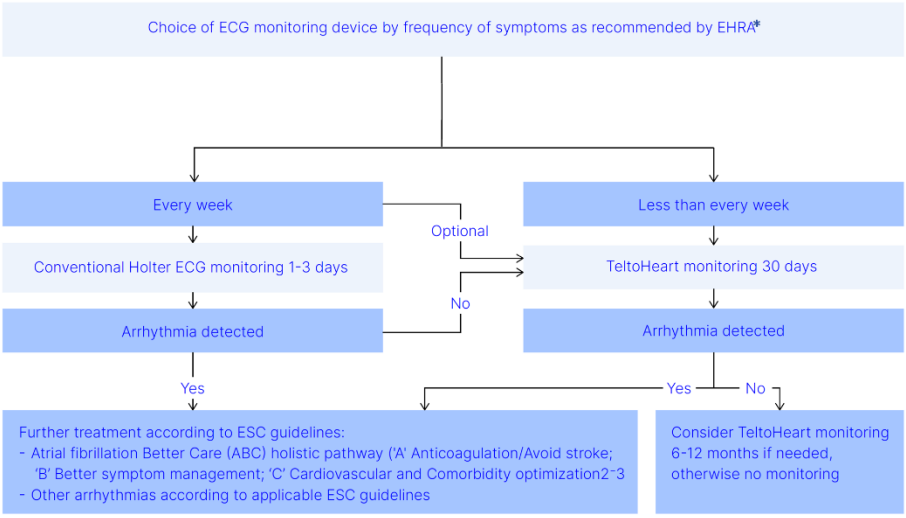

Figure 33. Use of TeltoHeart in patients **without** an established diagnosis of AF/ bradyarrhythmia/ tachyarrhythmia by symptom frequency.

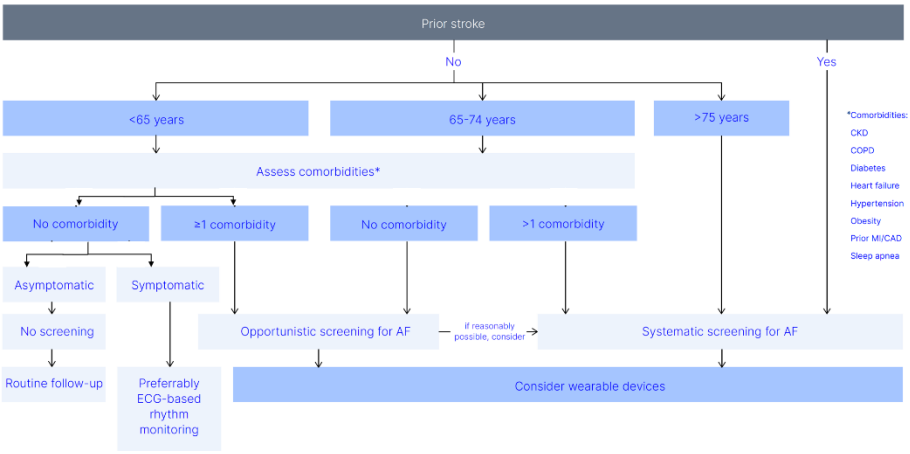

Figure 34. Use of TeltoHeart in patients **without** established diagnosis of AF/ bradyarrhythmia/ tachyarrhythmia by age and comorbidities: opportunistic vs. systematic screening for AF.

In addition, as reported in **Paper IV**, ECG-based risk markers identified within the first 24 hours of Holter—predictive of AF occurrence during the subsequent 2–30 days—may serve as an indication for initiating TeltoHeart monitoring. These criteria, comparing low- vs. high-risk patients for predicted AF, are as follows, respectively:

1) Number of single PACs, median (IQR): 12 (5, 23) vs. **839** (233, 3069), p <.001
2) Fastest rate of PAC couplets, bpm mean (SD): 123 (22) vs. **137** (26), p<.001
3) Fastest rate of PAC triplets, bpm mean (SD): 116 (22) vs. **130** (26), p<.001
4) SVTs ≥4 beats, median (IQR): 0 (0, 0) vs. **3** (1, 8), p<.001
5) Occurrence of VT runs of ≥4 beats: 79 (3.2) vs. **218** (8.8), p<.001. Note: In practice, these may represent short bursts of atrial tachycardia or AF with aberrancy, potentially misclassified as VT in the 2-channel ECG Holter monitoring.
6) the maximum heart rate, mean (SD): 114.7 (16.7) vs. **99.3** (14.8) <.001

8.2 Use of TeltoHeart in Patients With an Established Diagnosis of AF/ Bradyarrhythmia/ Tachyarrhythmia

In cases where an arrhythmia has previously been diagnosed, TeltoHeart facilitates ongoing monitoring to assess the effectiveness of treatment modalities and the early detection of recurrence or drug-induced side effects (e.g., QTc prolongation) (**Figure 35**).

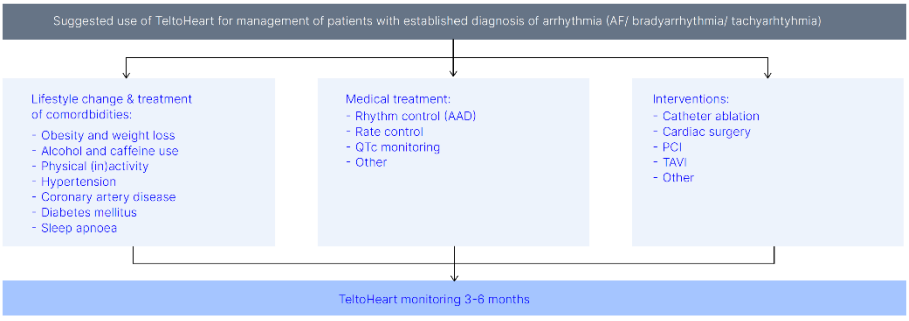

Figure 35. Use of TeltoHeart in Patients **With** an Established Diagnosis of AF/ Bradyarrhythmia/ Tachyarrhythmia.

Regarding the organization of this novel healthcare service, the typical TeltoHeart pathway involves prescribing the monitoring during an initial consultation with a physician (e.g., cardiologist), followed by 30 days of device use, subsequent data analysis, and a follow-up consultation (**Figure 36**).

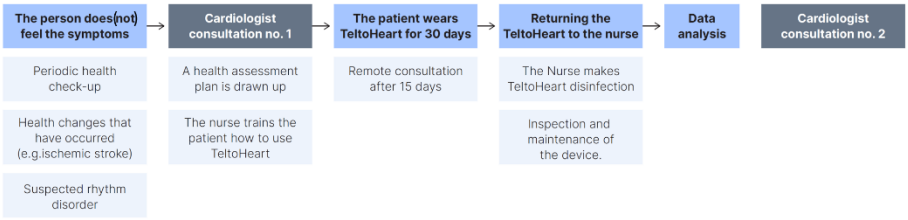

Figure 36. Suggested pathway of TeltoHeart service.

8.3 Future Directions

The scientific development and practical application of the invented device open several promising avenues for future research, which fall outside the scope of this PhD thesis but are nonetheless important to highlight.

In the TriggersAF trial (88), one of the objectives was to assess the long-term performance of the wearable device prototype during 7-day telemonitoring. As a general principle, the longer the device is worn, the greater its potential to detect atrial arrhythmias—especially in early-stage disease characterized by rare and brief paroxysms. However, extended use outside of hospital settings introduces additional challenges, such as patient literacy on proper device usage and ensuring timely medical response when needed.

Another direction—also developed independently of this thesis—involves expanding the indications for rhythm and conduction disorder monitoring. This includes conditions such as atrial flutter, ventricular arrhythmias, and bundle branch blocks, as well as broader cardiology applications like acute coronary syndrome. Notably, preliminary results from HRX 2024 on detecting acute myocardial infarction using the wrist-worn device showed encouraging potential and warrant further investigation.

Finally, multicenter clinical trials are planned to expand the use of the technology across broader populations and healthcare systems. These efforts could significantly contribute to the advancement of digital health and telemedicine—supporting earlier primary diagnosis that enables timely healthcare, improved secondary control following various treatment modalities, and more personalized cardiovascular care overall.

9 SANTRAUKA

Santrumpos

PV	prieširdžių virpėjimas
AIVR	akceleruotas idioventrikulinis ritmas
DI	dirbtinis intelektas
AVB	atrioventrikulinė blokada
KNT	konvoliucinis neuroninis tinklas
LSMP	ligos sukeltas metų praradimas
TGAK	tiesioginio veikimo geriamieji antikoaguliantai
DRDI	„DeepRhythm“ dirbtinio intelekto modelis
APA	ankstyviausia prieširdžių aktyvacija
EPR	ektopinis prieširdinis ritmas
EKG	elektrokardiograma
EŠRA	Europos širdies ritmo asociacija
EVA	Europos vaistų agentūra
EPB	Europos patentų biuras
EKD	Europos kardiologų draugija
PSVEA	padidėjęs supraventrikulinės veiklos ektopinis aktyvumas
MVA	maisto ir vaistų administracija
KN	klaidingai neigiami rezultatai
KT	klaidingai teigiami rezultatai
RS	rizikos santykis
IS	Istel HR 2000
IVR	idioventrikulinis ritmas
JPB	Japonijos patentų biuras
KM	Kardia Mobile 6L
MMMH	mažos molekulinės masės heparinas
TS	tikimybės santykis
MPR	medicinos prietaisų reglamentas
NPV	neigiama prognostinė vertė
GAK	geriamieji antikoaguliantai
ŠS	šansų santykis
PrE	priešlaikiniai prieširdžių susitraukimai
TPV	teigiama prognostinė vertė
FPG	fotopletizmografija
PSVT	paroksizminė supraventrikulinė tachikardija
PVI	plaučių venų izoliacija

SkE	priešlaikiniai skilvelių susitraukimai
QTc	koreguotas QT intervalas
DP	dešinysis prieširdis
SR	sinusinis ritmas
VTV	viršutinė tuščioji vena
PSIP	praeinantis smegenų išemijos priepuolis
TT	teisingai teigiami rezultatai
SkT	skilvelinė tachikardija
PINO	Pasaulinė intelektinės nuosavybės organizacija

9.1 Įvadas

9.1.1 Tyrimo kontekstas ir aktualumas

Prieširdžių virpėjimu (PV) – dažniausia širdies aritmija pasaulyje – pasaulyje serga maždaug 60 milijonų žmonių. PV yra daugiau nei 8 milijonų ligos sukelto metų praradimo (LSMP) priežastis (1). Paroksizmine supraventrikuline tachikardija (PSVT) serga apie vienas iš trijų šimtų asmenų (2). Jungtinėse Amerikos Valstijose sergamumas PSVT svyruoja nuo 1,26 milijono (neįtraukiant atvejų su gretutine PV ar prieširdžių plazdėjimo diagnoze) iki 2,06 milijono (įtraukiant gretutines diagnozes). PV paplitimui vis didėjant, reikšminga dalis atvejų lieka nediagnozuoti (3,4). Tai apima ne tik besimptominius asmenis, bet ir tuos, kurių simptomai, dažnai epizodiniai, nėra užfiksuojami standartine 12 derivacijų elektrokardiograma (EKG) ar įprastiniais metodais, tokiais kaip Holterio monitoravimas. Nediagnozuotas PV gali kelti rimtą grėsmę sveikatai, todėl ankstyvas diagnozavimas ir valdymas yra labai svarbūs (5).

Didėjantis nešiojamųjų prietaisų prieinamumas gerina PV ir kitų aritmijų nustatymą tiek besimptominiams, tiek simptomus turintiems, bet dar nediagnozuotiems pacientams (6). Įprastai, pirminiam atrankiniam vertinimui fotopletizmografijos (FPG) metodas yra tikslesnis už pulso čiuopimą. Tačiau jei FPG aptinka galimą PV, tik elektrokardiogramos (EKG) pagrindu veikiantis prietaisas yra pakankamas šiai diagnozei patvirtinti (7). Be to, Europos širdies ritmo asociacija (EŠRA) teigia, kad nešiojamieji įrenginiai yra tinkamas pasirinkimas pooperaciniam stebėjimui po abliacijos tiek klinikinėje praktikoje, tiek moksliniuose tyrimuose (8), įskaitant ir vyresnio amžiaus pacientus ilgalaikėje nuotolinėje sveikatos priežiūroje (9).

Praktikoje skaitmeninės sveikatos technologijų diegimą gali riboti įvairios kliūtys, susijusios su naudotojų, sveikatos priežiūros specialistų, kūrėjų bei pramonės atstovų požiūriais (10). Pagrindinės kliūtys apima integracijos su sveikatos priežiūros sistemomis trūkumą, MDR reguliacinio sertifikavimo nebuvimą, kaštų efektyvumo analizės trūkumą, ribotas klinikines taikymo galimybes, nepamatuotus pacientų lūkesčius, duomenų logistiką ir kibernetinio saugumo klausimus (11). Tokie barjerai gali reikšmingai pakenkti pacientams, atidėdami aritmijos nustatymą ir gydymą. Pavyzdžiui, net 40 % Europos šalių, po praeinančio smegenų išemijos priepuolio (PSIP), PV atmetimui naudoja tik konvencinę trumpalaikę ligoninės EKG, nesinaudojant ilgalaikio stebėjimo galimybėmis (12).

Tarp nešiojamųjų įrenginių parametrų, EKG signalo kokybė yra vienas svarbiausių veiksnių, lemiančių aritmijų nustatymo tikslumą. Net ir

įprastiniame kelių derivacijų EKG Holterio monitoravime, papildomų derivacijų įtraukimas leidžia tiksliau interpretuoti aritmijas esant artefaktams (13). Analogiškai ir nešiojamuosiuose prietaisuose artefaktai, triukšmai ir kitos gretutinės aritmijos, sukeliančios nereguliarius širdies susitraukimus, kaip priešlaikiniai susitraukimai, išlieka didžiausiais iššūkiais EKG pagrįstai PV diagnostikai (14). Dauguma šiuo metu esančių išmaniųjų laikrodžių fiksuoja tik I derivacijos tipo EKG, o tai, mūsų įsitikinimu, sukelia nemažai klaidingai teigiamų rezultatų, dėl ko ženkliai padidėja sveikatos priežiūros kaštų poreikis.

Šios daktaro disertacijos tikslas buvo reikšmingai prisidėti prie naujųjų nešiojamųjų prietaisų skaitmeninės sveikatos sektoriuje pažangos. Darbo autorius yra vienas iš išradėjų pirmojo MDR CE sertifikuoto ant riešo dėvimo įrenginio, kuris kombinuoja FPG pagrįstą PV atrankinio ištyrimo algoritmą ir gali užrašyti intermituojančą, bevielę 6 derivacijų EKG PV patvirtinimui (15–21). Be patento sukūrimo, šio darbo metu buvo publikuoti keturi straipsniai: du apie įrenginio diagnostinį tikslumą PV pacientams, kontroliuojant grupėmis su dažnais priešlaikiniais širdies susitraukimais, ir du apie dirbtinio intelekto algoritmą apdorojant didelius EKG duomenų srautus bei ilgalaikės EKG markeriais paremtą rizikos stratifikavimą atrenkant pacientus ilgesniam EKG monitoravimui dėl ankstyvos PV diagnostikos.

9.1.2 Tyrimo tikslas

Sukurti ir/ar įvertinti naujų medicininių priemonių diagnostinį tikslumą prieširdžių virpėjimui nustatyti ir prognozuoti, apimant nešiojamąjį elektroninį prietaisą su FPG ir daugiakanale EKG, programinius algoritmus bei dirbtinio intelekto metodus.

9.1.3 Tyrimo uždaviniai

1. Sukurti pirmąjį pasaulyje ant riešo dėvimą nešiojamąjį prietaisą, turintį ištisinę FPG, skirtą PV įtarimui, bei galimybę įrašyti belaidę panašią į 6 standartinių galūninių derivacijų EKG, leidžiančią gydytojui patvirtinti ritmą (**Patentai**).
2. Validuoti diagnostinį prietaisą įvertinant FPG paremto algoritmo, bevielės šešių derivacijų EKG ir sistemos iš abiejų metodų tikslumą trumpalaikėje stebėsenoje, siekiant įtarti ir diagnozuoti PV, įtraukiant ir dažnas ekstrasistoles kontrolinėje grupėje (**Straipsnis I**).
3. Ištirti, ar šešių derivacijų bevielė prietaiso EKG prideda papildomą diagnostinę naudą PV nustatymui lyginant su panašia į I derivacijos

EKG, kuri plačiai naudojama daugumoje išmaniųjų laikrodžių, bei automatiniu FPG principu veikiančiu detektoriumi (**Straipsnis II**).

4. Palyginti aritmijų nustatymo tikslumą panaudojant dirbtinio intelekto algoritmą su kardiologijos ekspertų išvadomis ilgalaikėse Holterio EKG (**Straipsnis III**).
5. Nustatyti PV rizikos žymenis ilgalaikiuose Holterio EKG įrašuose, atrenkančius pacientus, kuriems potencialiai tolimesnė ilgalaikė stebėsena nešiojamaisiais prietaisais ar kitais būdais galėtų būti naudinga (**Straipsnis IV**).

9.1.4 Disertacijos ginamieji teiginiai

1. Pirmasis nešiojamasis ant riešo dėvimas prietaisas, kombinuojantis FPG pagrįstą algoritmą aritmijos įtarimui ir 6 derivacijų bevielę EKG aritmijos patvirtinimui, yra reikšminga inovacija, kuri pagrįstai gali būti patentuotina. Dėl patikimo diagnostinio prietaiso poreikio tiek pacientų, tiek sveikatos priežiūros įstaigų tarpe, šis sprendimas buvo sėkmingai komercializuotas, gavo MDR sertifikavimą ir buvo įdiegtas į klinikinę praktiką kaip naujas CE ženklinimu pažymėtas medicinos prietaisas (**Patentas, MDR sertifikavimas, Komercializacija**).
2. Nepaisant dažnų priešlaikinių skilvelinių ir prieširdinių susitraukimų (PrE/ SkE) kontrolinėje grupėje, gydytojai galėjo tiksliai įtarti ir diagnozuoti prieširdžių virpėjimą trumpalaikių įrašų stebėjimo metu naudojant prietaisą, kuris turėjo diagnostinę sistemą, sudarytą iš FPG algoritmo ir bevielės šešių derivacijų EKG (**Straipsnis I**).
3. Šešių kanalų bevielė EKG, užfiksuota dėvimu įrenginiu, suteikia papildomą diagnostinę naudą nustatant prieširdžių virpėjimą, lyginant su vieno kanalo EKG, primenančia I derivaciją, kuri plačiai naudojama esamuose išmaniuosiuose laikrodžiuose, bei automatiniu FPG algoritmu (**Straipsnis II**).
4. Dirbtinio intelekto algoritmas aritmijų aptikimui buvo tikslesnis lyginant su sertifikuotų EKG technikų rankine analize ilgalaikiuose Holterio EKG įrašuose (**Straipsnis III**).
5. Pirmųjų 24 valandų Holterio EKG stebėsenos metu nustatyti EKG rizikos žymenys gali sėkmingai prognozuoti prieširdžių virpėjimo aptikimą per tolimesnes 2–30 dienų ir taip leisti atrinkti kandidatus išplėstiniam 1 mėnesio trukmės ištyrimui siekant ankstyvos aritmijos diagnostikos (**Straipsnis IV**).

9.1.5 Naujumas ir praktinė vertė

Naujųjų nešiojamųjų prietaisų naudojimas neturint medicininio prietaiso MDR CE sertifikavimo medicininiais tikslais neatitinka įrodymais pagrįstos medicinos principų. Nors teoriškai šie įrenginiai gali turėti tam tikrą vertę kaip atskiri diagnostikos metodai, vis dėlto dažnai jiems trūksta svarbių su MDR sertifikavimo procesu susijusių kokybės patikrinimų. Dažniausiai tokie trūkstami aspektai galėtų būti įvardijami kaip publikuotų straipsnių ar atviros prieigos duomenų apie veikimo tikslumą trūkumas, realiomis sąlygomis išbandyti diagnostiniai ypatumai atsižvelgiant į papildomus veiksnius (pvz. dažnų ekstrasistolių poveikis), aiškiai apibrėžta tikslinė prietaiso panaudojimo pacientų grupė bei sklandi integracija į gydymo įstaigų darbo eigą.

Šio mokslinio darbo naujovė yra tai, kad didele dalimi sprendžiami minėti iššūkiai, sukuriant ir validuojant naują diagnostinį medicinos prietaisą. Darbe apimamas tęstinis nuoseklus procesas: nuo pradinės autoriaus idėjos – užfiksuoti šešių derivacijų bevielę EKG, panaudojant tik ant riešo nešiojamą įrenginį – iki prototipo sukūrimo, kuris sujungia tiek FPG pagrįstą algoritmą PV įtarti, tiek šešių derivacijų EKG funkcionalumą PV diagnozuoti. Taip pat tyrimų grupė analizavo dirbtinio intelekto algoritmo panaudojimo galimybes ilgalaikei EKG analizei, siekiant palengvinti didelių EKG duomenų analizės iššūkius. Buvo nustatyti EKG rizikos žymenys pacientų grupėje, kuriai atliktas ilgalaikis Holterio monitoravimas. Pavyko nustatyti kriterijus, kuriais remiantis, galima atrinkti kandidatus išplėstiniam EKG stebėjimui iki 1 mėnesio, kuris leistų sudaryti prielaidas ankstyvai prieširdžių virpėjimo diagnostikai.

Vienas iš svarbių praktinių šio darbo rezultatų – komercializacija ir pasaulinė masinė gamyba įrenginio, dabar žinomo kaip TeltoHeart. Įrenginys buvo pripažintas Europos vaistų agentūros (EVA) ir gavo Medicinos prietaisų reglamento (MDR) sertifikavimą: I klasės – techninei įrangai (pačiam įrenginiui), IIa klasės – programinei įrangai, veikiančiai įrenginyje ir nuotolinėje platformoje. Be to, autorius aiškiai identifikavo tikslines pacientų grupes ir pasiūlė darbo eigos praktinius algoritmus TeltoHeart taikymui ilgalaikiame stebėjime, remiantis EHRA ir ESC gairėmis bei konsensuso dokumentais.

9.2 Metodika: bendras straipsnių serijos dizainas ir pagrindimas

Ši disertacija apima nuoseklų kūrybinį procesą nuo sukurtos idėjos patentavimo iki keturių tarpusavyje susijusių mokslinių straipsnių:

- Išradimo idėja ir jos realizavimas (**Patentas**) buvo pradėti ir įvykdyti iki disertacijos pradžios autoriaus ir kolegų iniciatyva. Šios tezės autoriaus esminis indėlis yra bevielės šešių derivacijų EKG fiksavimo metodo idėjos sugalvojimas panaudojant ant riešo dėvimą prietaisą, ir tolimesnis praktinis įgyvendinimas bendradarbiaujant su Kauno technologijos universiteto (KTU) Biomedicininės inžinerijos instituto kolegomis.
- **Straipsnis I** (doi: 10.3389/fcvm.2022.869730) – tai prospektyvus atvejo-kontrolės validacijos tyrimas, vykdytas Vilniuje (Lietuva). Jame buvo testuojamas naujo tipo ant riešo dėvimas prietaisas, integruojantis FPG ir šešių derivacijų belaidės EKG technologiją, siekiant įvertinti, ar prietaisas gali tiksliai aptikti prieširdžių virpėjimą (PV), net esant dažniems priešlaikiniams susitraukimams kontrolinėse grupėse.
- **Straipsnis II** (doi: 10.3389/fcvm.2023.1160242), taip pat prospektyvus tyrimas, atliktas Vilniuje, palygino šešių derivacijų EKG diagnostinę naudą aptinkant PV lyginant su vienos derivacijos EKG ir FPG pagrįsto algoritmo tikslumais.
- **Straipsnis III** (doi: 10.1038/s41591-025-03516-x) – tai dirbtinio intelekto (DI) validacijos tyrimas, kuriame naudota didelės apimties ambulatorinė EKG duomenų bazė iš JAV, lyginant automatizuotus gilaus mokymosi modelio rezultatus su sertifikuotų technikų anotacijomis aritmijų nustatymui.
- **Straipsnis IV** (doi: 10.1111/anec.13090) – retrospektyvus atvejo-kontrolės tyrimas, naudojant 24 valandų Holterio duomenis iš JAV, nustatė EKG pagrįstus rizikos žymenis, galinčius prognozuoti PV atsiradimą per artimiausias 2–30 dienų.

Išvardyti straipsniai nagrinėja pirminį išradimą, prietaiso diagnostinę validaciją, didelio EKG duomenų srauto analizę DI pagalba bei praktinį nenustatyto PV rizikos stratifikavimą atrenkant kandidatus ilgalaikei 1 mėnesio trukmės stebėsenai (**Lentelė**).

Lentelė. Patentai ir tyrimų dizainas paskelbtuose straipsniuose

	Straipsnis I	Straipsnis II	Straipsnis III	Straipsnis IV	Patentai
Patentų registravimo duombazės	Netaikoma	Netaikoma	Netaikoma	Netaikoma	Nešiojamasis prietaisas: 1) Lietuvos Patentų Biuras (17) 2) PINO (19) 3) EPB (18) 4) JAV Patentų ir Prekių Ženklų Biuras (20) 5) JPB (21) Papildomas patentas: 1) EPB (45)
Tyrimo dizainas	Prospektyvinis atvejo-kontrolės validacijos tyrimas	Prospektyvinis atvejo-kontrolės tyrimas	DI validacijos tyrimas vertinant pacientų EKG įrašų kohortą	Retrospektyvinis atvejo-kontrolės tyrimas	Netaikoma
Pagrindinė įtraukimo vieta	Vilnius, Lietuva	Vilnius, Lietuva	JAV	JAV	Netaikoma
Tyrimo populiacija	Stacionaro ar ambulatoriniaipacientai, ≥18 m.	Stacionaro ar ambulatoriniai pacientai, ≥18 m.	Ambulatoriniai pacientai, ≥18 m.	Ambulatoriniai pacientai, ≥18 m.	Netaikoma
Populiacijos dydis	344 pacientai galutinėje analizėje	249 pacientai galutinėje analizėje	14.606 pacientai	18.220 pacientai	Netaikoma
Tikslas	Įvertinti, ar FPG algoritmas, šešių derivacijų EKG bei šių metodų sistema tiksliai atskiria PV nuo SR, kontroliuojant pacientų grupe, turinčia gausias priešlaikines skilvelines ar	Ištirti, kokią pridėtinę diagnostinę vertę atneša šešių derivacijų EKG lyginant su vienos derivacijos EKG bei FPG algoritmu nustatant PV su ant riešo dėvimu prietaisu.	Palyginti tik DeepRhythm DI algoritmu paremtą analizę su rankine sertifikuotų technikų analize aptinkant aritmijas ambulatorinėje EKG. Palyginimui naudotas referentinis vertinimas gautas iš 17 komandų konsensuso,	Nustatyti ar 24 valandų Holterio EKG parametrai gali patikimai prognozuoti PV aptikimą per kitas 2-30 dienas, taikant tolimesnį monitoravimą.	Netaikoma

	Straipsnis I	Straipsnis II	Straipsnis III	Straipsnis IV	Patentai
	prieširdines ekstrasistoles.		kurių kiekviena sudaryta iš 3 kardiologų ekspertų.		
Monitoravimo trukmė	1) 2-3 min EKG 2) 2-30 min FPG	1) 2-3 min EKG 2) 2-30 min FPG	14 dienų	Iki 31 dienos	Netaikoma
Monitoravimo prietaisai	a) tiriamasis ant riešo dėvimas prietaisas (TeltoHeart prototipas) b) referentinis EKG Holteris (eMotion Faros, Kuopijas, Suomija).	a) tiriamasis ant riešo dėvimas prietaisas (TeltoHeart prototipas) b) referentinis EKG Holteris (eMotion Faros, Kuopijas, Suomija).	PocketECG EKG Holteris (MEDICALgorithmics, Varšuva, Lenkija).	PocketECG EKG Holteris (MEDICALgorithmics, Varšuva, Lenkija).	Netaikoma
Tyriamoji grupė	Pacientai su įtraukimo metu esamu PV, nustatytu EKG.	Pacientai su įtraukimo metu esamu PV, nustatytu EKG.	EKG įrašai su atsitiktiniais aritmijos epizodais, įskaitant kritines aritmijas: PV ≥30s, skilvelinė tachikardija ≥10s + ≥120 k/min, SVT ≥30 s, 3 laipsnio AV blokada, asistolija ≥3,5 s.	"Didelės rizikos" pacientai, apibrėžti kaip prognozuojama PV rizika 2-30 dienomis ≥10% (išlyginta pagal amžių, lytį ir įrašo trukmę).	Netaikoma
Kontrolinė grupė (-ės)	Pacientai su įtraukimo metu esamu ir EKG nustatytu: a) stabiliu SR b) SR su dažnomis skilvelinėmis ar prieširdinėmis ekstrasistolėmis (≥1 ekstrasistolė per 2 min).	Pacientai su įtraukimo metu esamu ir EKG nustatytu SR su dažnomis skilvelinėmis ar prieširdinėmis ekstrasistolėmis (≥1 ekstrasistolė per 2 min).	Netaikoma	"Mažos rizikos" pacientai, apibrėžti kaip prognozuojama PV rizika 2-30 dienomis <5% (išlyginta pagal amžių, lytį ir įrašo trukmę).	Netaikoma

	Straipsnis I	Straipsnis II	Straipsnis III	Straipsnis IV	Patentai
EKG derivacijų skaičius monitoravimo metu	a) 6 derivacijų belaidė EKG (ant riešo dėvimas prietaisas) b) 3 derivacijų EKG su klijuojamais elektrodais ir laidais (referentinis Holteris).	a) 6 derivacijų belaidė EKG (ant riešo dėvimas prietaisas) b) 1 derivacijos belaidė EKG (ant riešo dėvimas prietaisas) c) 3 derivacijų EKG su klijuojamais elektrodais ir laidais (referentinis Holteris).	2 derivacijų EKG su 3 klijuojamais elektrodais ir laidais, vienas kurių atlieka atskaitos funkciją (Holteris).	2 derivacijų EKG su 3 klijuojamais elektrodais ir laidais, vienas kurių atlieka atskaitos funkciją (Holteris).	Netaikoma
Tyrimo baigtys	PV nustatymo tikslumas	PV nustatymo tikslumas	Klaidingai neigiamų kritinių aritmijų įvykių kiekis ir bendras aritmijų aptikimo tikslumas naudojant DI algoritmą	PV epizodų ≥30 s atsiradimas 2–30 dienomis	Netaikoma
Statistinė analizė	Jautrumas, specifiškumas, tikslumas, teigiamas ir neigiamas tikimybės santykis; nepriklausomos imties Studento T-testas / Mann-Whitney U testas; chi kvadrato testas / dvipusis Fisher tikslusis testas; Cramerio V testas.	Jautrumas, specifiškumas, tikslumas, teigiamas ir neigiamas tikimybės santykis; nepriklausomas imties Studento T-testas / Mann-Whitney U testas; chi kvadrato testas / dvipusis Fisher tikslusis testas; Cramerio V testas, Coheno kappa.	Jautrumas, specifiškumas, tikslumas, teigiama ir neigiama prognostinė vertė, F1 balas; absoliutūs teisingai ir klaidingai teigiamų bei neigiamų atvejų rodikliai.	Lasso modelis PV epizodų prognozavimui; didelės ir mažos rizikos grupės lyginamos naudojant logistinę regresijos analizę; ROC statistika. Prognozavimo modelis „tik EKG“ apėmė tik EKG žymenis, o „pilnas modelis“ papildomai įtraukė amžių ir lytį.	Netaikoma

9.3 Rezultatai

9.3.1 Intelektinė nuosavybė ir indėlis į vystymą: patentai, MDR sertifikavimas ir prietaiso komercializacija

Darbo pirminės idėjos naujumas ir tolimesnis vystymas sudarė prielaidas sukurti pirmąjį pasaulyje ant riešo dėvimą prietaisą, kuris leidžia atlikti nuolatinę FPG stebėseną dėl prieširdžių virpėjimo (PV) aptikimo bei galimybę registruoti belaidę šešių derivacijų EKG, leidžiančia gydytojui diagnozuoti aritmiją. Pradinis patentas buvo pateiktas kaip nacionalinis patentas Lietuvoje dar iki pradedant šią disertaciją – 2018 m. lapkričio 22 d. (prioriteto data) (17), bendradarbiaujant su KTU kolegomis. Vėliau, 2019 m. lapkričio 21 d., patentas buvo išplėstas tarptautiniu mastu pagal Pasaulinės intelektinės nuosavybės organizacijos (PINO) paraišką nr. WO/2020/104986A (19). Vėliau jis buvo sėkmingai paskelbtas Jungtinių Amerikos Valstijų patentų ir prekių ženklų biuro (20), Japonijos patentų biuro (JPO) (21) ir Europos patentų biuro (EPO) (18) paraiškose.

Komercinė versija, šiuo metu parduodama prekės ženklu „TeltoHeart“, sėkmingai praėjo medicinio prietaiso sertifikavimo procesą. Techninei įrangai buvo suteiktas MDR I klasės CE ženklinimas, o programinei įrangai ir nuotolinei debesų platformai – IIa klasės CE ženklinimas (53). Šios disertacijos autorius atliko pagrindinio klinikinio konsultanto vaidmenį.

2025 m. balandžio mėn. duomenimis, „TeltoHeart“ buvo įdiegtas daugiau kaip 30 pasaulio gydymo įstaigų. Šiuo metu įrenginys parduodamas per trisdešimt šalių penkiuose pasaulio žemynuose.

9.3.2 Straipsnis I: įrenginio diagnostinio tikslumo validacija

Sistema, apjungianti FPG pagrįstą algoritmą ir šešių derivacijų EKG, pasiekė 94.2 % jautrumą ir 99.6 % specifiškumą. Atskirai vertinant tik šešių derivacijų EKG, jautrumas siekė 99.2 % ir specifiškumas – 99.1 % (**Straipsnis I**). Nepaisant dažnų priešlaikinių skilvelių ir prieširdžių susitraukimų kontrolinėje grupėje, gydytojai galėjo tiksliai aptikti ir diagnozuoti prieširdžių virpėjimą trumpalaikio stebėjimo metu.

9.3.3 Straipsnis II: šešių derivacijų EKG palyginimas su vienos derivacijos EKG nustatant prieširdžių virpėjimą

Vienos derivacijos EKG metodui užteko 3.4 karto mažiau ekstrasistolių nei šešių derivacijų EKG, kad atsirastų klaidingai teigiamas rezultatas. Ant riešo nešiojamo prietaiso užfiksuota šešių derivacijų EKG suteikia aiškią

papildomą diagnostinę naudą prieširdžių virpėjimo nustatymui lyginant su vienos derivacijos EKG, kuri dažniausiai naudojama išmaniuosiuose laikrodžiuose, ir automatiniu FPG algoritmu (**Straipsnis II**).

9.3.4 Straipsnis III: dirbtinio intelekto ir rankinio aritmijų nustatymo palyginimas ambulatorinėje EKG

DI algoritmo diagnostinis tikslumas nustatant aritmijas pranoko sertifikuotų EKG technikų išvadas ilgalaikėje Holterio EKG analizėje (**Straipsnis III**). DeepRhythm DI modelis aplenkė technikų analizę, pasiekdamas aukštą neigiamą prognostinę vertę – 99.9 % (klaidingai neigiami atvejai – 3.2/1000 paciento dienų) kritinių aritmijų kategorijoje, palyginti su 99.1 % (44.3/1000 paciento dienų). Šis reikšmingas klaidingai neigiamų rezultatų sumažėjimas pasiektas esant nedideliam klaidingai teigiamų atvejų padidėjimui (12 /1000 vs. 5 /1000 paciento dienų).

9.3.5 Straipsnis IV: EKG rizikos žymenys ir prognostinis prieširdžių virpėjimo modeliavimas ilgalaikiame Holterio monitoravime

EKG rizikos žymenys, nustatyti per pirmąsias 24 valandas ilgalaikės Holterio stebėsenos metu, gali sėkmingai prognozuoti PV atsiradimą per artimiausias 2–30 dienas (**Straipsnis IV**). Patikimi tik EKG paremti prognostinio modelio žymenys buvo pavienių priešlaikinių prieširdžių susitraukimų skaičius, didžiausias prieširdinių kupletų ir tripletų sukibimo greitis, ilgiausia SVT trukmė, didžiausias skilvelinių kupletų sukibimo greitis, didžiausias SkT su ≥4 susitraukimais greitis ir maksimalus širdies susitraukimo dažnis.

9.4 Išvados

1. Sukurtas pirmasis ant riešo dėvimas prietaisas, apjungiantis FPG algoritmą su šešių derivacijų belaide EKG, tapo reikšminga inovacija, verta būti apsaugota tarptautiniu patentu. Reali paklausa tiek iš sveikatos priežiūros įstaigų, tiek iš pacientų lėmė šio naujo medicininio prietaiso sėkmingą MDR sertifikavimą, komercializavimą ir integraciją į klinikinę praktiką (**Patentas**, **MDR Sertifikavimas**, **Komercializavimas**).
2. Nepaisant dažnų priešlaikinių skilvelinių ir prieširdinių susitraukimų (SkE/PrE) kontrolinėje grupėje, gydytojai galėjo tiksliai įtarti PV naudojant FPG algoritmą ir pilnai diagnozuoti PV naudojant šešių derivacijų belaidę EKG trumpalaikio stebėjimo metu išlaikant aukštą specifiškumą. Abiejų metodų, integruotų į vieną sistemą, specifiškumas buvo 99.6 % (97.5–100) ir bendras tikslumas buvo 99.5 % (98.9–100) (**Straipsnis I**).
3. Šešių derivacijų belaidė EKG, įrašyta nešiojamuoju prietaisu, suteikė papildomos diagnostinės naudos aptinkant PV, nes buvo tikslesnė už vienos derivacijos EKG, dažniausiai naudojamą išmaniuosiuose laikrodžiuose, bei automatinį FPG algoritmą (**Straipsnis II**). Šešių derivacijų EKG buvo atspariausia ekstrasistolėms – jai reikėjo 3.4 karto daugiau priešlaikinių susitraukimų nei vienos derivacijos EKG ir 4.9 karto daugiau nei FPG algoritmui, kad įvyktų klaidingai teigiamas atvejis.
4. DeepRhythm DI modelis pranoko technikų analizę, pasižymėdamas aukšta neigiama prognostine verte – 99.9 % (klaidingai neigiami atvejai – 3.2/1000 paciento dienų) kritinių aritmijų kategorijoje, palyginti su 99.1 % (44.3/1000 paciento dienų) (**Straipsnis III**). Reikšmingas klaidingai neigiamų rezultatų sumažėjimas buvo pasiektas su nuosaikiu klaidingai teigiamų rezultatų padidėjimu (12/1000 vs. 5/1000 paciento dienų).
5. EKG rizikos žymenys, aptikti per pirmąsias 24 valandas ilgalaikėje Holterio EKG stebėsenoje, gali sėkmingai prognozuoti PV atsiradimą per 2–30 dienas po stebėsenos pradžios (**Straipsnis IV**). Patikimi prognostiniai žymenys buvo pavienių priešlaikinių prieširdžių susitraukimų skaičius, didžiausias prieširdinių kupletų ir tripletų sukibimo greitis, ilgiausia SVT trukmė, didžiausias skilvelinių kupletų sukibimo greitis, didžiausias SkT su ≥4 susitraukimais greitis ir maksimalus širdies susitraukimo dažnis.

10 REFERENCES

1. Elliott AD, Middeldorp ME, Van Gelder IC, Albert CM, Sanders P. Epidemiology and modifiable risk factors for atrial fibrillation. Nat Rev Cardiol. 2023 Jun;20(6):404–17.
2. Rehorn M, Sacks NC, Emden MR, Healey B, Preib MT, Cyr PL, et al. Prevalence and incidence of patients with paroxysmal supraventricular tachycardia in the United States. Journal of Cardiovascular Electrophysiology. 2021;32(8):2199–206.
3. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. International Journal of Stroke. 2021 Feb 1;16(2):217–21.
4. Turakhia MP, Shafrin J, Bognar K, Trocio J, Abdulsattar Y, Wiederkehr D, et al. Estimated prevalence of undiagnosed atrial fibrillation in the United States. PLOS ONE. 2018 Apr 12;13(4):e0195088.
5. Kahwati LC, Asher GN, Kadro ZO, Keen S, Ali R, Coker-Schwimmer E, et al. Screening for Atrial Fibrillation: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2022 Jan 25;327(4):368–83.
6. Ikeda T, Ashihara T, Iwasaki Y ki, Ono M, Kagiyama N, Kimura T, et al. 2025 Japanese Heart Rhythm Society / Japanese Circulation Society Consensus Statement on the Appropriate Use of Ambulatory and Wearable Electrocardiographs. Circulation Journal. 2025;advpub.
7. Svennberg E, Tjong F, Goette A, Akoum N, Di Biase L, Bordachar P, et al. How to use digital devices to detect and manage arrhythmias: an EHRA practical guide. EP Europace. 2022 Jun 1;24(6):979–1005.
8. Tzeis S, Gerstenfeld EP, Kalman J, Saad EB, Sepehri Shamloo A, Andrade JG, et al. 2024 European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on catheter and surgical ablation of atrial fibrillation. EP Europace. 2024 Apr 1;26(4):euae043.
9. Savelieva I, Fumagalli S, Kenny RA, Anker S, Benetos A, Boriani G, et al. EHRA expert consensus document on the management of arrhythmias in frailty syndrome, endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). EP Europace. 2023 Apr 28;25(4):1249–76.
10. Leclercq C, Witt H, Hindricks G, Katra RP, Albert D, Belliger A, et al. Wearables, telemedicine, and artificial intelligence in arrhythmias and

heart failure: Proceedings of the European Society of Cardiology Cardiovascular Round Table. EP Europace. 2022 Sep 1;24(9):1372–83.
11. Bayoumy K, Gaber M, Elshafeey A, Mhaimeed O, Dineen EH, Marvel FA, et al. Smart wearable devices in cardiovascular care: where we are and how to move forward. Nat Rev Cardiol. 2021 Aug;18(8):581–99.
12. Webb A, Heldner M, Aguiar de Sousa D, Sandset E, Randall G, Bejot Y, et al. Availability of secondary prevention services after stroke in Europe: An ESO/SAFE survey of national scientific societies and stroke experts. European Stroke Journal. 2019 Jun 1;4(2):110–8.
13. El-Sherif N, Turitto G. Ambulatory Electrocardiographic Monitoring between Artifacts and Misinterpretation, Management Errors of Commission and Errors of Omission. Annals of Noninvasive Electrocardiology. 2015;20(3):282–9.
14. Tooley JE, Perez MV. Role of digital health in detection and management of atrial fibrillation. Heart. 2022 Jun 1;108(11):834–9.
15. Bacevicius J, Abramikas Z, Dvinelis E, Audzijoniene D, Petrylaite M, Marinskiene J, et al. High Specificity Wearable Device With Photoplethysmography and Six-Lead Electrocardiography for Atrial Fibrillation Detection Challenged by Frequent Premature Contractions: DoubleCheck-AF. Frontiers in Cardiovascular Medicine [Internet]. 2022 [cited 2023 Apr 7];9. Available from: https://www.frontiersin.org/articles/10.3389/fcvm.2022.869730
16. Bacevicius J, Taparauskaite N, Kundelis R, Sokas D, Butkuviene M, Stankeviciute G, et al. Six-lead electrocardiography compared to single-lead electrocardiography and photoplethysmography of a wrist-worn device for atrial fibrillation detection controlled by premature atrial or ventricular contractions: six is smarter than one. Front Cardiovasc Med [Internet]. 2023 Jun 9 [cited 2025 Apr 29];10. Available from: https://www.frontiersin.orghttps://www.frontiersin.org/journals/cardiovascular-medicine/articles/10.3389/fcvm.2023.1160242/full
17. Lithuanian (LT) Patent
Title: Long-Term Non-Invasive System for Monitoring and Characterizing Atrial Arrhythmias in Patients with Post-Stroke Conditions International Application Number: Not Applicable
PCT Number: Not Applicable
Publication Number: LT6743A
Database: State Patent Bureau of the Republic of Lithuania
Website Link: https://search.vpb.lt/pdb/patent/dossier/2018%20550
18. European Patent Office (EPO) Patent

Title: Long-Term Non-Invasive System for Monitoring and Characterizing Atrial Arrhythmias in Patients with Post-Stroke Conditions
International Application Number: Not Applicable
PCT Number: Not Applicable
Publication Number: EP3883463 and EP19845615
Database: European Patent Office
Website Link:
https://register.epo.org/application?number=EP19845615&tab=main

19. WIPO (World Intellectual Property Organization) Patent
Title: Long-Term Non-Invasive System for Monitoring and Characterizing Atrial Arrhythmias in Patients with Post-Stroke
Conditions
International Application Number: PCT/IB2020/054099
PCT Number: WO/2020/104986A
Publication Number: WO/2020/104986A
Database: WIPO's PATENTSCOPE
Website Link:
https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2020104986

20. United States Patent
Title: Long-Term Non-Invasive System for Monitoring and Characterizing Atrial Arrhythmias in Patients with Post-Stroke Conditions
International Application Number: Not Applicable
PCT Number: Not Applicable
Publication Number: US20220015683
Database: United States Patent and Trademark Office
Website Link:
https://patents.google.com/patent/US20220015683A1/en?oq=US20220015683

21. Japanese Patent
Title: デバイスによる心房不整脈のモニタリングおよびサーバによる特性評価の非侵襲的方法 (Non-Invasive Method for Monitoring Atrial Arrhythmias by Device and Characterizing by Server)
International Application Number: Not Applicable
PCT Number: Not Applicable
Publication Number: JP2022508124
Database: Japan Patent Office (JPO) - J-PlatPat
Website Link:

https://www.j-platpat.inpit.go.jp/c1800/PU/JP-2022-508124/6A8E92C3B8B875AC3FD6DF8A7D49372E24CCD2F0164F673EA7AD3D66B3019061/11/en
22. Xintarakou A, Sousonis V, Asvestas D, Vardas PE, Tzeis S. Remote Cardiac Rhythm Monitoring in the Era of Smart Wearables: Present Assets and Future Perspectives. Front Cardiovasc Med [Internet]. 2022 Mar 1 [cited 2025 Apr 29];9. Available from: https://www.frontiersin.orghttps://www.frontiersin.org/journals/cardiovascular-medicine/articles/10.3389/fcvm.2022.853614/full
23. Sološenko A, Petrenas A, Paliakaite B, Sörnmo L, Marozas V. Detection of atrial fibrillation using a wrist-worn device. Physiol Meas. 2019 Feb;40(2):025003.
24. Krzowski B, Skoczylas K, Osak G, Żurawska N, Peller M, Kołtowski Ł, et al. Kardia Mobile and ISTEL HR applicability in clinical practice: a comparison of Kardia Mobile, ISTEL HR, and standard 12-lead electrocardiogram records in 98 consecutive patients of a tertiary cardiovascular care centre. European Heart Journal - Digital Health. 2021 Sep 1;2(3):467–76.
25. Scholten J, Jansen WPJ, Horsthuis T, Mahes AD, Winter MM, Zwinderman AH, et al. Six-lead device superior to single-lead smartwatch ECG in atrial fibrillation detection. American Heart Journal. 2022 Nov 1;253:53–8.
26. 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) | European Heart Journal | Oxford Academic [Internet]. [cited 2025 Apr 29]. Available from: https://academic.oup.com/eurheartj/article/45/36/3314/7738779
27. Mannhart D, Lischer M, Knecht S, du F de LJ, Strebel I, Serban T, et al. Clinical Validation of 5 Direct-to-Consumer Wearable Smart Devices to Detect Atrial Fibrillation. JACC: Clinical Electrophysiology. 2023 Feb;9(2):232–42.
28. Strik M, Ploux S, Fontagne L, Tixier R, Alrub SA, Zande J van der, et al. Combining electrocardiogram smartwatches and remote monitoring to diagnose palpitations and presyncope. Heart Rhythm. 2024 Dec 1;21(12):2593–4.
29. Mahajan A, Heydari K, Powell D. Wearable AI to enhance patient safety and clinical decision-making. npj Digit Med. 2025 Mar 22;8(1):1–3.
30. Svennberg E, Han JK, Caiani EG, Engelhardt S, Ernst S, Friedman P, et al. State of the Art of Artificial Intelligence in Clinical Electrophysiology in 2025. A Scientific Statement of the European

Heart Rhythm Association (EHRA) of the ESC, the Heart Rhythm Society (HRS), and the ESC Working Group in e-Cardiology. EP Europace. 2025 Mar 31;euaf071.

31. Deisenhofer I, Albenque JP, Busch S, Gitenay E, Mountantonakis SE, Roux A, et al. Artificial intelligence for individualized treatment of persistent atrial fibrillation: a randomized controlled trial. Nat Med. 2025 Apr;31(4):1286–93.
32. Boniol M, Kunjumen T, Nair TS, Siyam A, Campbell J, Diallo K. The global health workforce stock and distribution in 2020 and 2030: a threat to equity and 'universal' health coverage? BMJ Glob Health [Internet]. 2022 Jun 27 [cited 2025 Apr 29];7(6). Available from: https://gh.bmj.com/content/7/6/e009316
33. Hannun AY, Rajpurkar P, Haghpanahi M, Tison GH, Bourn C, Turakhia MP, et al. Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network. Nat Med. 2019 Jan;25(1):65–9.
34. Zhu H, Cheng C, Yin H, Li X, Zuo P, Ding J, et al. Automatic multilabel electrocardiogram diagnosis of heart rhythm or conduction abnormalities with deep learning: a cohort study. The Lancet Digital Health. 2020 Jul 1;2(7):e348–57.
35. Doehner W, Boriani G, Potpara T, Blomstrom-Lundqvist C, Passman R, Sposato LA, et al. Atrial fibrillation burden in clinical practice, research, and technology development: a clinical consensus statement of the European Society of Cardiology Council on Stroke and the European Heart Rhythm Association. EP Europace. 2025 Mar 1;27(3):euaf019.
36. van der Velden RMJ, Verhaert DVM, Hermans ANL, Duncker D, Manninger M, Betz K, et al. The photoplethysmography dictionary: practical guidance on signal interpretation and clinical scenarios from TeleCheck-AF. European Heart Journal - Digital Health. 2021 Sep 1;2(3):363–73.
37. Manninger M, Lercher I, Hermans ANL, Isaksen JL, Prassl AJ, Zirlik A, et al. Machine-learning guided differentiation between photoplethysmography waveforms of supraventricular and ventricular origin. Computer Methods and Programs in Biomedicine. 2025 Jul 1;267:108798.
38. Manninger M, Zweiker D, Hovakimyan T, Matusik PT, Conti S, Ollitrault P, et al. Physician Preferences in Using Novel Digital Devices for the Management of Atrial Fibrillation—A DAS-CAM III Survey. Clinical Cardiology. 2024;47(12):e24331.

39. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, et al. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. New England Journal of Medicine. 2019 Nov 14;381(20):1909–17.
40. Perino AC, Gummidipundi SE, Lee J, Hedlin H, Garcia A, Ferris T, et al. Arrhythmias Other Than Atrial Fibrillation in Those With an Irregular Pulse Detected With a Smartwatch: Findings From the Apple Heart Study. Circulation: Arrhythmia and Electrophysiology. 2021 Oct;14(10):e010063.
41. Lubitz SA, Faranesh AZ, Selvaggi C, Atlas SJ, McManus DD, Singer DE, et al. Detection of Atrial Fibrillation in a Large Population Using Wearable Devices: The Fitbit Heart Study. Circulation. 2022 Nov 8;146(19):1415–24.
42. Charlton P, Kyriacou P, Mant J, Alastruey J. Acquiring Wearable Photoplethysmography Data in Daily Life: The PPG Diary Pilot Study. Engineering Proceedings. 2020 Nov 14;2:80.
43. Hermans ANL, Isaksen JL, Gawalko M, Pluymaekers NAHA, Van Der Velden RMJ, Snippe H, et al. Accuracy of continuous photoplethysmography-based heart rate assessment during atrial fibrillation. EP Europace. 2023 Jun 1;25(Supplement_1):euad122.547.
44. Rizas KD, Freyer L, Sappler N, von Stülpnagel L, Spielbichler P, Krasniqi A, et al. Smartphone-based screening for atrial fibrillation: a pragmatic randomized clinical trial. Nat Med. 2022 Sep;28(9):1823–30.
45. Petrenas A, Butkuviene M, Paliakaite B, Bacevicius J, Plusciauskaite V, Solosenko A, et al. Method for Establishing a Causality Score Between Atrial Fibrillation Triggers and Atrial Fibrillation Pattern. EP4105941A1, 2022.
46. Petrėnas A, Marozas V, Sörnmo L. Low-complexity detection of atrial fibrillation in continuous long-term monitoring. Comput Biol Med. 2015 Oct 1;65:184–91.
47. Johnson LS, Zadrozniak P, Jasina G, Grotek-Cuprjak A, Andrade JG, Svennberg E, et al. Artificial intelligence for direct-to-physician reporting of ambulatory electrocardiography. Nat Med. 2025 Mar;31(3):925–31.
48. Oord A van den, Dieleman S, Zen H, Simonyan K, Vinyals O, Graves A, et al. WaveNet: A Generative Model for Raw Audio [Internet]. arXiv; 2016 [cited 2025 Apr 29]. Available from: http://arxiv.org/abs/1609.03499

49. Vaswani A, Shazeer N, Parmar N, Uszkoreit J, Jones L, Gomez AN, et al. Attention Is All You Need [Internet]. arXiv; 2023 [cited 2025 Apr 29]. Available from: http://arxiv.org/abs/1706.03762
50. Dosovitskiy A, Beyer L, Kolesnikov A, Weissenborn D, Zhai X, Unterthiner T, et al. An Image is Worth 16x16 Words: Transformers for Image Recognition at Scale [Internet]. arXiv; 2021 [cited 2025 Apr 29]. Available from: http://arxiv.org/abs/2010.11929
51. Sandler M, Howard A, Zhu M, Zhmoginov A, Chen LC. MobileNetV2: Inverted Residuals and Linear Bottlenecks. In: 2018 IEEE/CVF Conference on Computer Vision and Pattern Recognition [Internet]. 2018 [cited 2025 Apr 29]. p. 4510–20. Available from: https://ieeexplore.ieee.org/abstract/document/8578572
52. Johnson LS, Måneheim A, Slusarczyk M, Grotek A, Witkowska O, Bacevicius J, et al. Can 24 h of ambulatory ECG be used to triage patients to extended monitoring? Annals of Noninvasive Electrocardiology. 2023;28(6):e13090.
53. TeltoHeart Certification & Approvals - Teltonika Telemedic Wiki [Internet]. [cited 2025 Apr 29]. Available from: https://wiki.teltonika-telemedic.com/view/TeltoHeart_Certification_%26_Approvals
54. Fredriksson T, Gudmundsdottir KK, Frykman V, Friberg L, Al-Khalili F, Engdahl J, et al. Brief episodes of rapid irregular atrial activity (micro-AF) are a risk marker for atrial fibrillation: a prospective cohort study. BMC Cardiovascular Disorders. 2020 Apr 10;20(1):167.
55. Manninger M, Zweiker D, Svennberg E, Chatzikyriakou S, Pavlovic N, Zaman JAB, et al. Current perspectives on wearable rhythm recordings for clinical decision-making: the wEHRAbles 2 survey. EP Europace. 2021 Apr 11;euab064.
56. Gawałko M, Duncker D, Manninger M, van der Velden RMJ, Hermans ANL, Verhaert DVM, et al. The European TeleCheck-AF project on remote app-based management of atrial fibrillation during the COVID-19 pandemic: centre and patient experiences. EP Europace. 2021 Jul 1;23(7):1003–15.
57. Fredriksson T, Stridh M, Friberg L, Svennberg E. Prognostic implications of supraventricular ectopy. European Heart Journal [Internet]. 2020 Nov 1 [cited 2021 May 6];41(ehaa946.0687). Available from: https://doi.org/10.1093/ehjci/ehaa946.0687
58. Afzal MR, Mease J, Koppert T, Okabe T, Tyler J, Houmsse M, et al. Incidence of false-positive transmissions during remote rhythm monitoring with implantable loop recorders. Heart Rhythm. 2020 Jan;17(1):75–80.

59. Lopez Perales CR, Van Spall HGC, Maeda S, Jimenez A, Laţcu DG, Milman A, et al. Mobile health applications for the detection of atrial fibrillation: a systematic review. EP Europace. 2021 Jan 1;23(1):11–28.
60. Scholten J, Mahes A, De Groot JR, Winter MM, Zwinderman AH, Keijer JT, et al. A comparison of over-the-counter available smartwatches and devices for electrocardiogram based detection of atrial fibrillation. European Heart Journal. 2021 Oct 1;42(Supplement_1):ehab724.3047.
61. Einthoven W. Die galvanometrische Registrirung des menschlichen Elektrokardiogramms, zugleich eine Beurtheilung der Anwendung des Capillar-Elektrometers in der Physiologie. Pfläger, Arch. 1903 Nov 1;99(9):472–80.
62. Chen X, Lu Y, Liu Y, Chen Q, Chen H, Ju W, et al. Three-dimensional electroanatomic mapping characteristics of superior vena cava myocardial sleeve and sinoatrial node in patients with atrial fibrillation. Frontiers in Cardiovascular Medicine [Internet]. 2022 [cited 2023 Apr 7];9. Available from: https://www.frontiersin.org/articles/10.3389/fcvm.2022.902828
63. Ploux S, Strik M, Caillol T, Ramirez FD, Abu-Alrub S, Marchand H, et al. Beyond the wrist: Using a smartwatch electrocardiogram to detect electrocardiographic abnormalities. Archives of Cardiovascular Diseases. 2022 Jan 1;115(1):29–36.
64. Behzadi A, Sepehri Shamloo A, Mouratis K, Hindricks G, Arya A, Bollmann A. Feasibility and Reliability of SmartWatch to Obtain 3-Lead Electrocardiogram Recordings. Sensors. 2020 Jan;20(18):5074.
65. Kistler PM, Chieng D, Tonchev IR, Sugumar H, Voskoboinik A, Schwartz LA, et al. P-Wave Morphology in Focal Atrial Tachycardia: An Updated Algorithm to Predict Site of Origin. JACC Clin Electrophysiol. 2021 Dec;7(12):1547–56.
66. Al'Aref SJ, Ip JE, Markowitz SM, Liu CF, Thomas G, Frenkel D, et al. Differentiation of Papillary Muscle From Fascicular and Mitral Annular Ventricular Arrhythmias in Patients With and Without Structural Heart Disease. Circulation: Arrhythmia and Electrophysiology. 2015 Jun;8(3):616–24.
67. El Hamriti M, Braun M, Molatta S, Imnadze G, Khalaph M, Lucas P, et al. EASY-WPW: a novel ECG-algorithm for easy and reliable localization of manifest accessory pathways in children and adults. EP Europace. 2023 Feb 1;25(2):600–9.
68. Lowry MTH, Doudesis D, Boeddinghaus J, Kimenai DM, Bularga A, Taggart C, et al. Troponin in early presenters to rule out myocardial infarction. European Heart Journal. 2023 Aug 7;44(30):2846–58.

69. Chapman AR, Lee KK, McAllister DA, Cullen L, Greenslade JH, Parsonage W, et al. Association of High-Sensitivity Cardiac Troponin I Concentration With Cardiac Outcomes in Patients With Suspected Acute Coronary Syndrome. JAMA. 2017 Nov 21;318(19):1913–24.
70. Than M, Herbert M, Flaws D, Cullen L, Hess E, Hollander JE, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: A clinical survey. International Journal of Cardiology. 2013 Jul 1;166(3):752–4.
71. Sandoval Y, Nowak R, deFilippi CR, Christenson RH, Peacock WF, McCord J, et al. Myocardial Infarction Risk Stratification With a Single Measurement of High-Sensitivity Troponin I. Journal of the American College of Cardiology. 2019 Jul 23;74(3):271–82.
72. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes: Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal. 2023 Oct 7;44(38):3720–826.
73. Fiorina L, Maupain C, Gardella C, Manenti V, Salerno F, Socie P, et al. Evaluation of an Ambulatory ECG Analysis Platform Using Deep Neural Networks in Routine Clinical Practice. Journal of the American Heart Association. 2022 Sep 20;11(18):e026196.
74. Sqalli MT, Al-Thani D, Elshazly MB, Al-Hijji M, Alahmadi A, Houssaini YS. Understanding Cardiology Practitioners' Interpretations of Electrocardiograms: An Eye-Tracking Study. JMIR Human Factors. 2022 Feb 9;9(1):e34058.
75. Hahn M, Lawson R, Lee YG. The effects of time pressure and information load on decision quality. Psychology & Marketing. 1992;9(5):365–78.
76. Phillips-Wren G, and Adya M. Decision making under stress: the role of information overload, time pressure, complexity, and uncertainty. Journal of Decision Systems. 2020 Aug 18;29(sup1):213–25.
77. Luck SJ, Vogel EK. The capacity of visual working memory for features and conjunctions. Nature. 1997 Nov;390(6657):279–81.
78. Miller GA. The magical number seven, plus or minus two: Some limits on our capacity for processing information. Psychological Review. 1956;63(2):81–97.
79. Singh JP, Fontanarava J, de Massé G, Carbonati T, Li J, Henry C, et al. Short-term prediction of atrial fibrillation from ambulatory monitoring

ECG using a deep neural network. European Heart Journal - Digital Health. 2022 Jun 22;3(2):208–17.
80. Grundvold I, Skretteberg PT, Liestøl K, Erikssen G, Engeseth K, Gjesdal K, et al. Low Heart Rates Predict Incident Atrial Fibrillation in Healthy Middle-Aged Men. Circulation: Arrhythmia and Electrophysiology. 2013 Aug;6(4):726–31.
81. Johnson LSB, Juhlin T, Juul-Möller S, Hedblad B, Nilsson PM, Engström G. A prospective study of supraventricular activity and incidence of atrial fibrillation. Heart Rhythm. 2015 Sep 1;12(9):1898–904.
82. Xiao J, Persson AP, Engström G, Johnson LSB. Supraventricular arrhythmia, N-terminal pro-brain natriuretic peptide and troponin T concentration in relation to incidence of atrial fibrillation: a prospective cohort study. BMC Cardiovascular Disorders. 2021 Mar 12;21(1):134.
83. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous Initiation of Atrial Fibrillation by Ectopic Beats Originating in the Pulmonary Veins. New England Journal of Medicine. 1998 Sep 3;339(10):659–66.
84. Persson AP, Fedorowski A, Hedblad B, Persson M, Juul-Möller S, Engström G, et al. Heart rate and premature atrial contractions at 24hECG independently predict atrial fibrillation in a population-based study. Heart. 2020 Feb 1;106(4):287–91.
85. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach: The Euro Heart Survey on Atrial Fibrillation. CHEST. 2010 Feb 1;137(2):263–72.
86. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB, et al. Simple Risk Model Predicts Incidence of Atrial Fibrillation in a Racially and Geographically Diverse Population: the CHARGE-AF Consortium. Journal of the American Heart Association. 2013 Mar 12;2(2):e000102.
87. Benz AP, Hijazi Z, Lindbäck J, Connolly SJ, Eikelboom JW, Oldgren J, et al. Biomarker-Based Risk Prediction With the ABC-AF Scores in Patients With Atrial Fibrillation Not Receiving Oral Anticoagulation. Circulation. 2021 May 11;143(19):1863–73.
88. Vilnius University. Personalized Detection of Triggers and Risk Factors for Recurrence of Atrial Fibrillation and Other Atrial Arrhythmias With the Use of Long-term Monitoring [Internet]. clinicaltrials.gov; 2024 Jun [cited 2025 Apr 29]. Report No.: NCT05526170. Available from: https://clinicaltrials.gov/study/NCT05526170

11 OTHER SCIENTIFIC PAPERS

1. Article: Šimaitytė-Butkuvienė M et al. Quantitative evaluation of temporal episode patterns in paroxysmal atrial fibrillation. 2018, Computing in Cardiology. IF 0,67. DOI: 10.22489/CinC.2018.059
2. Article: Masiliūnas R et. al. High Prevalence Of Atrial Fibrillation In A Lithuanian Stroke Patient Cohort, Medicina. IF 2.948 (2022). DOI: 10.3390/medicina58060800
3. Article of EHRA 2022 congress (summary): Bacevičius et al. Head-to-head comparison of single-lead and six-lead electrocardiography of a wrist-worn device for atrial fibrillation detection, bacevicius et al, Europace. IF 5.486 (2022). DOI: 10.1093/europace/euac053.583
4. Initial results of long-term remote monitoring, publication in Zenodo open access database: Bacevicičius J et al. Long-term electrocardiogram and wrist-based photoplethysmogram recordings with annotated atrial fibrillation episodes, bacevicius et al. Open access dataset in zenodo database, February 2022. DOI: 10.5281/zenodo.5815073
5. Article of ESC 2023 congress (summary): Bacevičius J et al. Snoring and lack of REM sleep is associated with same-day atrial arrhythmias in a cohort of patients with atrial fibrillation: initial results of TriggersAF. European Heart Journal, Volume 44, Issue Supplement_2, November 2023. IF 39.3 (2023). DOI: 10.1093/eurheartj/ehad655.422
6. Article: Charlton PH et al. The Acceptability of Wearables for Atrial Fibrillation Screening: Interim Analysis of the SAFER Wearables Study. https://cinc.org/ DOI: 10.22489/CinC.2024.060

12 PRESENTATIONS 2020-2025

1. Moderated poster session: A high specificity wearable with photoplethysmography and 6 lead electrocardiography for atrial fibrillation detection: preliminary results of a new device. 16th International Dead Sea Symposium (IDSS) on Innovations on Cardiac Arrhythmias & Heart Failure, Tel Aviv, Israel, February 24-26, 2020
2. Oral presentation: Cardiac monitoring using new wearable devices. Annual meeting of Lithuanian Society of Cardiology. Vilnius, Lithuania, 2020.
3. Oral presentation: Heart monitoring for patients with atrial fibrillation: validation of a user-friendly wearable technology. 14th conference of Lithuanian Academy of Sciences „Bioateitis: gamtos ir gyvybės mokslų perspektyvos“, Kaunas, Lithuania, 2021. The oral presentation received a 3rd place award in the section of "Medicine and health sciences".
4. Moderated poster session: Head-to-head comparison of single-lead and six-lead electrocardiography of a wrist-worn device for atrial fibrillation detection. EHRA Congress, April, 2022. Denmark, Copenhagen.
5. Coordination of preparing the oral presentation of the preliminary results: TriggersAF: Rationale of Conception and Preliminary Results of the Temporal Relation Between the Rise of Arterial Blood Pressure and Onset of Atrial Fibrillation. Presented by student Guostė Stankeviciute. Joint International Meeting: 22nd EAA Congress, 15th ISGA Congress & 5th International Conference of Evolutionary Medicine. Vilnius, Lithuania, 2022.
6. Best European participant and presentation award of the year for case report of ventricular arrhythmias, European Interventional Abbott EP Curriculum. Passed 35th Training Course of Ventricular tachycardia. Brussels, Linz, Brighton, Milan 2022–2023. Organized by Prof. Paolo Della Bella.
7. Moderated poster session: Snoring and lack of REM sleep are associated with same-day atrial arrhythmias in a cohort of patients with atrial fibrillation: initial results of TriggersAF. ESC congress, 2023, Amsterdam, the Netherlands.
8. Coordination of preparing students' oral presentation V. Radavicius ir E. Sauklyte preliminary results: Snoring and lack of REM sleep association with same-day atrial arrhythmias. Life Sciences Baltics 2023, Vilnius, Lithuania, 2023. https://lifesciencesbaltics.com/agenda/

9. Oral presentation: Snoring and lack of REM sleep association with same-day atrial arrhythmias. 16th conference of Lithuanian Academy of Sciences „Bioateitis: gamtos ir gyvybės mokslų perspektyvos“, Vilnius, Lithuania, 2023. The oral presentation received a 2nd place award in the section of “Medicine and health sciences”.
10. Oral presentation in the “Three Minute Thesis 2024” competition organized by Vilnius University and the University of Queensland.
11. Co-authorship in moderated poster session: Identifying Acute Myocardial Infarction Early: Clinical Utility of a 12-Lead Electrocardiogram Synthesized from a Single Touch of a Wrist-Worn Device. HRX 2024, Heart Rhythm Society, Atlanta, USA.
12. Coordination of preparing students' G. Pudinskaite, V. Radavicius and G. Stankeviciute oral presentation: Association of changes in arterial blood pressure with the development of atrial arrhythmia episodes. Joint International Meeting: 24th EAA Congress, 17th ISGA Congress & 7th International Conference of Evolutionary Medicine. Vilnius, Lithuania, 2024.
13. Coordination of preparing students' V. Radavicius oral presentation: Ischemic ventricular tachycardia ablation using AI-based advanced cardiac imaging software. Joint International Meeting: 24th EAA Congress, 17th ISGA Congress & 7th International Conference of Evolutionary Medicine. Vilnius, Lithuania, 2024.
14. Oral presentation: Use of new wearable device for cardiac arrhythmia diagnosis. TeltoHeart. Summer Camp of Lithuanian Cardiologists, organized by Lithuanian Society of Cardiology. Dubingiai, Lithuania, 2024.
15. Moderated poster session: Relative blood pressure increase is associated with subsequent atrial fibrillation episodes in long-term out-patient monitoring: TriggersAF. EHRA Congress, April, 2025. Austria, Vienna.

13 BRIEF INFORMATION ABOUT THE AUTHOR

1997-2005 primary education at Panevėžio Saulėtekio school

2005-2009 secondary education at Panevėžio Juozo Balčikonio gymnasium

2009-2015 Doctor of Medicine, Faculty of Medicine, Vilnius University. Grades average – 9,15.

2009–2013 Member of the Association of Lithuanian Science Olympiads.

2011 Member of Students' Representation, Vilnius University, Faculty of Medicine.

02/2015-05/2015 Clinical Internship in Heart Center, Kuopio University Hospital, Kuopio, Finland.

06/2015-07/2015 Research fellowship in University of Eastern Finland, Kuopio, Finland.

2015-2019 Cardiology residency in Vilnius University hospital Santaros Clinics.

2018-2019 Fellowship in Helios Heart Center Leipzig, Department of Electrophysiology, Leipzig, Germany.

2019-present Cardiologist Electrophysiologist in Vilnius University hospital Santaros Klinikos.

2022, Invasive Cardiac Electrophysiology Certification of European Heart Rhythm Association (fully certified after passed exam and sufficient count of EP procedures).

Best European participant and presentation award for case report of ventricular arrhythmias 2022-2023, European Interventional Abbott EP Curriculum. Passed 35th Training Course of Vetricular tachycardia. Organized by Prof. Paolo Della Bella and Abbott, 2022–2023.

05/2023-07/2023 Fellowship in Centre Hospitalier Universitaire (CHU) Bordeaux, Department of Electrophysiology, Bordeaux, France

2020-2025 Doctoral (PhD) studies in Vilnius University, Faculty of Medicine in the field of telemedicine technologies in cardiology

14 ACKNOWLEDGMENTS

This research evolved into a PhD thesis and has been a genuine passion since 2015. Along the way, I have met very bright and supportive people whose insights and encouragement helped turn challenges into progress. The creative interdisciplinary project involving medical and engineering research groups has always been about teamwork and collaboration. I would like to thank the following people wholeheartedly.

First and most importantly, my smart and beautiful wife, Viktorija, for supporting me daily and co-raising our two happy and inspiring children – Vytautas and Elzė. Thank you for sharing our duties and everyday life with love and compassion, making things possible. This means the world to me.

My supervisor, Prof. Audrius Aidietis, for always being available and trusting me since I was a student, analyzing my first ECGs in his cardiology seminars, and supporting me in pursuing a PhD degree.

My colleagues from Vilnius University – Guostė Stankevičiūtė, Žygimantas Abramikas, Ernestas Dvinelis, Ričardas Kundelis, Gintarė Pudinskaitė, Artiomas Širvys, Dominika Širvienė, Ignas Badaras, Vytautas Radavičius, Deimilė Audzijonienė, Margarita Kiseliūtė, Julija Marinskienė, Justina Staigytė, Rusnė Jakaitė, Vytautas Juknevičius, Džiugilė Kersnauskaitė, Neringa Taparauskaitė, Aistė Pilkienė, Edvardas Jukna, Paulius Čižiūnas, Eugenijus Jasiūnas, Nomeda Budrikienė, Aušra Kalasauskienė, and others – for a shared enthusiasm to dive into the unknown waters of arrhythmology and telemedicine, and the motivation to go the extra mile in turning our ideas into reality. I am happy to see you grow, and to grow together with you.

My colleagues from Kaunas University of Technology – Prof. Vaidotas Marozas, Daivaras Sokas, Andrius Petrėnas, Monika Butkuvienė, Karolina Jančiulevičiūtė, and others – for constant and honest partnership, merging the clinical perspective with your crafty technological engineering, and your willingness to engage in team-building activities.

My thesis reviewers – Prof. Pranas Šerpytis, Dr. Tomas Baltrūnas, and Prof. Minvydas Kazys Ragulskis – for your time and valuable insights.

My colleagues electrophysiologists – Germanas Marinskis, Paulius Jurkuvėnas, Diana Sudavičienė, Gediminas Račkauskas, Mantė Agnė Rimkienė, Kęstutis Bagdonas, Valentinas Sitas, Jūratė Barysienė, Neringa Bileišienė, and all the nurses – for your trust in my skills and the numerous hours dedicated to maintaining a stable sinus rhythm in so many thankful patients.

My friends – Marius, Simas, Petras, Matas and Lina – for your support.

My parents, Rasa and Robertas, and my brother, Mykolas, for raising me, passing on true family values, and sincerely supporting me.

And finally, I would like to thank myself for staying strong, patient, and curious throughout this interesting journey with many demanding roles.

NOTES

NOTES

NOTES

Vilniaus universiteto leidykla
Saulėtekio al. 9, III rūmai, LT-10222 Vilnius
El. p. info@leidykla.vu.lt, www.leidykla.vu.lt
bookshop.vu.lt, journals.vu.lt
Tiražas 20 egz.