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Autonomic function after myocardial infarction: An epidemiological approach

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Zusammenfassung

Einleitung: Weltweit sind Herz-Kreislauf-Erkrankungen die häufigste Todesursache. Prävention ist der Schlüssel zur Verringerung der Mortalität. Daher hat Innovation im Präventionsbereich hohe Priorität in der öffentlichen Gesundheitsforschung. Telemedizinische Überwachung und Risikostratifizierung auf Basis neuartiger Biosignalmarker sind Beispiele für solche innovativen Präventionsbemühungen. Die Dezelarationskapazität der Herzfrequenz (DC) und die periodische Repolarisationsdynamik (PRD) sind neue Biomarker der autonomen Herzfunktion, die bei der Risikostratifizierung verwendet werden können, um Hochrisikopatienten zu identifizieren, die ansonsten mit herkömmlichen Präventions- und Screening-Methoden unerkannt bleiben.

Zielsetzung: Ziel dieser Arbeit ist die Beurteilung der kardialen autonomen Funktion nach akutem Myokardinfarkt auf Basis eines epidemiologischen Ansatzes. Der Einfluss veränderbarer und nicht veränderbarer Risikofaktoren auf die Funktion des sympathischen und parasympathischen Nervensystems, die Wahrscheinlichkeit des Vorhandenseins einer kardialen autonomen Dysfunktion (AD) sowie die Sterbewahrscheinlichkeit werden als Post-hoc Analyse im Patientenkollektiv der SMART-MI-DZHK9 Studie erforscht.

Methoden: Die SMART-MI-DZHK9-Studie war eine prospektive, multizentrische, randomisierte, kontrollierte klinische Studie. Die Patientenrekrutierung erfolgte von Mai 2016 bis Juli 2020. Postinfarkt Patienten mit erhaltener Pumpfunktion und Sinusrhythmus, wurden innerhalb von 40-Tagen nach einem akuten Myokardinfarkt für eine AD anhand einer pathologischen DC und/oder PRD gescreent. Anschließend sind Patienten mit AD auf intensiviertes Monitoring mittels eines implantierbaren Ereignisrekorders oder auf konventionelles Monitoring randomisiert worden. Alle Patienten wurden bis zum Studienende verfolgt. In dieser prädefinierten Substudie werden alle gescreenten Patienten analysiert. Ko-primäre Endpunkte sind das Vorhandensein einer AD zum Zeitpunkt des Screenings, sowie die 3-Jahres-Gesamtmortalität. Der epidemiologische Zusammenhang zwischen veränderbaren und nicht veränderbaren Risikofaktoren mit einer AD wird mittels logistischer Regressionsanalyse untersucht. Die Assoziation der Risikofaktoren mit der 3-Jahres-Gesamtmortalität wird mittels Cox-Regressionsanalyse getestet.

Ergebnisse: Die Studie umfasste 1.305 Patienten, von denen 400 Patienten als Hochrisikopatienten mit AD und 905 Patienten als Niedrigrisikopatienten mit normaler autonomer Funktion eingestuft worden sind. Logistische Regressionsanalysen zeigten, dass ein erhöhtes glykosyliertes Hämoglobin A1c (OR 1,19; 95% KI 1,06 - 1,33; p-Wert = 0,002), zunehmendes Alter (OR 1,06; 95%KI 1,04 – 1,08; p-Wert < 0,001) und niedrige linksventrikuläre Auswurffraktion (OR 0,90; 95% KI 0,87 – 0,94; p-Wert < 0,001) mit dem Vorhandensein einer AD assoziiert waren. In Cox-Regressionsanalysen konnte gezeigt werden, dass die AD (HR 2,68; 95% KI 1,39 – 5,18; p-Wert = 0,003), Diabetes mellitus (HR 2,58; 95% KI 1,38 – 5,19; p-Wert = 0,004), zunehmendes Alter (HR 1,07; 95%KI 1,04 – 1,11; p-Wert < 0,001) und ein niedriger Hämoglobinwert (HR 0,80; 95%KI 0,70 – 0,91; p-Wert < 0,001) mit einer erhöhten 3-Jahres-Gesamtmortalität verbunden waren. Bei allen anderen veränderbaren und nicht-veränderbaren Risikofaktoren ist es kein signifikanter Zusammenhang mit dem Vorhandensein einer AD und der 3-Jahres-Gesamtmortalität nachgewiesen worden.

Schlussfolgerung: Dies ist die erste epidemiologische Analyse, die den Zusammenhang von veränderbaren und nicht veränderbaren Risikofaktoren mit einer AD, im Sinne einer pathologischen DC und/oder PRD untersucht hat. Patienten mit AD waren älter, hatten einen niedrigere linksventrikuläre Auswurffraktion und ein erhöhtes Hämoglobin A1c. Wie auch in anderen Studien gezeigt worden ist, war eine AD mit erhöhtem Mortalitätsrisiko assoziiert. In zukünftigen Studien sollte getestet werden, ob primärpräventive Maßnahmen bei Patienten mit AD zu einer Mortalitätsreduktion führen könnten. Darüber hinaus sollte in zukünftigen Studien getestet werden, ob die Behandlung von veränderbaren Risikofaktoren bei Patienten mit AD zu einer Normalisierung der autonomen Funktion im Zeitablauf führen könnte.

Abstract

Introduction: Worldwide, cardiovascular diseases (CVDs) are the dominating cause of death. Prevention is key in reducing the mortality and disease burden; hence innovation in prevention is a high priority in public health research. Telemedical monitoring and risk stratification based on novel biosignal markers are examples of such innovative prevention efforts. Deceleration capacity (DC) and periodic repolarisation dynamics (PRD) are new biomarkers of the cardiac autonomic function that might be used in risk stratification to identify patients that otherwise remain unrecognised with conventional prevention and screening methods.

Aims: The aim of this dissertation is the assessment of cardiac autonomic function after acute myocardial infarction based on an epidemiological approach. The effect of modifiable and non-modifiable risk factors on the function of sympathetic and parasympathetic nervous system, the probability for developing cardiac autonomic dysfunction (AD) and the risk of death will be explored as post-hoc analysis in the study population of the SMART-MI-DZHK9 Trial.

Methods: The SMART-MI-DZHK9 Trial was a prospective, investigator-initiated, open-label randomized controlled trial. Patients were recruited from May 2016 until July 2020. Post-myocardial infarction (MI) patients with preserved left-ventricular ejection fraction and sinus rhythm were screened for AD within 40-days after MI based on elevated DC and/or PRD. Patients with AD were subsequently randomized to an intensified screening strategy by means of an implantable event recorder or to standard treatment. Every patient was followed-up until the end of the trial. In this predefined sub-study, all screened patients are included. The co-primary endpoints are the presence of AD at baseline and the 3-year total mortality. The epidemiological association between modifiable and unmodifiable risk factors is analysed by means of logistic regression. The association of the risk factors with the 3-year total mortality is tested with Cox-Regression.

Results: The study included 1,305 patients, of which 400 patients were identified as high-risk patients with AD and 905 patients were classified as low risk with normal autonomic function. The logistic regression analyses revealed an association of higher glycated haemoglobin (HbA1c) (OR 1.19, 95% CI 1.06 - 1.33, p-value= 0.002), increased age (OR 1.06, 95%CI 1.04 - 1.08, p-value < 0.001) and low left-ventricular ejection fraction (LVEF) (OR 0.90, 95% CI 0.87 - 0.94, p-value < 0.001) as continuous variables with the presence of AD.

The Cox-Regression analyses showed an association of AD (HR 2.68, 95% CI 1.39 – 5.18, p-value = 0.003), diabetes mellitus (HR 2.58, 95% CI 1.38 – 5.19, p-value = 0.004), increased age (HR 1.07, 95%CI 1.04 – 1.11, p-value < 0.001) and low haemoglobin levels (HR 0.80, 95%CI 0.70 – 0.91, p-value < 0.001) with a higher 3-year total mortality. All other risk factors were not significantly associated with the presence of AD and 3-year total mortality.

Conclusion: This is the first epidemiological analysis that examines the association between (non-)modifiable risk factors and pathological DC and/or PRD. The latter being defined as AD. Patients with AD were older, had lower LVEF and higher HbA1c levels. As it has been shown already previously in other studies, AD was significantly associated with increased risk of death. Future studies should test whether primary preventive measures can lead to a reduction in mortality in patients with AD. Furthermore, it should be evaluated whether treatment of modifiable risk factors can lead to a normalization of the cardiac autonomic function in patients with AD.

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List of abbreviations

AF = atrial fibrillation

AD = autonomic dysfunction

ANS = autonomic nervous system

AV = atrioventricular

BARC = bleeding Academic Research Consortium

CE = Communauté Européenne

CHD = coronary heart disease

CI = confidence interval

COPD = chronic obstructive pulmonary disease

CVD = cardiovascular disease

CK-MB = creatine kinase myocardial band

DALY = disability-adjusted-life-year

DC = deceleration capacity

DZHK = Deutsches Zentrum für Herz-Kreislauf-Forschung (German Centre for Cardiovascular Research)

ECG = electrocardiogram

eCRF = electronic case report form

ESC = European Society of Cardiology

GBD = Global Burden Disease

GCP = Good Clinical Practice

HBA1C = glycated haemoglobin

HF = heart failure

HRT = heart rate turbulence

ICD = implantable cardioverter defibrillator

ICM = implantable cardiac monitor

IHD = ischemic heart disease

LMU = Ludwig Maximilian University

LV = left ventricular

LVEF = left ventricular ejection fraction

MACCE = major adverse cardiac and cerebrovascular events

MADIT-2 Trial = Multicentre Automatic Defibrillator Implantation Trial

MI = myocardial infarction

MRA = mineralocorticoid receptor antagonists

MRI = magnetic resonance imaging

MSZ = Münchner Studienzentrum (Munich Study Centre)

NAF = normal autonomic function

NCD = non-communicable disease

NSTEMI = non-ST segment elevation myocardial infarction

PAD = peripheral artery disease

PCI = percutaneous coronary intervention

PM = particulate matter

PRD = periodic repolarization dynamics

PRSA = phase-rectified signal averaging

QoL = quality of life

RAS = renin-angiotensin system

R-R = beat-to-beat intervals

RM = remote monitoring

RR = relative risk

SAE = serious adverse event

SES = socioeconomic status

SMART-MI = Implantable cardiac monitor**S** in high-risk post-infarction patients with cardiac autono**M**ic dysfunction **A**nd mode**R**a**T**ely reduced left ventricular ejection fraction

STEMI = ST-segment elevation myocardial infarction

TIMI = thrombolysis in myocardial infarction

TWA = microvolt T-wave

VF = ventricular fibrillation

VT = ventricular tachycardia

WHO = World Health Organization

1. Introduction

1.1 Cardiovascular diseases

1.1.1 Epidemiology

Worldwide, cardiovascular diseases (CVDs) are the dominating cause of death[1]. Approximately 17.9 million people die each year, mostly prematurely, due to cardiovascular complications, accounting for 32% of all deaths worldwide. More specifically, 85% of those deaths are attributable to heart attacks and strokes[1]. Worrisome is the fact that a about third of the deaths due to non-communicable diseases (NCDs), encompassing CVDs, occur prematurely in people below the age of 70[2]. Explicitly CVDs account for 38 % of these premature deaths[1]. Furthermore, the global burden of disease (GBD) study shows that 80.6% [95% confidence interval (CI) 78.2–82.5] of age-standardized years lived with disability are due to NCDs[3].

CVDs are non-communicable, generally chronic diseases, which tend to be long-term and caused by multiple factors such as genetic, physiological, environmental, and behavioural factors, factors also known as risk factors for NCD[2]. In general, NCDs, including CVDs, affect people from all age groups, all over the world, and are largely preventable by addressing behavioural risk factors mainly[2].

CVDs specifically describe a cluster of conditions of the heart and blood vessels, including amongst other conditions coronary heart disease, cerebrovascular disease and/or rheumatic heart disease[1]. A selection of the most common forms of CVDs may be found in Table 1[1]. The conditions listed in Table 1 are predominantly chronic and long lasting, whereas heart attacks and strokes are momentary and acute, induced by a blockage of the blood flow to such a degree that the blood supply to the heart or brain cannot be ensured[1].

Table 1. **Types of cardiovascular diseases** as outlined by the World Health Organisation[1]	
Cardiovascular disease type	**Description**
Coronary heart disease	Vascular disease impeding the blood supply to the myocardium (heart muscle)
Cerebrovascular disease	Vascular disease impeding the blood supply to the brain

Peripheral arterial disease	Vascular disease impeding the blood supply to the limbs (i.e., arms and legs)
Rheumatic heart disease	Damaged heart muscle and valves due to rheumatic fever, triggered by streptococci
Congenital heart disease	Innate abnormality/malformation of the heart structure (birth defect) that impedes a normal cardiac development and functioning
Deep vein thrombosis and pulmonary embolism	Blood clots in the leg veins which can detach and potentially advance to the heart and/or lungs

Blood vessel diseases frequently exhibit no symptoms or symptoms only show once at a more serious stage of disease, in presence of a heart attack or stroke[1]. Pain or discomfort in the chest and/or in the arms, in the left shoulder, elbows, back or even the jaw for instance are common signs of a heart attack[1]. Other symptoms of a heart attack may include breathing difficulties or shortness of breath, nausea with or without vomiting, light-headedness and/or fainting, a cold sweat and paleness[1]. Oftentimes women experience slightly different symptoms than men and tend to present more often shortness of breath, feeling unwell (nausea, vomiting), lumbago (back pain) or jaw pain[1]. Strokes become most apparent when the person senses a sudden weakness of the face, arm, or leg, in most cases one-sided[1]. The sudden onset of numbness of the face, or in the limbs (specifically one-sided); confusion, difficulty speaking or seeing with at least one eye; unstable walk, dizziness and/or loss of balance or coordination problems; strong headache with unknown cause; and/or fainting or unconsciousness[1].

1.1.2 Risk factors

Some people may be more at risk than others to develop a CVD in their lifetime[1]. Major risk factors include elevated blood pressure, glucose levels and lipids, as well as excessive body weight (overweight and obesity)[1]. Those risk factors are easily identifiable in the primary care setting and thereby create a relevant window of opportunity in CVD prevention with the aim to avoid premature deaths[1]. However, avoiding and controlling for those apparent risk factors may seem simple but than it is, millions of people worldwide are going through the daily struggle of trying to adopt healthier life choices or simply are not aware of the detrimental elements in their lifestyle[1]. CVD risk factors are yet not all lifestyle-induced, and may be divided in 4

categories: predisposing, metabolic, behavioural, and environmental risk factors. Each of those categories is explained more in detail below.

Predisposing risk factors

There are determinants, which make a person naturally more susceptible for developing a CVD, alleged predisposing factors, as for instance age, gender, medical history, or genetic factors[4]. Age, or more specifically high age is an independent CVD risk factor, predisposing elderly people for CVD complications[5]. Combined with other conditions like frailty, obesity, diabetes mellitus, the risk for developing CVD at a higher age is enhanced[5].

In general, women tend to develop CVD 10-15 years later than men[6,7]. This presupposes gender to play a role in CVD risk profiling, namely whether there are female properties which are potentially risk-reducing, or male properties which tend to raise the CVD risk[6]. A precise explanation to the age difference in CVD onset, based on gender, has not yet been found, nevertheless sex hormones are suspected to play a role, as these characterise best the biological gender expressions[6]. Rodgers et al. (2019) claim gender to be a risk factor especially at higher age, as it is only then that females seem to be at greater risk for CVD compared to men at similar age[5]. This finding supports the presumption of sex hormones playing a role in risk profiling as women after menopause, hence after a significant drop in hormone levels, seem less protected from CVD than before menopause, when hormone levels, e.g., oestrogen, were still high[5]. In that sense, studies have found oestrogen to be considered as cardioprotective[7]. Similar findings were found for men, for testosterone, but the evidence for testosterone's cardioprotective feature is limited[8]. Yet experiments with hormone replacement therapies have not yielded the expected results and hereby not shown any benefit in protecting elderly people from CVD[5].

Metabolic/physiological risk factors

Elevated blood pressure (hypertension), blood cholesterol/lipids (hypercholesterolemia) and blood sugar levels/glucose (hyperglycaemia) are preeminent metabolic risk factors for cardiovascular diseases[1]. Hypertension for instance is found to be attributable to about a fifth of all deaths worldwide, thereby a leading risk factor globally, followed by overweight and obesity, as well as high blood glucose[2,9]. Moreover, Landini (2014) postulates homocysteine, serum uric acid concentrations, and L-arginine demethylated derivatives as further metabolic risk fac-

tors and mentions the metabolic syndrome as such[4]. There is no fixed definition of the metabolic syndrome, but it essentially describes the co-occurrence of different, interrelated physiological cardiovascular risk factors, namely insulin resistance, obesity, atherogenic dyslipidaemia and hypertension[10]. Underlying mechanisms, pathways and properties are similar and shared among those conditions[10]. The metabolic syndrome represents a composite pathophysiology, requiring that a person has several of these conditions, excluding people who present only isolated metabolic risk factors e.g., hypertension alone[10].

Despite being apprehended as metabolic or physiological risk factors, thus in general unmodifiable, it shall not remain unmentioned that metabolic factors are still largely affected by external, environmental, and social influences such as age, SES, or urbanisation[1]. An example of such is homocysteine, an independent cardiovascular risk factor but to significant extent modifiable by nutrition and physical activity[11].

Behavioural risk factors

Behavioural, modifiable, risk factors are an essential driving force in the development of NCDS, including CVDs[1,2]. On the one hand they have a strong influence on disease development, and on the other hand they present a simple but powerful point of entry in CVD prevention[1]. The use of tobacco, unhealthy eating, alcohol abuse and insufficient physical activity are the main drivers or behavioural risk factors for CVDs[1]. These aforementioned behavioural patterns lead most likely to an increase in blood pressure, lipids and/or glucose, as well as overweight and obesity, which in turn implicate an increased risk for the development of cardiovascular impairments such as a heart attack or stroke[1]. The latter for instance unfold, given a clogging of blood vessels due to fatty deposits on the inner walls, in a way that the heart or the brain cannot be sufficiently supplied with blood. Strokes are provoked either by such a blood clot or by cerebral blood vessel bleeding[1].

Every year, tobacco claims the lives of 7.2 million people[9]. These include deaths caused by exposure as well as second-hand smoke, and these numbers are suspected to increase in the upcoming years[9]. Excessive salt or sodium intake account for 4.1 million deaths per year, whereas alcohol (ab)use is responsible for 3.3 million deaths each year and half of those are due to NCDs, including cancer[2,9]. In 2019, data from the GBD study delineated the diet induced CVD burden at that time, claiming worldwide 6.9 million deaths and 153.2 million disability-adjusted life years (DALYs), which equivalates to 43.8 % and 34.3% increases respectively

when compared to 1990[12]. The lack of physical activity and sedentary lifestyle accounts for 1.6 million deaths each year[9]. Also, the risk for developing CVD increases by more than 20% when being physically inactive and about a quarter of Europeans are estimated to have not enough physical activity in their daily lives[13]. Northern Europeans are on average considered as more active than Southern Europeans, and there is a slight difference between men and women in all age groups, with men being somewhat more active than women (78% vs 75%)[13].

Environmental risk factors

In general, risk factors for NCDs, including CVDs, are found to originate predominantly from the environment[14]. The CVD risk factors reflect the social environment and its determinants of change in which we live[1]. Globalisation, urbanisation and/or population ageing are examples of such determinants, as well as poverty, stress, artificial light (at night) and noise[1,15]. Climate change is a very important health stressor, expressed by heat extremes, desert storms and wild-fires, and air pollution, including even volcano eruptions, is considered as the most influential health hazard among the environmental risk factors[15]. The cumulative exposure to environmental risk influences, together with classic health risk factors (e.g., overnutrition, lack of physical activity, hypertension) leads to alterations in biological pathways and overlap in pathomechanisms and thereby to adverse cardiovascular health outcomes[15]. In that sense, the term 'exposome' describes the 'cumulative measure of environmental influences and associated biological responses throughout the life span'[15](p.3).

Urbanisation is thought to accumulate and intensify environmental stressors, this being reinforced by bad urban city planning[15]. Noise refers mainly to transportation noise, including road traffic noise, rail, and aircraft noise[15]. Road traffic noise accounts for the most part of adverse noise-associated health effects whereas for the health effects of noise coming from other modes of transportation there is only low evidence to be found[15]. In 2018, a WHO expert panel, working on guidelines regarding environmental noise in the European region, established the relative risk (RR) of road noise for the development of IHD[16]. They estimated a RR of 1.08 (95% CI 1.01–1.15) per each 10 dB increase in road noise for IHD, setting chronic exposure levels of 53 dB as threshold where notable health effects became apparent[16]. More than IHD, total environmental noise for instance has also been found to be positively associated to MI in a study from the island of Montréal in Canada[17].

Furthermore, air pollution, being a significant and powerful environmental risk factor, is considered as one main health stressor leading to excess morbidity and mortality[14,15,18]. Based on data from the Global Burden of Disease (GBD) study, the Lancet Commission on pollution and health postulates that air pollution (in- and outdoor) is the single most important environmental health hazard, dominating over the combined effect of stressors like water pollution, soil contamination and occupational exposures[14]. It is estimated that ambient air pollution in Europe is responsible for 790 000 deaths (excess mortality rate) (95% CI 645 000-934 000)[19]. Most health outcomes are of cardiovascular nature, thus heart attacks and strokes and account for 40%-80% of those aforementioned deaths[19]. A quarter of all ischaemic heart disease (IHD) seems to be associated with an environment which is harmful for health, air-polluted particularly[14]. Composed of a heterogenous mixture of gases, air pollution is like a mosaic of different particles[20]. Nevertheless, the focus of emission mitigation efforts and environmental health research on fine particulate matter (particles ≤2.5 μm in diameter (PM2.5)) and ozone gas, as the latter have been found to be most significant in provoking adverse health effects[20]. More than half the deaths stemming from PM2.5 induced non-communicable diseases are of cardiovascular nature[14,20]. Additionally, PM2.5 exposure was linked several times to the risk of non-fatal MI[21]. Acute increases in PM2.5 together with PM10 and other reactive gases were identified in a metanalysis to be connected to a higher incidence in hospitalisations due to heart failure and death[19,22]. In that sense, the average European is expected to lose 2.2 years of life due to air pollution, and this would be reduced to 1.7 years if emissions were controlled for[19].

Along with air pollution or climate change, socioeconomic status (SES) is another environmental risk factor[23]. Petrelli et al. (2021) used in their investigation the education level as an indicator of SES[23]. As we have seen already previously, SES is a risk factor which in turn can be influenced again by other risk factors, such as behavioural or metabolic determinants[23]. The data shows, after adjustment for sociodemographic factors e.g., smoking, BMI, diabetes, hypertension, diabetes, and BMI, that men with the least education presented a 21% higher risk of CVD and 17% higher risk for coronary heart disease (CHD) compared to the highest educated men[23]. The trend is observed similarly but stronger in women, with a heightened risk of 41% for CVD and 61% for CHD for the least educated compared to the most educated women[23].

1.1.3 Treatment

All patients in need should have access to appropriate care and medical treatment, independent of location or social status[1]. Acute events such as hearts attacks or strokes need instantaneous treating action, whereas chronic conditions tend to entail chronic treatment[1]. CVD management interventions, ideally integrated in universal health coverage packages, are essential in the reduction of cardiovascular disease burden[1]. Specific hypertension programmes, tried out and approved in 18 countries, represent for instance an efficient and cost-effective tool in CVD treatment and prevention of heart attacks and strokes at primary care level[1]. Furthermore, a selection of basic and specific medicines should be accessible and prescribed in the cardiovascular disease treatment[1]. These include aspirin; angiotensin-converting enzyme inhibitors; beta-blockers and statins[1]. Surgical treatment is occasionally needed in CVD handling, and encompasses interventions such as coronary artery bypass, valve repair and replacement, heart transplantation, balloon angioplasty and artificial heart operations[1]. Besides medical and surgical treatment options, medical devices, such as pacemakers, event recorders, prosthetic valves, or sealing patches for holes in the heart, are often considered, or even required in successful CVD treatment[1]. One of the latter, implantable cardiac monitors, or so-called event recorders, will be explained more in detail and focused further on in this research.

Recently, the use of alternative cardiac treatment or rehabilitation options, such as mind-body therapies, has attracted some interest[24]. The systematic review of Sharma et al. (2021) suggests yoga as such a promising mind-body practice and considers it as efficient in reducing the burden of cardiac arrythmia, including paroxysmal atrial fibrillation (AF), ventricular tachycardia (VT) and palpitations, and improves respective related conditions such as blood pressure, heart rate, mental health, and health-related quality of life (QoL)[24]. Another study even identified a beneficial effect of yoga on (initially impaired) left-ventricular ejection fraction (LVEF), leading up to 6% increase in LVEF[25]. However, since this field of alternative cardiac treatments and/or even prevention efforts, is only emerging, current scientific evidence is still low and more studies, including randomized controlled trials, bigger sample sizes and a more homologous protocols are needed[24].

1.2 Cardiovascular disease prevention

1.2.1 Conventional prevention

Greater lifestyle interventions or drug treatment are often necessary to reduce CVD risk factors to avoid heart attacks or strokes[1]. In that sense, on the macro-level of society, the World Health Organization (WHO) provides supportive action to countries in matters of disease prevention[1]. The WHO manages and monitors CVDs, by developing and providing global strategies with the aim to reduce the incidence, prevalence, morbidity, and mortality of CVDs[1]. Examples of such strategies are the reduction of individual risk factors, the development of standards of care, the support of local health systems, the enhancement of capacity of care for CVD patients, and the monitoring of disease patterns and trends[1,2]. Cost-effective and equitable health care innovations are wanted and needed, as much as adequate health insurance coverage and universal access to NCD interventions are[1,2]. Governments and stakeholders can rely on low-cost but effective solutions to mitigate CVD risk factors in the population[2]. Health policies can be an economical but powerful tool to support people in making healthier and sustainable life choices and they should be accessible to everyone[1]. Monitoring and surveillance enable stakeholders to stay informed about the occurrence of CVD in their communities[2]. Detection and screening at primary health care centres for instance facilitates early detection of CVD and gives way to timely treatments, which in turn avoids potentially expensive medical care[2].

A comprehensive and multisectoral approach, in the sense of ´health-in-all-policies´, is needed to plan and manage health promoting interventions, to reach high-impact effects[2]. This implies a collaboration of sectors like agriculture, finance, education, transport, health, planning and more[2]. It is not possible to reach the global target of 25% relative reduction in the risk of premature death from NCD by 2025, as foreseen in the WHO Global Action Plan, nor the sustainable development goal of one third reduction of those by 2030, without increased prevention efforts in which these disease management interventions are indispensable[2,26]. Other targets of this WHO Global Action Plan include a 10% reduction in relative risk in alcohol abuse and in prevalence of insufficient physical activity respectively, as well as a 30% relative reduction in each the prevalence of tobacco use in people ≥ 15 years and in salt/sodium consumption in the general population[26]. Moreover, the WHO aims for a 25% relative reduction in hypertension and an end to increasing prevalence of diabetes and obesity[26].

On the micro-level of society, individuals are encouraged to become aware of their respective risk factors, including their unmodifiable predisposing risk factors, and to become proactive in the matter of their own health as much as possible[1]. The modifiable, behavioural risk factors represent an unparalleled point-of-entry opportunity for prevention efforts[2]. NCDs, including

CVDs, originating largely from the individual´s lifestyle, present hereby an especially efficient target for prevention[2]. The counterwork on behavioural risk factors and adoption of healthier lifestyles has led to a significant reduction in CVD[1]. Examples of the latter are tobacco control and cessation, a wholesome and healthy diet, an active lifestyle, and responsible alcohol consumption habits[1]. A healthy diet as suggested by a very recent reviews, should be plant-based, fruit-and vegetable-rich, include whole grains and primarily plant-based proteins, or secondarily fish and poultry[27]. In general, the intake of dairy is supported, exceptions are cream and butter for people at risk for CVD[27]. The same goes for (high)cholesterol foods like eggs and crustaceans, which are not advised for people with a high CVD risk profile[27]. A regular active lifestyle, as suggested by a recent report of the European Heart Network in collaboration with the WHO, foresees at least 150 minutes of moderate intensity training per week; 75 minutes of higher intensity training or an equivalent mixture of different intensity trainings and preferably spread over the week[13]. Physical activity is a simple, accessible, and natural prevention tool with low carbon footprint, presenting low to none, unwanted side-effects[13]. Even less so, it is a sustainable and environmentally friendly public health promoting activity, leading even to less air pollution, more social inclusion, and less resort to fossil fuels[13]. Yet, the benefit of physical activity in CVD has oftentimes been forgotten and not taken enough into account in preventive health policies[13].

As far as the metabolic risk factors are concerned, people in need should have unimpeded access to the essential drug treatment for their condition such as for hypertension, diabetes mellitus and high cholesterol to prevent CVD complications such as MI or stroke[1]. This is also reflected in the targets of the WHO Global Action Plain which entail the target that at least half of the people in need obtain the appropriate medication and medical counselling, and that leastways 80% of the people have access to it[26].

In the matter of environmental risk factors, the mitigation of air pollution represents a simple yet high-impact health promotion intervention[19]. By improving air quality, the years of life lost could be reduced from 2.2 to 1.7 years of life[19]. Nevertheless, the environmental impact to CVDs has so far largely been unrecognised, as illustrated by the WHO NCD Global Action Plan form 2013, which failed to recognise and address the environmental effect on NCDs[26]. In that sense the environmental share to healthcare funding, research and prevention is considered as largely insufficient with respect to its disease burden, evidence is low and more high-quality research is needed[28]. To counteract the influence of SES on CVD development, Petrelli et al.

(2021) suggest investing in education, as the latter is often an indicator of SES and a simple tool for CVD prevention efforts[23].

1.2.2 Innovative prevention efforts

State-of-the-art of current prevention practices

After long disregard of the influence on the environment on CVD risk profiling, the new European Society of Cardiology (ESC) 2021 Guidelines now classify climate change and air pollution as major novel CVD risk factors and threat to public health and emphasize even the potential influence of elevated noise levels and soil pollution on CVD risk[29]. Furthermore, the ESC 2021 Guidelines define in their ten commandments recommendations on each the individual and on the population level[29]. On the individual level, they suggest an improved CVD risk estimation, as for instance 10-year or lifetime CVD risk estimations, including also risk prediction algorithms for healthy people[29]. They advocate treatment decisions to be inclusive and individually personalised, supporting thereby patient involvement, and shared decision-making processes by the patient and health care provider[29]. The treatment should consider individual patient characteristics, such as age, gender, life expectancy, risk factor profile, ethnicity, and geographic location[29]. In that way, people can be classified in individual risk groups, based on their clinical characteristics, which in turn enables risk profile specifications like the development of age-specific thresholds, covering thereby even predisposing, usually unmodifiable, risk factors[29]. The ESC 2021 Guidelines stress in addition the importance of the identification of cost-benefit issues, which fosters prevention efficiency[29]. On the population level, the ESC fosters refined and upstream policy measures, originating from and targeting the general population[29]. Also, the ESC strives for changes in the social environment including individual determinants of health, ideally with the help of incentives to support individual behaviour change[29]. With these measures on the individual and population level respectively, the ESC 2021 Guidelines aim to reduce the risk in CVD burden considerably[29].

Telemedical monitoring

Telemedical monitoring, also known as remote monitoring (RM), is a novel and allegedly valuable tool in CVD prevention or prevention of complications[30]. RM enables a holistic and integrated approach in CVD prevention and disease management, by scanning for and recording cardiac arrythmias[30]. It has been proven especially profitable in (chronic) heart failure (HF)

management and early detection of deterioration, all essential elements contributing to a reduction of hospitalisations due to HF, including readmissions[31]. For the RM, small cardiac implantable monitors (ICMs) are implanted subcutaneously in the heart area[32,33]. A common device used, as later explained more in detail in this research, is the miniaturized Reveal LINQ[34]. The device's effective sensoring performance is reliable in detecting and recording cardiac arrythmias, all whilst ensuring patient safety[34]. Hazard-free and simple implantation procedures, ECG quality, assurance of daily transmissions in RM, as well as absence of device-related severe adverse events (e.g., device migration after 1 month) qualify the ICM as a safe and effective tool in cardiac prevention and care[34].

RM, in combination with conventional screening methods like surveillance and reporting of body weight and patient symptoms, guides efficiently prevention and therapy activities[31]. Hence, RM plays an undeniably significant role in the continuous care of CVD patients and could improve patient's compliance to and understanding of (pharmacological) therapy, whilst being cost-effective by averting unnecessary in- hospital visits and invasive interventions[30,31]. Nevertheless, some challenges remain in telemedical monitoring, namely data protection and integration in clinical care; patient selection (compliance, resources, most benefits); device safety, cost-effectiveness, and user-friendliness (for physician and patient); choice of monitored parameters as well as cut-offs for treatment decisions[30,31].

Novel biosignal markers in postinfarction patients

Medical history of myocardial infarction (MI) poses patients at increased risk of early mortality, despite advanced interventional and pharmaceutical treatments[35]. Sudden cardiac death represents about half of all CVD attributable deaths and are largely preventable by prophylactic implantation of an implantable cardioverter defibrillator (ICD)[35]. Since many years, the identification of high-risk patients who may profit from such a prophylactic procedure is fundamental to CVD prevention efforts[35]. The MADIT-2 Trial (Multicentre Automatic Defibrillator Implantation Trial) was the first trial to use impaired left ventricular ejection fraction (LVEF) as sole indicator and criterion for prophylactic ICD implantation in patients with ischaemic cardiomyopathy, and thereby succeeded in defining an efficacious, efficient, and even cost-effective method, confirmed by the findings of several following trials[36]. The findings of the trial led to the establishment of a first-grade recommendation in medical guidelines[37]. However, soon it became clear that this criterion was not enough, as the majority of postinfarction

deaths (70%) occurred in patients with preserved or only moderately impaired LVEF[38,39]. In that sense, innovative approaches in risk stratification in postinfarction patients were and are still needed due to its high clinical relevance[40]. Moreover, as MADIT-2 was published 21 years ago, trial participants were not treated according to current standards for therapy of heart failure. Cardiac autonomic dysfunction, independent of LVEF, is considered to entail prognostic potential[41]. This damage of the autonomic nervous system may be expressed as the absence of vagal activity or excessive sympathetic activity and this in turn is likely to induce to poor health outcomes[40]. Deceleration capacity (DC) and periodic repolarisation dynamics (PRD) are novel biomarkers that may be used in risk stratification efforts[35,42,43].

The deceleration capacity (DC) of the heart is a novel indicator measuring heart rate variability by capturing the vagal activity of the heart at the level of the sinus node[40]. Studies have shown that DC is a significant predictor of mortality in patients with ischaemic cardiomyopathy, as well as in patients with structural heart disease[44,45]. Moreover, DC was demonstrated to be valuable in the identification of patients at high risk that have been previously remained unidentified in the day-to-day practice of the clinical emergency medicine, thereby advancing current triage schemes[46,47]. A large-scale observational study encompassing 2711 post-MI patients showed that DC dominated standard HRV measures as well as LVEF or both combined in predicting post-MI mortality[42,48]. In addition, two big cohort studies (Munich Cohort, ISAR-Risk, n=908 and Tübingen Cohort, PRD-MI, n=478) tested the prognostic value of DC by means of short-term ECGs after MI and both cohorts demonstrated a restricted DC of the heart to be a strong and independent predictor for 3-year all-cause mortality and cardiovascular mortality[44]. High test consistency in combination with computational algorithm simplicity found the basis for declaring DC as a suitable, low-cost, accessible, and non-invasive prevention and screening tool[42]. It may be used as an index to identify patients in need for further prophylactic therapies, and to exclude those at low risk for whom further treatment is dispensable[42].

The periodic repolarisation dynamics (PRD) of the heart are low-frequency modulations that capture the sympathetic activity of the cardiac autonomous nervous system amidst the ventricular repolarization[49,43]. PRD is confirmed to be independent of respiratory activity ($p<0.001$) and heart rate variability ($p=0.002$) and is found to be enhanced by sympathetic nervous activity[43]. In turn, pharmacological induced blockages of the sympathetic nervous system have been found to restrain PRD ($p\leq0.005$)[43]. PRD is found to provide incremental predictive value on top of other established risk stratification markers, including LVEF and TWA[43]. Three large-scale cohort studies showed that PRD is a significant independent predictor of all-cause and

cardiac mortality respectively in patients with proven ischaemic cardiomyopathy, as well as patients undergoing exercise testing because of suspected coronary artery disease[49,43]. An elevated PRD presents a hazard ratio of 4.75 (95% CI 2.94–7.66; P < 0.001) in predicting 5-year total mortality in postinfarction patients[43]. PRD even identified vulnerable patients in the outstanding MADIT-2 Trial cohort which could benefit from a prophylactic ICD implantation and predicted all-cause and cardiac mortality, as well as non-sudden cardiac death reliably[49,36].

By means of using DC and PRD in combination, capturing the loss of vagal activity and the excess of sympathetic activity of the heart, patients with cardiac autonomic dysfunction can be singled out[50]. They represent a new high-risk group diagnosed with cardiac autonomic failure, presenting prognostics like patients with low LVEF (≤35%)[32,50]. Patients with preserved LVEF (>35%) and abnormal DC and PRD values showed a 10 times higher risk of 5-year mortality, when compared to patients with normal DC and PRD values[50]. This new high-risk group has until recently not been addressed by current medical guidelines[32]. The SMART-MI Trial is a randomised controlled, diagnostic trial, that focused specifically on this new risk group, including post-MI patients with a moderately reduced LVEF (35-50%) and cardiac autonomic dysfunction, defined as increased PRD or/and decreased DC[32]. An increased PRD or an increased DC was sufficient to label a patient as high-risk and to randomise him 1:1 to the diagnostic intervention or control group[32]. The intervention group received an ICM and underwent RM during the trial, the control group received conventional follow-up therapy[32]. The patients in the intervention group were thereby screened for detection of predefined arrhythmic events and received therapy upon confirmation of the arrythmia[32].

These innovative, non-invasive, but simple approaches assist in the adequate identification of high-risk patients, who remain unrecognised with conventional prevention and screening methods[40]. Guided by novel biomarkers, more accurate prognostics and personalised treatment plans can be established in patients suffering from an impaired cardiac autonomic function[40].

1.3 Aims of this dissertation

The general aim of this dissertation is to take on an epidemiological approach in the assessment of autonomic function after myocardial infarction. This dissertation is a post-hoc analysis of the data from the SMART-MI Trial and aims to add on to the body of knowledge already available from the main trial analyses.

The goal of this dissertation is to analyse the effect of modifiable and non-modifiable risk factors on:

- the function of sympathetic and parasympathetic nervous system, quantified as the absolute value of PRD and/or DC,
- the probability of autonomic dysfunction, defined as abnormal PRD and/or DC (cross-sectional analysis at baseline),
- survival (up to 3 years after index-MI).

2. Material and methods

2.1 The SMART-MI-DZHK9 Trial

The SMART-MI-DZHK9 Trial was a prospective, investigator-initiated, open-label, randomized controlled trial, registered with ClinicalTrials.gov (NCT02594488) and lead by Univ.-Prof. Dr. Axel Bauer from Munich, Germany[32,33]. SMART-MI is an abbreviation for 'Implantable cardiac monitor**S** in high-risk post-infarction patients with cardiac autono**M**ic dysfunction **A**nd mode**R**a**T**ely reduced left ventricular ejection fraction'[32,33]. It was a multicentre trial, with 32 centres in Germany and 1 in Austria[33]. The German Centre for Cardiovascular Research (DZHK) supported the trial by providing funding and an already well-established clinical-scientific infrastructure[32,33]. Good Clinical Practice (GCP) principles and the corresponding national regulations were followed, in accordance with the Declaration of Helsinki[32,33]. Responsible for monitoring activities and safety assessment was the Munich Study Centre (MSZ) at the Technical University Munich, Germany[32,33]. This dissertation is a post-hoc analysis of the data from the SMART-MI Trial. As the trial serves as a basis for this dissertation's analyses, a detailed description of the trial can be found in the subsequent paragraphs.

2.1.1 Study design

The ethics committee of the Ludwig Maximilian University (LMU) hospital in Munich, as well as other legal authorities in question, approved the design of the trial (number 118-15) [32,33]. Written informed consent was provided by all study participants[33]. The design and hypothesis of the SMART-MI Trial have been previously described in detail by Hamm et al. in 2017[32]. All screened patients, that met the in- and exclusion criteria and provided written informed consent, received 48h after index MI or when their laboratory value CK-MB was normalized, a high resolution (1kHz) resting ECG, recorded during 20 minutes in Frank leads configuration (Medilog AR4plus, Schiller AG, Bar, Switzerland)[32,33]. The ECG assessed, and its interpretation indicated whether the patient presented a cardiac autonomic dysfunction or not, by determining two complementary biomarkers, namely PRD and DC[32,33]. Details about the in- and exclusion criteria, the devices or biomarkers are explained below. If the patient had either one or both markers trespassing the previously determined thresholds (PRD $\geq$5.75 deg^2; DC $\leq$2.5 ms), he was considered as high-risk[32,33]. If the patient had none of both values out of norm, he was considered as low risk[32,33]. The diagnostic nature of the primary endpoint in SMART-MI

influenced the sample size calculation, which indicated that 400 study participants would be needed to reach 90% power in the detection of statistically significant differences in time to first arrhythmic event ($p \leq 0.05$)[32]. A yearly event rate of 5% in the control arm and 13% in the intervention arm, in total 46 events, served as basis for sample size calculation while considering a 15% dropout rate[32].

After randomization of the high-risk patients, patients were allocated in the intervention or control arm of the trial[32,33]. The intervention arm comprised ICM (Reveal LINQ, Medtronic Minneapolis, MN, USA) implantation and intensified surveillance by telemedical monitoring; the control arm represented conventional standard care follow-up and in-hospital visits as foreseen by current guidelines[32,33]. The 1:1 randomisation was carried out by using a predefined block randomization list (random block size = 4) and by running a computer-generated, web-based sequence (secutrial®, interActive Systems, Berlin, Germany) that included a stratification respecting study centre, age (< / ≥70 years) and LVEF (< / ≥45%)[32,33]. Once a patient in a centre got diagnosed as high-risk, following the interpretation of the 20-min resting ECG, the staff at the core lab in the LMU hospital triggered the randomisation process in secutrial®, which belonged to the eCRF module used in this study[32,33] . The eCRF was provided and managed by the Department of Medical Informatics situated at the University of Göttingen, Germany[33]. In that way, the local study centre in Germany or Austria was able to access the randomization result by visiting the web-based eCRF [33]. Neither patients, nor investigators were blinded to group allocation of the study participants[33].

2.1.2 Study population

The study population of the SMART-MI Trial was delineated by the trial's in- and exclusion criteria, which were already outlined previously by Hamm et al. (2017) (Table 2)[32,33]. A patient was eligible when he was between the ages of 18 and 80 years and a recent (<39 days) acute MI survivor, as defined by current ESC guidelines, that required percutaneous coronary intervention. The LVEF was required to be between 36% and 50%. Evaluation of LVEF was based on echocardiography, left ventricular angiography or magnetic resonance imaging, and was performed at least 48h after index MI or once the laboratory marker CK-MB was normalized. Sinus rhythm as well as optimal guideline-based medical therapy were also prerequisites. Not eligible for the study were patients with ICD or pacemaker indication, patients suffering from previously diagnosed paroxysmal or permanent AF, with short life expectancy (≤12 months) or when they were unlikely to abide by the scheduled follow-up visits. Pregnant women or

patients that participated already in other clinical trials that may interfere with the SMART-MI aims were also excluded from study participation. It was mandatory for all study participants to provide a written informed consent [33].

Table 2. **Inclusion and exclusion criteria of the SMART-MI-DZHK9 Trial** as defined by Hamm et al. (2017)[32]	
Inclusion criteria	**Exclusion criteria**
Acute MI >40 days ago: STEMI and/or NSTEMI as defined by current ESC guidelines, with evidence of a coronary lesion on a coronary angiogram and requiring PCI	Indication for ICD or pacemaker
LVEF 36%-50% as assessed by echography, LV angiogram or MRI; measured >48 h after index MI or when CK-MB has normalized	Previously diagnosed paroxysmal or persistent atrial fibrillation
Evidence of cardiac autonomic dysfunction: abnormal heart rate DC <2.5 ms and/or abnormal PRD ≥5.75 deg2; measured >48 h after index MI or when CK-MB has normalized	Life expectancy <12 months
Age 18-80 years	Inability to comply with follow-up visits
Sinus rhythm	Pregnancy
Optimal medical therapy	Participation in a competing trial
Written informed consent	
Abbreviations: MI, myocardial infarction; *STEMI*, ST-segment elevation MI; *NSTEMI*, non–ST-segment elevation MI; *ESC,* European Society of Cardiology; *PCI*, percutaneous coronary intervention; *LVEF*, left ventricular ejection fraction; *LV*, left ventricular; *MRI,* magnetic resonance imaging; *CK-MB*, creatine kinase myocardial band; *DC,* deceleration capacity; *PRD*, periodic repolarization dynamics; *ICD*, implantable cardioverter defibrillator	

2.1.3 Trial endpoints

The primary outcome of the SMART-MI Trial is the 'time to detection of predefined serious arrhythmic events' (Table 3)[32,33]. These serious arrhythmic events have been precisely defined before the start of the study and included the following conditions and criteria as laid out by Hamm et al. (2017): atrial fibrillation ≥6 minutes, AV-Block ≥IIb, fast non-sustained ventricular tachycardia (nsVT with a cycle length of ≤320 ms / frequency of >187 bpm which lasts

for ≥12 seconds and corresponds to ≥40 beats) and sustained ventricular tachycardia (VT)/ventricular fibrillation[32,33]. If not already an established criteria in diagnostic or therapeutic guidelines, the respective thresholds and limits of these endpoint components have been set up, based on results from previous clinical trials[32,33]. Examples of such clinical trials are the ASSERT study, the CARISMA study, and the ADVANCE III study[5152,53]. The ASSERT study indicated that AF for more than 6 minutes was connected to an increased stroke risk[51]. Then, the CARISMA study showed that an AV-Block ≥IIb detected by the ICM was linked to mortality[52]. Eventually the ADVANCE III study determined the nsVT thresholds in its long detection arm by adhering to the conventional ICD device settings with a cycle length of ≤320 ms[53].

Secondary outcomes of the SMART-MI Trial enclosed the respective single elements of serious arrhythmic events as listed above, as well as sinus arrest >6 seconds, all-cause mortality, cardiovascular mortality, major adverse cardiac and cerebrovascular events (MACCE) and quality of life[32,33]. MACCE includes and is determined by cardiovascular death, systemic arterial thromboembolism, stroke and unplanned hospitalisations for decompensated heart failure. Moreover, the composite of death and MACCE, the composite of sinus arrest >6 seconds and AV-Block ≥ IIb and, the composite of AV-Block ≥ IIb, fast nsVT, and sustained VT/VF were examined[32,33].

ICM-related complications (e.g., infections) and TIMI major bleedings (BARC ≥2) represented the safety endpoints of the SMART-MI Trial[32,33]. An independent event adjudication committee, blinded to patient information and allocation, meticulously analysed, and arbitrated all primary and secondary outcomes of the study[32,33].

***Table 3*. Primary and secondary endpoints of the SMART-MI-DZHK9 Trial** as defined by Hamm et al. (2017)[32]	
Primary endpoint: Composite of predefined arrythmias	**Secondary endpoints:** Composite of all-cause mortality, systemic arterial thromboembolism, stroke, unplanned hospitalizations for decompensated heart failure
Atrial fibrillation ≥ 6 minutes	All-cause mortality
Higher degree AV-Block ≥ IIb	Cardiovascular mortality
Sustained VT or VF	Unplanned hospitalizations for decompensated heart failure

Ventricular tachycardia (VT) with a cycle length ≤ 320 ms lasting for ≥ 12 seconds (corresponding to 40 heart beats (12))	Sinus arrest >6 seconds
	Non-sustained VT ≥ 16 beats
	Bradycardias
	Ventricular arrythmias
	Quality of life
	Device-related complications including infections and major bleedings (BARC ≥2)
**Abbreviations: AV,* atrioventricular; *VT*, ventricular tachycardia; *VF*, ventricular fibrillation; *BARC*, bleeding Academic Research Consortium´	

2.1.4 Biosignal analysis and risk stratification

To calculate PRD and DC, a high-resolution (1kHz) ECG in Frank leads configuration (Medilog AR4plus, Schiller AG, Bar, Switzerland) and under standardized resting conditions was performed for the duration of 20min[33]. Details about the device may be found below. The test was carried out at least 48h after the index MI or when the laboratory value CK-MB had normalized[33]. The patient was placed in resting, supine position and the examination was carried out under standardized circumstances[33]. After the test, the raw data of the ECGs were transmitted to the core lab of the trial at the LMU hospital in Munich, Germany, where a trained and blinded study physician evaluated the ECG recordings, for computation of the digital biomarkers DC and PRD, which have been explained in detail elsewhere[33,42,43]. By means of determining DC and PRD from the high-resolution ECG, cardiac autonomic function of a patient can be assessed[33,42,43]. A customized, open-source software (SMARTlab 1.5) following previously established technologies was used to compute the two digital biomarkers[33]. A patient was diagnosed with signs of cardiac autonomic dysfunction if one or both biomarkers were abnormal (PRD ≥5.75deg^2; DC ≤ 2.5ms [33, 43,44].

2.1.5 Baseline and Follow-Up Visits

At baseline, following written informed consent of the patient but before randomization, the patient underwent a targeted assessment of his medical history and corresponding physical examination[32]. The latter included heart rate, blood pressure, height, and weight (i.e., body mass index). Cardiac health at resting state was examined with a 12-lead ECG and LVEF was determined by echography (at least 48h after index MI or when the laboratory values CK-MB had

normalized). Standard screening laboratory blood tests were organized, with a special focus on the following parameters: white blood cell counts, haemoglobin, haematocrit, platelet count, electrolytes, activated partial thromboplastin time, serum creatinine, international normalized ratio, troponin-T or troponin-I and CK and its MB fraction. The 20-min resting ECG was run to assess the two biomarkers PRD and DC and thereby cardiac autonomic function, at least 48h after index MI or when the laboratory value CK-MB had normalized[32]. Following these steps, randomization was authorized, representing time zero in the trial for the study participant[32].

Thereafter, the intervention and the control group were studied concurrently, and all patients enrolled were eventually eligible for the final intention to treat analysis[32]. After randomization, in-hospital follow-up visits at the local study centre were scheduled for the study participant every 6 months until the end of the trial according to a predefined protocol (timeframe ± 14 days), regardless of the study group they were in[32,33]. With the start of the Covid-19 pandemic in 2020, follow-up visits via telephone were occasionally allowed and conducted if not otherwise feasible in the first months[33]. During these visits, the participant was questioned by the study physician for the occurrence or symptoms of specific events relevant to the study outcomes, which encompassed the following: MI, systemic thromboembolism, unplanned hospitalization, stroke, bleeding, infection, and arrhythmic events[32,33]. Patients underwent a 12-lead ECG recording at every visit, but a 20-min resting ECG was only carried out every full year, for the purpose of reassessment of cardiac autonomic function[32,33]. The only difference in outpatient visit schedule between patient groups was the ICM interrogation for patients in the intervention group[32,33]. If deemed necessary by the local treating physician, further diagnostics or therapies were organized or administered[33].

Complementing information about patient health collected outside of the in-hospital visits were retrieved by telephone and sometimes by mail from patients, family members, general practitioners, or local authorities and meticulously logged in the eCRF[33]. Hospital records were scanned on occasion for indispensable information regarding diagnostic or therapeutic measures encompassing device im- or explanations, invasive procedures of various nature or pharmacological therapy, e.g., medication list[33]. Original source data documents were solicited in case of serious adverse events (SAE) that could be potentially relevant for the study outcome and confirmed endpoints and were monitored on-site by the MSZ[33]. In general, all original source documents were monitored on-site for all study participants on risk basis, only for the Covid-19 pandemic remote monitoring online and via telephone was allowed[33]. The minimum follow-up period for study participants was 6 months, with at the same time the first enrolled

patient having about 4 years of follow-up[32]. Average follow-up duration was expected to be around 18 months[32].

All 1,305 patients underwent the baseline visit, but only the high-risk participants, the intention-to-treat group, received regular outpatient follow-up visits[33]. The low-risk, registry patients received only one final follow-up just before study closure assessing survival state. The data from the regular follow-ups (apart from the final follow-up), were not used in the analyses of the dissertation.

2.2 Devices used in the SMART-MI Trial

2.2.1 12-lead resting electrocardiogram

An electrocardiogram (ECG) is a painless and non-invasive test that measures and registers cardiac electrical function, ergo electrical impulses or signals emitted during each contraction of the heart[54,55]. By means of electrodes, an ECG determines heart rhythm, chamber size and muscle thickness[55]. There are several types of ECGs, amongst which the resting 12-lead ECG represents the essential standard test in the assessment of a heart's electrical activity when the patient is at rest, the so-called baseline ECG[55].

2.2.2 3-lead Schiller medilog® AR4plus Holter ECG

The 3-lead Schiller medilog® AR4plus Holter ECG s a 20-minute resting ECG with high resolution (1kHz), recorded in Frank leads configuration (Medilog AR4plus, Schiller AG, Bar, Switzerland)[33]. A standardized protocol was followed for the recordings done on study participants in supine position. If the recordings were not done by the study core lab itself, but in an external centre, raw data of the ECGs were sent to the trial core lab at LMU University Hospital in Munich, Germany. There, the staff of the core lab, blinded, processed the raw data for computation of digital biomarkers with the help of a specially developed, open-source software (SMARTlab 1.5). Cardiac autonomic function was then assessed by determining two specific and complementary digital biomarkers, namely DC and PRD, as described previously[33].

2.2.3 Implantable cardiac monitor

Study participants in the intervention group were according to protocol planned to receive a Communauté Européenne (CE)-marked implantable cardiac monitor (ICM) which is commercially available (Reveal LINQ, Medtronic Minneapolis, MN, USA)[32,33]. Hundred seventy-six patients in this group received such a device. One patient received a Reveal XT monitor (n=1), other patients refused to get a device implanted (n = 21), one patient died before the implantation (n=2) and another one received a pacemaker (n=1) [33]. The device was implanted subcutaneously around the heart, following local standard operating procedures, and using local anaesthesia[32,33]. The ICM was deployed with standard settings and was connected to the Medtronic CareLink Network by enabling the telemonitoring function of the device[33]. Standard settings of the ICM include arrythmia detection parameters, such as 'AF management', which has been used here as monitoring rationale, just as recommended in the operating manual[32]. In that sense, the ICM was capable to detect and record automatically arrythmias of the heart, it basically works like a long-term ECG monitor[32]. On daily basis, the collected device data were conveyed telemetrically to the ICM core lab at the LMU university hospital in Munich, Germany and double-checked by an experienced study physician on the same day[32,33]. If a finding of the ICM was confirmed to be true and met the predefined criteria of a study endpoint (see below), the local study team was contacted via telephone or email within 48 hours[32]. Treatment decisions were then made at the local study centres at discretion of the responsible local treating physicians in line with current guideline recommendations[32,33]. The details of the treatment decision, as well as the initial ICM findings, were all meticulously documented by both the study core lab and local study centre combined in the eCRF (secutrial ®)[33]. It is important to mention that Medtronic, whilst covering the expenses for the ICM devices, staff and related telemonitoring, they were not involved in any scientific matter such as the design of the study, the data collection, the statistical analysis, or the writing of reports[32].

2.3 Parameters used in the SMART-MI Trial

2.3.1 Demographic parameters

Data concerning standard demographic parameters were collected such as age, sex, height, and weight, race, as well as cardiovascular risk factors[33]. The latter included diabetes mellitus, use of insulin for diabetes mellitus, current smoking status, arterial hypertension, hypercholesterinaemia, CHA_2DS_2-VASc and CHA_2DS_2-VASc ≥ 3[33]. The CHA_2DS_2-VASc comprises several

parameters, mainly risk factors for stroke (C: congestive heart failure, H: hypertension, A: age of ≥75 years, D: diabetes mellitus, S: previous stroke, V: vascular disease, A: age 65-74 years, Sc: female gender) and is used as a common risk assessment tool to assess the risk for stroke in patients with atrial fibrillation[56]. A thorough examination of the medical history of the patient encompassed history of previous MI, renal dysfunction, peripheral artery disease, history of stroke and chronic obstructive pulmonary disease (COPD)[33].

2.3.2 Clinical parameters

Clinical parameters included blood pressure, heart rate (beats/min), index MI (STEMI or NSTEMI), Killip class ≥ II, culprit lesion (LAD, RCA, other) and included 12-lead ECG parameters[33]. Information about treatment was acquired and entailed PCI, Aspirin, Clopidogrel, Prasugrel, Ticagrelor, betablocker, renin-angiotensin system (RAS) inhibition, mineralocorticoid receptor antagonists (MRA), loop diuretics, Thiazide diuretics and statins[33]. Cardiac autonomic function (DC, PRD) was determined by biosignal analysis as listed separately below.

2.3.3 Echocardiographic parameters

The main echocardiographic parameter of interest in this research was LVEF, one of the main in- and exclusion criteria of the SMART-MI Trial[33].

2.3.4 Laboratory values

There were no trial-specific blood samples taken[32]. Notwithstanding, basic standard laboratory blood tests were screened, with a special focus on the following parameters: white blood cell counts, haemoglobin, haematocrit, platelet count, serum creatinine (mg/dl), electrolytes, activated partial thromboplastin time, international normalized ration, troponin-T or troponin-I and CK and its MB fraction[32]. For some study participants in selected study centres, a blood sample for biobanking is collected, following specific informed consent of the patient[32]. More specifically, CK-MB may give signal to cardiac damage and served mostly in this trial as an indicator, for once the values had normalized, LVEF and the biomarkers DC and PRD could be determined[32]. Whereas troponin-T or/and -I, particularly specific and sensitive markers for cardiac myocytes, serve as highly reliable indicators for cardiac damage, namely acute coronary syndrome[57]. Hence, those markers permit to diagnose or exclude STEMI or/and NSTEMI in combination with the findings from a 12-lead ECG[57].

2.3.5 Biosignal analysis

PRD is a biomarker that quantifies low frequency (<0.1Hz) oscillations of cardiac repolarization, linked to sympathetic innervation of the heart and has been described previously in detail by Rizas et al. (2014)[43]. The assessment of PRD is illustrated in Figure 1. To calculate PRD, four distinct steps need to be performed which are stated in Bauer et al. 2022 as follows:

> *'(1) Frank-leads are converted to a set of polar coordinates defined by azimuth and elevation, and the amplitude; (2) T-wave vectors (T°) are constructed for all T waves, representing the spatiotemporal characteristics of each cardiac repolarization; (3) instantaneous repolarization instability is estimated by the angle dT°, defined by the scalar product of two successive repolarization vectors T°; (4) periodic repolarisation dynamics is calculated as the average wavelet coefficient corresponding to frequencies of 0.1 Hz or lower after applying continuous wavelet transformation on the dT°- signal.'* [33] *(p.e107)*

PRD is considered abnormal if ≥5.75deg^2 [43].

DC is a biomarker that measures integrally all deceleration-related oscillations of heart rate, presumably linked to the parasympathetic activities of the heart[42]. An illustration of the assessment of DC can be found below in Figure 2. For DC computation, the sequence of beat-to-beat (R-R) intervals is transformed into a new time series by phase-rectified signal averaging (PRSA)[33,42]. This preserves periodic components, but eliminates non-periodic components such as noise, non-stationarities, or artifacts[42]. The calculation is based on three steps and is described in Bauer et al. (2022) as follows:

> *'(1) intervals between successive heartbeat intervals (RR intervals) are identified; (2) segments around anchors are averaged to obtain the so-called phase-rectified signal; (3) the central part of the phase-rectified signal averaging signal is quantified by wavelet-analysis.'* [44] *(p.e107)*

DC is considered abnormal if ≤ 2.5ms[44].

A patient is diagnosed with cardiac autonomic dysfunction if at least one of both biomarkers is abnormal[33].

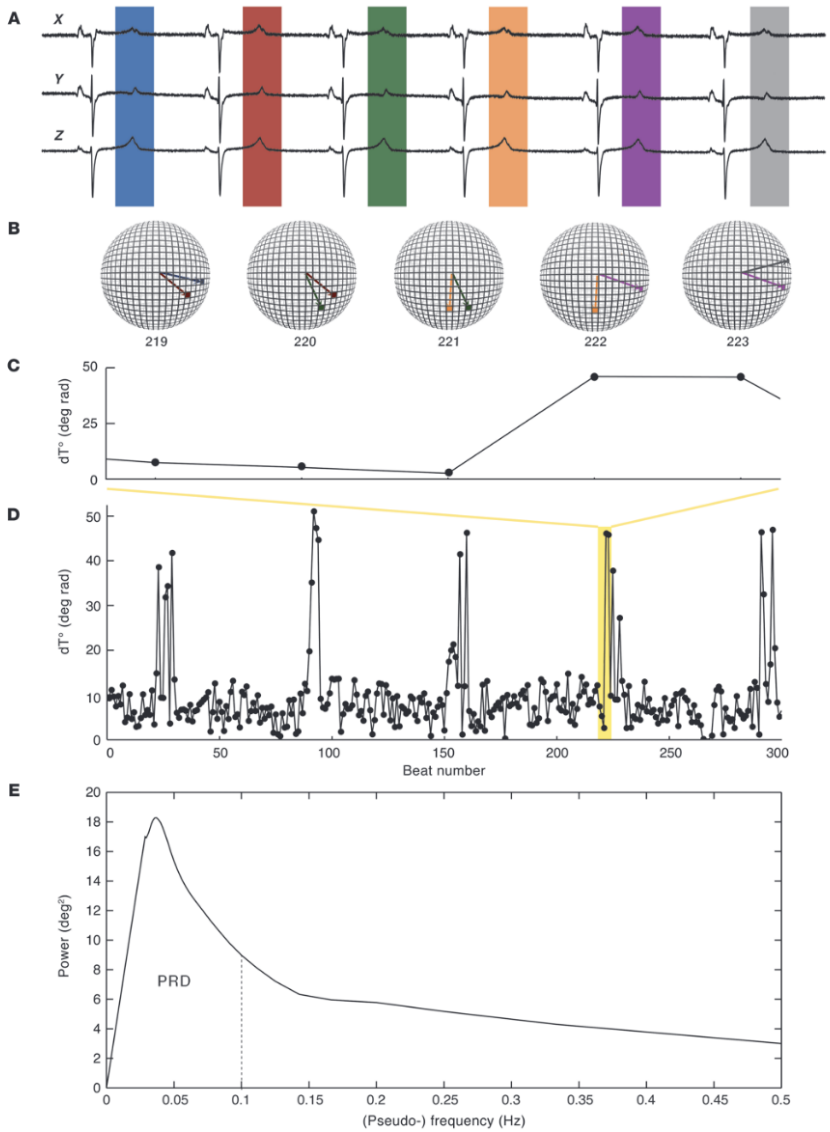
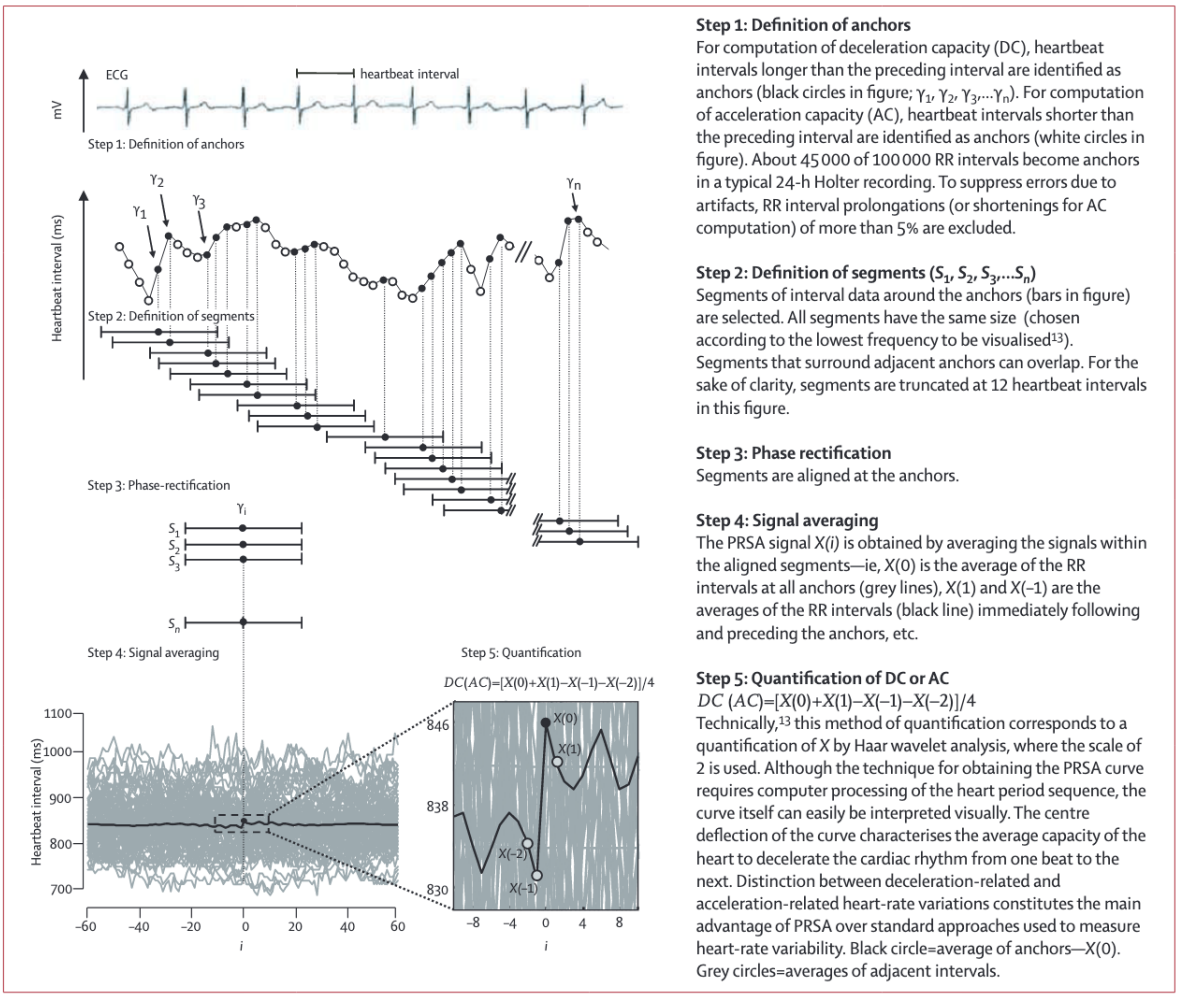


Figure 1. **Assessment of Periodic Repolarization Dynamics (PRD)**[43] Figure description as in Rizas et al. 2014: '(A) Illustration of the weight-averaged vector of repolarization (T°) for each T-wave from surface ECG recorded in the Frank leads configuration. (B) Three-dimensional visualization of successive T° vectors projected into virtual spheres. The angle dT° between successive repolarization vectors was used as an estimate of instantaneous repolarization instability. (C and D) The dT° signal exhibits characteristic low-frequency oscillations. C shows dT° values for beats #219-223, corresponding to the spheres in B. (E) Quantification of PRD using wavelet analysis. PRD was defined as the average wavelet coefficient corresponding to frequencies of 0.1 Hz or less.'[43] Figure © 2023 American Society for Clinical Investigation. Permission granted.



Step 1: Definition of anchors
For computation of deceleration capacity (DC), heartbeat intervals longer than the preceding interval are identified as anchors (black circles in figure; γ_1, γ_2, γ_3,...γ_n). For computation of acceleration capacity (AC), heartbeat intervals shorter than the preceding interval are identified as anchors (white circles in figure). About 45 000 of 100 000 RR intervals become anchors in a typical 24-h Holter recording. To suppress errors due to artifacts, RR interval prolongations (or shortenings for AC computation) of more than 5% are excluded.

Step 2: Definition of segments (S_1, S_2, S_3,...S_n)
Segments of interval data around the anchors (bars in figure) are selected. All segments have the same size (chosen according to the lowest frequency to be visualised[13]). Segments that surround adjacent anchors can overlap. For the sake of clarity, segments are truncated at 12 heartbeat intervals in this figure.

Step 3: Phase rectification
Segments are aligned at the anchors.

Step 4: Signal averaging
The PRSA signal *X(i)* is obtained by averaging the signals within the aligned segments—ie, X(0) is the average of the RR intervals at all anchors (grey lines), X(1) and X(–1) are the averages of the RR intervals (black line) immediately following and preceding the anchors, etc.

Step 5: Quantification of DC or AC
$DC\ (AC)=[X(0)+X(1)-X(-1)-X(-2)]/4$
Technically,[13] this method of quantification corresponds to a quantification of X by Haar wavelet analysis, where the scale of 2 is used. Although the technique for obtaining the PRSA curve requires computer processing of the heart period sequence, the curve itself can easily be interpreted visually. The centre deflection of the curve characterises the average capacity of the heart to decelerate the cardiac rhythm from one beat to the next. Distinction between deceleration-related and acceleration-related heart-rate variations constitutes the main advantage of PRSA over standard approaches used to measure heart-rate variability. Black circle=average of anchors—X(0). Grey circles=averages of adjacent intervals.

***Figure 2*. Assessment of Deceleration Capacity (DC)**[42] As described by Bauer et al. 2006 'by PRSA in a 24-h recording of heartbeat intervals; i=index of PRSA signal X(i)' [42]. Figure © 2006 Elsevier Ltd. Permission granted.

2.4 Endpoints of the dissertation

In the original SMART-MI publication only patients with cardiac autonomic dysfunction (N = 400) have been presented[33]. In this post-hoc analysis we included the entire screened population (N = 1,305) and we defined following endpoints:

- presence of cardiac autonomic dysfunction, defined by abnormal DC and/or PRD (at baseline);
- risk of death (within 3 years after index MI).

2.5 Statistical analysis

Before conducting the statistical analyses, several variables of the dataset underwent unit conversions. Among those were the variables for HbA1c (transformation of mmol/mol into % ((/10.929) +2.15), cholesterol (transformation of mmol/l into mg/dl (*38.67)), creatinine (transformation of µmol/l=nmol/ml into mg/dl (*0.0113)), hemoglobin (transformation of nmol/l into g/dl (*1.6113)) and LDH (transform µkatal/L into U/l (*60)). As part of this dataset preparation was also the transformation of some string or continuous variables into categorical or dichotomous variables. Among those variables were autonomic dysfunction, sex, age, heart failure, diabetes, family history and smoking.

Upon readiness of the final dataset, the calculation of the baseline characteristics was the first step in the statistical analyses of this dissertation. Continuous data are shown as medians with interquartile ranges (IQRs) and tested on difference by using the Wilcoxon test. Categorical data are summarized in frequencies and proportions (n/N) and the chi-square ($\chi 2$) test was used for the comparative analysis. Histograms were created to summarize and display continuous data of essential variables in these analyses. Shapiro-Wilk normality tests were performed for the variables for which histograms were displayed. Following this, the correlations between selected variables were analyzed using Pearson correlation testing (alpha = 0.05), and the data are presented as correlation coefficients and p-values in a table and a corresponding correlation plot. The guidelines of Cohen (1988) were used to interpret the magnitude of a correlation[58]. Univariate logistic regression was then used to estimate the probability of autonomic dysfunction and predictive relationship between the selected variables. Multivariate logistic regression followed then for all the predictor variables where the association's p-value was <0.1 Data are displayed as odds ratios with 95% confidence interval (95% CI) and p-value in a table.

Time-to-event methods were used to analyze the outcome (death). Cox regression analyses were performed to investigate the effect of several predictor variables on death as outcome. Data are summarized in a table presenting hazard ratios with 95% CI. Kaplan Meier curves were created to display the probability of surviving in a given length of time under the influence of several predictor variables. All statistical analyses in this thesis were conducted with the use of CRAN R (version 4.2.2).

3. Results

3.1 Study population characteristics

Study participants were recruited between May 12, 2016, and July 20, 2020. Of the 1305 recruited patients who were subjected to risk-stratification, 400 patients were categorized as high-risk patients with autonomic dysfunction and were randomized 1:1 for the continuation of the study, as intention-to-treat group. The resting 905 patients were classified as low risk and entered a registry as they presented a normal autonomic function. The characteristics at baseline of all study participants are presented in Table 4. PRD and DC present naturally significant differences in both groups, namely for PRD 2.05 [1.28, 3.13] in the normal autonomic function (NAF) group and 6.46 [3.42, 9.30] in the autonomic dysfunction (AD) group (p-value < 0.001) and for DC 5.46 [4.06, 7.65] in the NAF group and 1.90 [0.36, 2.80] in the AD group (p-value < 0.001).

More significant differences have been found in participant age, as the participants are slightly older in the AD group (64 years, [57.00, 73.00]) than in the NAF group (58 years, [51.00, 65.00]) (p-value < 0.001). Significant differences have been found also in participant's height (176 cm [170.00, 181.00] in the NAF group and 175 cm [170.00, 180.00] in the AD group, p-value $= 0.009$) and BMI (26.88 [24.62, 30.04] in the NAF group and 27.78 [24.74, 30.78] in the AD group, p-value $= 0.022$).

As far as the cardiovascular risk factors are concerned, diabetes, where almost double the proportion of diabetics can be found in AD group (29.8%) when compared to the NAF group (18.1%) (p-value < 0.001) has shown significant differences between the groups. Similarly for arterial hypertension, where more people with this condition appear in the AD group (71.5%) than in the NAF group (59.6%) (p-value $= 0.001$). More smokers can though be found in the NAF group (51.2%) than in the AD group (31.5%) (p-value < 0.001). More people from the AD group (125.00 [111.00, 138.75]) present higher SAP than in the NAF group (120.00 [110.00, 134.00], p-value $= 0.007$).

Within the frame of the medical history of the study participants, more patients with a history of renal dysfunction are shown in the AD group (10.8%) than in the NAF group (4.5%) (p-value < 0.001). In the AD group, more participants appear to have peripheral artery disease

(PAD) (5.2% vs. 1.9%, p-value = 0.004) and a history of stroke (5.0% vs. 2.3%, p-value = 0.012) than in the NAF group. Lower heart rate values occur in the NAF group (70.00 [64.00, 80.00] than in the AD group (74.00 [66.00, 83.00] p-value < 0.001) and LVEF is slightly higher in the NAF group (46.00 [44.00, 49.00] than in the AD group (45.00 [40.00, 48.00], p-value < 0.001). As far as the laboratory parameters are concerned, significant differences have been found in creatinine (0.99 [0.82, 1.19] in the NAF group and 1.02 [0.90, 1.25] in the AD group, p-value < 0.001); cholesterol (189.50 [154.68, 221.25] in the NAF group and 178.00 [143.00, 210.00] in the AD group, p-value = 0.001), hemoglobin (14.10 [12.90, 15.10] in the NAF group and 13.70 [12.40, 14.90] in the AD group, p-value = 0.003) and HbA1c (5.63 [5.40, 6.00] in the NAF group and 5.90 [5.60, 6.70] in the AD group, p-value < 0.001).

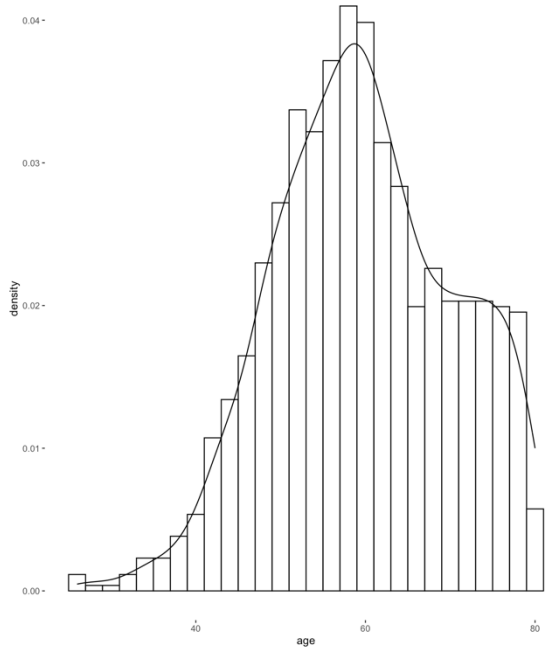
Table 4. **Baseline characteristics of the study population**			
	Normal autonomic function* (NAF) (n=905)	**Autonomic dysfunction*(AD) (n=400)**	**p-value**
Age, years	58.00 [51.00, 65.00]	64.00 [57.00, 73.00]	<0.001
Sex			0.159
Male	759 (83.9%)	322 (80.5%)	
Female	146 (16.2%)	78 (19.5%)	
Height, cm	176.00 [170.00, 181.00]	175.00 [170.00, 180.00]	0.009
Weight, kg	85.00 [75.00, 95.00]	85.00 [75.00, 96.00]	0.499
Caucasian	875 (96.7%)	389 (97.2%)	0.236
Cardiovascular risk factors			
Diabetes	164 (18.1%)	119 (29.8%)	<0.001
Current smoker	463 (51.2%)	126 (31.5%)	<0.001
Arterial hypertension	539 (59.6%)	286 (71.5%)	0.001
Systolic arterial pressure (SAP), mmHg	120.00 [110.00, 134.00]	125.00 [111.00, 138.75]	0.007
Diastolic arterial pressure (DAP), mmHg	75.00 [67.75, 81.00]	75.00 [66.00, 81.00]	0.907
Hypercholesterinemia	457 (50.5%)	198 (49.5%)	0.955
Medical history			
Renal dysfunction	41 (4.5%)	43 (10.8%)	<0.001
Peripheral artery disease (PAD)	17 (1.9%)	21 (5.2%)	0.004
History of stroke	21 (2.3%)	20 (5.0%)	0.012
Chronic obstructive pulmonary disease	43 (4.8%)	29 (7.2%)	0.112
Heart rate, beats per minute	70.00 [64.00, 80.00]	74.00 [66.00, 83.00]	<0.001
Body-mass index, kg/m^2	26.88 [24.62, 30.04]	27.78 [24.74, 30.78]	0.022
Laboratory parameters			
Creatine Kinase (CK) total, U/l	940.50 [302.25, 2332.00]	955.50 [280.90, 2488.75]	0.908
Creatine Kinase (CK) max., U/l	109.00 [42.25, 259.60]	119.40 [43.00, 278.00]	0.522
Creatinine, mg/dl	0.99 [0.82, 1.19]	1.02 [0.90, 1.25]	<0.001

Lactate dehydrogenase (LDH), U/l	348.00 [243.00, 567.00]	370.00 [258.00, 605.50]	0.186
Cholesterol, mg/dl	189.50 [154.68, 221.25]	178.00 [143.00, 210.00]	0.001
Leucocytes, G/l	10.20 [8.27, 12.58]	10.30 [8.18, 13.00]	0.920
Hemoglobin, g/dl	14.10 [12.90, 15.10]	13.70 [12.40, 14.90]	0.003
Glycated hemoglobin (HbA1c), %	5.63 [5.40, 6.00]	5.90 [5.60, 6.70]	<0.001
Left ventricular ejection fraction, %*	46.00 [44.00, 49.00]	45.00 [40.00, 48.00]	<0.001
Cardiac autonomic dysfunction			
Periodic repolarization dynamics (PRD), deg^2	2.05 [1.28, 3.13]	6.46 [3.42, 9.30]	<0.001
Deceleration capacity (DC), ms	5.64 [4.06, 7.65]	1.90 [0.36, 2.80]	<0.001

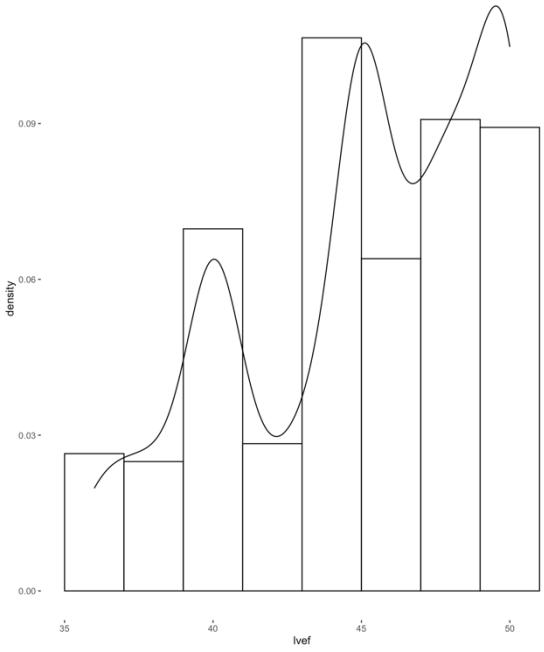
Data are median (IQR) or n/N (%).

*Normal autonomic function (NAF) = normal DC and PRD; Autonomic dysfunction (AD) = abnormal DC and/or PRD.
**Assessed by echocardiography in all patients.

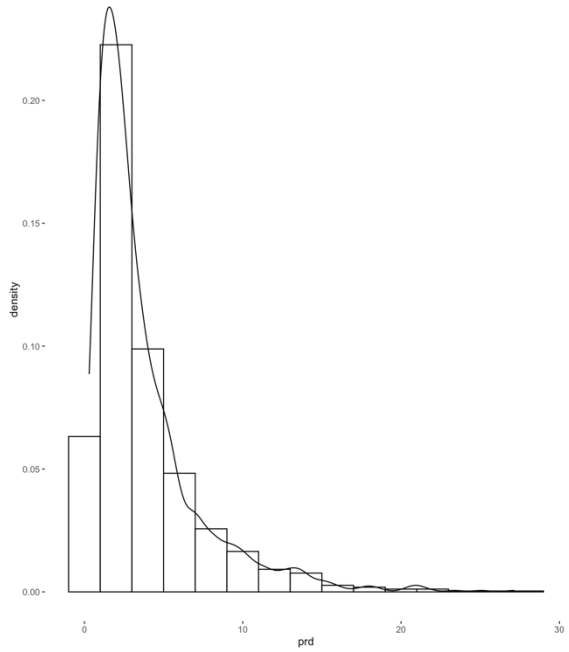
Figure 3 displays the distribution of the selected variables in histograms. The age is evenly distributed over the study population and includes a predominantly elderly population with most people being around 60 years old. Furthermore, more people with a LVEF above 45% have been included than below 45%, which reflects the study design. Both PRD and DC have their clear peaks with some outliers, with most people having a PRD and a DC between 2-5 deg^2 or ms respectively. Based on the Shapiro-Wilk normality test, none of the variables displayed in the histograms presented a normal distribution.



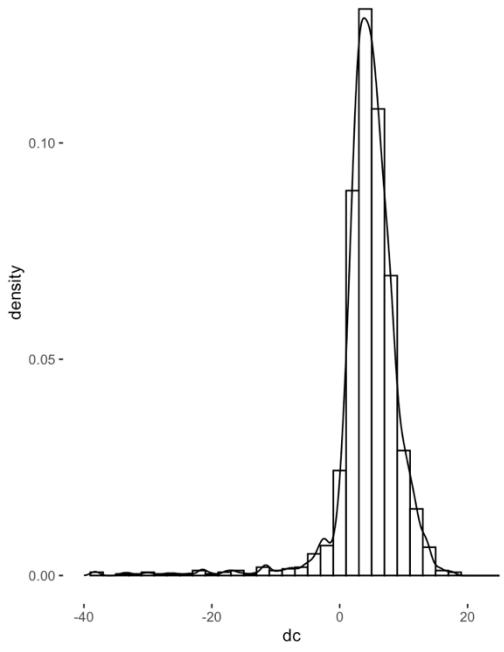
Age, years



Left ventricular ejection fraction, %



Periodic repolarization dynamics (PRD), deg^2



Deceleration capacity (DC), ms

Figure 3. **Histograms.**

The line represents the respective mean values.

3.2 Correlation

Several significant positive or negative correlations result from the correlation analysis (Table 5, Figure 4). Selected modifiable and unmodifiable risk factors correlate with either HR, SAP, DAP, PRD and/or DC. The magnitude of the correlations is interpreted according to the guidelines of Cohen (1998), who classify r = 0.10 as small, r = 0.30 as medium and r = 0.50 as large in magnitude[58]. In these analyses, all significant correlations are small in magnitude or even completely negligible (r < 0.10). Significantly positively correlated with HR are CK total (r=0.10, [p-value<0.001]), CK max (r=0.11, [p-value<0.001]) and HbA1c (r=0.10, [p-value=0.004]). Significantly negatively correlated with HR are height (r=-0.07, [0.019]), creatinine (r=-0.08, [p-value=0.006]), hemoglobin (r=-0.07, [p-value=0.010] and LVEF (r=-0.15, [p-value<0.001]), whereas LVEF is the only relevant correlation in this list. Then, significant positive correlations with SAP are age (r=0.16, [p-value<0.001]), weight (r=0.10, [p-value<0.001]), hemoglobin (r=0.08, [p-value=0.007]) and cholesterol (r=0.06, [p-value=0.045]), with the latter two being negligible correlations. Whereas two risk factors are significantly negatively correlated with SAP, namely CK total (r=-0.15, [p-value<0.001]) and CK max (r=-0.14, [p-value<0.001]). Similarly, to the correlations of SAP, are those from DAP. Positive and significant correlations with DAP are weight (r=0.15 [p-value<0.001]), hemoglobin (r=0.15 [p-value<0.001]) and cholesterol (r=0.07, [p-value=0.021]), the latter being negligible. Significantly negatively correlated with DAP are age (r=-0.07 [p-value=0.016]) and CK total (r=-0.07, [p-value=0.009]), but both are not relevant in magnitude. As far as the biosignal PRD is concerned, significant positive correlations can be found with age (r=0.18, p-value<0.001) and HbA1c (r=0.10, [p-value=0.003]). Significantly negatively correlated with PRD are cholesterol (r=-0.11, [p-value<0.001]) and LVEF (r=-0.13, [p-value<0.001]). Lastly, three risk factors have been found to be significantly positively correlated with DC, namely hemoglobin (r=0.07, [p-value=0.009]), cholesterol (r=0.08, [p-value=0.013]) and LVEF (r=0.13, [p-value<0.001]), the latter being the only relevant correlation. Significant negative correlations with DC have been found with age (r=-0.26, [p-value<0.001]), which almost presents a correlation of medium magnitude and HbA1c (r=-0.09, [p-value=0.005]), which is negligible.

Table 5. **Correlation Table**

	Heart rate (HR)	Systolic arterial pressure (SAP)	Diastolic arterial pressure (DAP)	Periodic repolarization dynamics (PRD)	Deceleration capacity (DC)
Age, years	<-0.01 (0.985)	**0.16 (< 0.001)**	**-0.07 (0.016)**	**0.18 (< 0.001)**	**-0.26 (< 0.001)**
Weight, kg	0.04 (0.179)	**0.10 (<0.001)**	**0.15 (< 0.001)**	0.001 (0.971)	0.01 (0.597)
Height, cm	**-0.07 (0.019)**	-0.02 (0.525)	0.05 (0.053)	-0.50 (0.091)	0.03 (0.360)
Creatine Kinase (CK) total, U/l	**0.10 (<0.001)**	**-0.15 (<0.001)**	**-0.07 (0.009)**	0.01 (0.710)	-0.01 (0.736)
Creatine Kinase (CK) max., U/l	**0.11 (<0.001)**	**-0.14 (<0.001)**	-0.056 (0.101)	0.03 (0.433)	0.02 (0.649)
Lactate dehydrogenase (LDH)	0.02 (0.453)	-0.01 (0.701)	-0.01 (0.684)	0.06 (0.058)	-0.01 (0.649)
Creatinine, mg/dl	**-0.08 (0.006)**	0.02 (0.461)	0.03 (0.260)	0.04 (0.192)	0.02 (0.447)
Hemoglobin, g/dl	**-0.07 (0.010)**	**0.08 (0.007)**	**0.15 (<0.001)**	-0.04 (0.144)	**0.07 (0.009)**
Cholesterol, mg/dl	-0.04 (0.232)	**0.06 (0.045)**	**0.07 (0.021)**	**-0.11 (<0.001)**	**0.08 (0.013)**
Glycated hemoglobin (HbA1c), %	**0.10 (0.004)**	0.05 (0.149)	0.02 (0.471)	**0.10 (0.003)**	**-0.09 (0.005)**
Leucocytes, G/l	0.056 (0.051)	-0.05 (0.105)	-0.02 (0.503)	0.01 (0.820)	0.03 (0.251)
Left ventricular ejection fraction, %*	**-0.15 (<0.001)**	0.05 (0.108)	0.01 (0.640)	**-0.13 (<0.001)**	**0.13 (<0.001)**

Data are correlation coefficients (r) and p-values.
*Assessed by echocardiography in all patients.

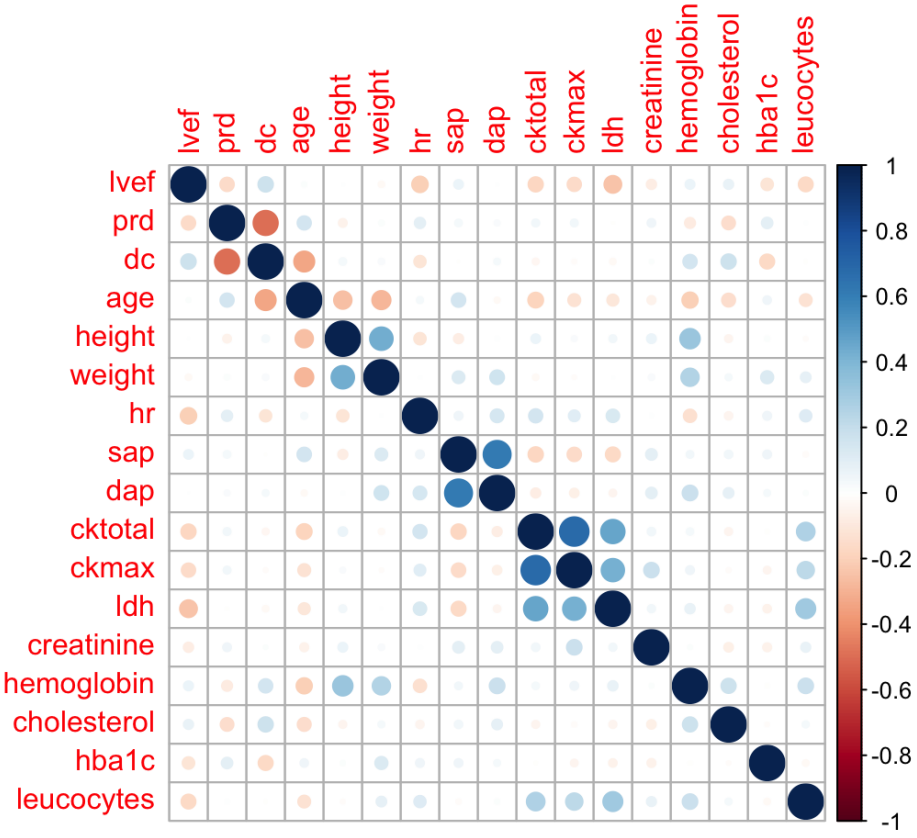


Figure 4. **Correlation plot**

lvef = left-ventricular ejection fraction, prd = periodic repolarization dynamics, dc = deceleration capacity, hr = heart rate, sap = systolic arterial pressure, dap = diastolic arterial pressure, ck total = creatine kinase total, ck max = creatine kinase maximum, ldh = lactate dehydrogenase, hba1c = glycated hemoglobin.

3.3 Logistic Regression

Several statistically significant associations have been identified between modifiable and un-modifiable variables and the endpoint autonomic dysfunction in the univariate logistic regression, with the cut-off for the statistical significance at a p-value of <0.05 (Table 6). Among those associations are age (Odds ratio (OR) 1.06 [1.05-1.07], p-value < 0.001), height (OR 0.98 [0.99-1.01], p-value = 0.012), cholesterol (OR 1 [0.99-1], p-value < 0.001), HbA1c (OR 1.23 [1.11-1.37], p-value < 0.001), LVEF (OR 0.92 [0.89-0.95], p-value < 0.001). Hemoglobin (OR 0.96 [0.91-1], p-value = 0.051) presents an OR on the edge of statistical significance and creatinine (OR 1.2 [0.99 – 1.45], p-value = 0.065) is not statistically significant but both variables have been included in the multivariable logistic regression which encompasses all variables

with a p-value under 0.1 in the univariate logistic regression. In the multivariate logistic regression, age (OR 1.06 [1.04 – 1.08], p-value < 0.001), HbA1c (OR 1.19 [1.06 – 1.33], p-value = 0.002) and LVEF (OR 0.90 [0.87 – 0.94]), p-value < 0.001) have been proven significant predictors.

Table 6. **Univariate and Multivariate Logistic Regression**

	AUTONOMIC DYSFUNCTION			
	Univariable Logistic Regression		**Multivariable Logistic Regression**	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age, per year	**1.06 (1.05 – 1.07)**	**< 0.001**	**1.06 (1.04 – 1.08)**	**< 0.001**
Sex	1.26 (0.93 – 1.70)	0.137		
Weight, kg	1 (0.99 – 1.01)	0.798		
Height, cm	**0.98 (0.97 – 1)**	**0.012**	1 (0.98 – 1.02)	0.931
Creatine Kinase (CK) total, U/l	1 (1 – 1)	0.980		
Creatine Kinase (CK) max., U/l	1 (1 – 1)	0.468		
Lactate dehydrogenase (LDH), U/l	1 (1 – 1)	0.250		
Creatinine, mg/dl	1.2 (0.99 – 1.45)	0.065	1.17 (0.75 – 1.82)	0.488
Hemoglobin, g/dl	0.96 (0.91 – 1)	0.051	1 (0.92 – 1.07)	0.902
Cholesterol, mg/dl	**1 (0.99 – 1)**	**<0.001**	1 (0.99 – 1)	0.067
Glycated hemoglobin (HbA1c), %	**1.23 (1.11 – 1.37)**	**<0.001**	**1.19 (1.06 – 1.33)**	**0.002**
Leucocytes, G/l	1 (0.98 – 1.02)	0.900		
Left ventricular ejection fraction, %*	**0.92 (0.89 – 0.95)**	**<0.001**	**0.90 (0.87 – 0.94)**	**< 0.001**

*Assessed by echocardiography in all patients.

Autonomic dysfunction as endpoint.

3.4 Univariate Cox Regression

The results of the Univariate Cox Regression are displayed in Table 7. The endpoint in these analyses is death. The influence of autonomic dysfunction (HR 2.68 [1.39-5.18], p-value = 0.003), as well as PRD (HR 1.07 [1.1-1.15], p-value = 0.049) and DC respectively (HR 0.98 [0.96-1], p-value = 0.014) on death as outcome have been proven significant. Next to those variables, age (HR 1.07 [1.04-1.11], p-value < 0.001), hemoglobin (HR 0.80 [0.70-0-91], p-value < 0.001), cholesterol (HR 0.99 [0.98-1], p-value = 0.039), heart rate (HR 1.03 [1.01 – 1.05], p-value = 0.034) and diabetes (HR 2.68 [1.38 – 5.19], p-value = 0.004) show significant associations.

Table 7. **Cox Regression**

	M O R T A L I T Y **Univariate Cox Regression**	
	Hazard ratio (95% CI)	p-value
Autonomic dysfunction	**2.68 (1.39 – 5.18)**	**0.003**
Age, per year	**1.07 (1.04 – 1.11)**	**<0.001**
Sex	1.16 (0.51 – 2.66)	0.720
Periodic repolarization dynamics (PRD), deg^2	**1.07 (1 – 1.15)**	**0.049**
Deceleration capacity (DC), ms	**0.98 (0.96 – 1)**	**0.014**
Weight, kg	0.99 (0.97 – 1.01)	0.441
Height, cm	0.99 (0.95 – 1.03)	0.614
Creatine Kinase (CK) total, U/l	1 (1 – 1)	0.371
Creatine Kinase (CK) max., U/l	1 (1 – 1)	0.566
Lactate dehydrogenase (LDH), U/l	1 (1 – 1)	0.705
Creatinine, mg/dl	1 (0.99 – 1.01)	0.720
Hemoglobin, g/dl	**0.80 (0.70 – 0.91)**	**<0.001**
Cholesterol, mg/dl	**0.99 (0.98 – 1)**	**0.039**
Glycated hemoglobin (HbA1c), %	1.13 (0.99 – 1.28)	0.067
Leucocytes, G/l	0.99 (0.93 – 1.06)	0.741
Left ventricular ejection fraction, %*	0.95 (0.88 – 1.03)	0.221

Heart rate, beats per minute	**1.03 (1.01 – 1.05)**	**0.034**
Systolic arterial pressure (SAP), mmHg	1 (0.98 – 1.02)	0.909
Diastolic arterial pressure (DAP), mmHg	0.97 (0.95 – 1.01)	0.068
Diabetes	**2.68 (1.38 – 5.19)**	**0.004**
Heart failure	1.67 (0.84 – 3.30)	0.142
Family history	1.12 (0.55 – 2.31)	0.754
Smoking	0.78 (0.50 – 1.23)	0.282

* Autonomic dysfunction = abnormal DC and/or PRD.
**Assessed by echocardiography in all patients.

The endpoint is 3-year mortality.

Figure 5 displays the survival curves for selected variables. Among those, as already seen in Table 7, autonomic dysfunction, diabetes and age present significant associations and differences between the groups of AD and NAF.

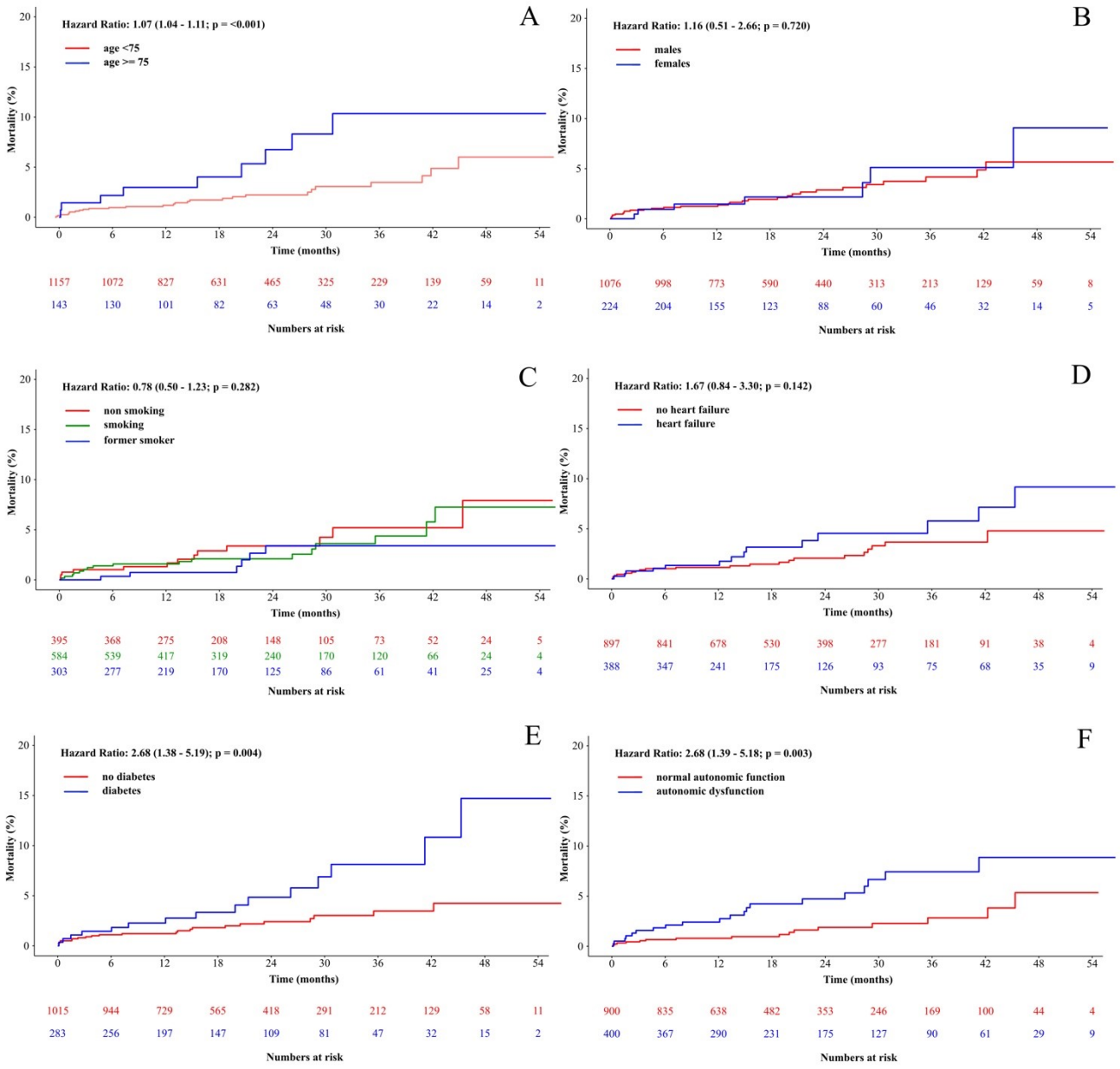


Figure 5. Survival curves

(A) age. (B) gender. (C) smoking. (D) heart failure. (E) diabetes. (F) autonomic dysfunction (abnormal DC and/or PRD). Hazard Ratios and p-values bear on the complete follow-up period.

4. Discussion

4.1 Summary of key findings

This dissertation is the first epidemiological analysis of autonomic function in postinfarction patients with sinus rhythm and preserved LVEF, investigating essential underlying epidemiological aspects of this patient collective. It is the first time, that the influence of modifiable and unmodifiable risk factors on the function of the ANS and the probability of cardiac AD has been investigated. Also, it is the unprecedented mortality analysis encompassing the complete study population of the SMART-MI trial.

As far as the population characteristics at baseline are concerned, the patients in the AD group are on average 6 years older than in the NAF group and tend to have a higher BMI, both in the overweight range. Cardiovascular risk factors like diabetes and arterial hypertension are considerably more prominent in the AD group, with up to a third of the people in the AD group being diabetic. More smokers can though be found in the NAF group with half the NAF group being smokers. As far as the patient history is concerned, twice as many people in the AD group list renal dysfunction and PAD than in the NAF group. However, a history of stroke is more prominent in the NAF group. Laboratory values don't show major significant differences except that cholesterol values are more elevated in the NAF group and HbA1c is on average only 0.3% higher in the AD group.

The fact whether selected risk factors are related to either HR, SAP, DAP, DC, or PRD, is reflected in the correlation analysis. The data suggest no moderate or high correlation between the selected variables. Noteworthy may be a negligible correlation between age, and DC (negative correlation) and PRD (positive correlation) respectively.

To identify the effect of selected risk factors on the ANS and probability for the development of AD, univariate and multivariate logistic regression analyses were performed on several modifiable and unmodifiable risk factors. In the univariate logistic regression, age, height, cholesterol HbA1c and LVEF were significantly associated with developing AD. However, after the multivariate logistic regression analysis, only three of those risk factors remained as significant predictors for AD. First, HbA1c, which has been identified as a novel and important significant predictor variable. A higher HbA1c value is shown to increase the odds for developing AD by almost 20%. Second is age, which is also considered as significant predictor variable. With increasing age, the probability for developing AD raises by 6% per year. Third, LVEF, which

appears to provide a negative predicting effect for autonomic dysfunction. A higher LVEF (closer to normal) lowers the risk for AD by 10%.

Four risk factors were significantly associated with all-cause mortality. First, AD is shown as powerful significant predictor variable of death. Patients with AD have 2.7 times higher risk of death within 3 years after myocardial infarction than patients with normal autonomic function. Second and similarly interesting is diabetes, which appears to multiply the risk of death by 2.7 times as well. The third predictor is age, which naturally increases the mortality risk by 7% per year. Fourth, haemoglobin, which stands out on the contrary as a negative predictor variable, reducing the risk of death at any time point by 20% with increasing number in haemoglobin count. Other risk factors show also significant predicting qualities, but with a low to negligible effect. Those are cholesterol (1% risk reduction) and heart rate (3% risk enhancement). DC and PRD alone also only showed weak predicting characteristics when analysed separately. DC reduces the risk of death by 2% per 1ms increase, and PRD increases the risk of death by 7% per 1 deg^2 increase.

4.2 Research in context

In the analyses of this thesis, we found a correlation of age with DC ($r = -0.26$; p-value < 0.001) and PRD ($r = 0.18$; p-value < 0.001). Zhao et al. investigated in their Chinese study population of healthy individuals the relationship of DC and HRV and explored the opportunities of risk stratification based on DC in different age groups[59]. They found that DC decreases with age in healthy individuals, and that DC was particularly low in people above the age of 50, as compared to people below that age[59]. A negative correlation was apparent with increasing age ($r=-0.312$, p-value ≤ 0.05)[59], similar to the findings in this dissertation, whereas it is worth bearing in mind that the study populations differ, healthy individuals as compared to postinfarction patients in these analyses. Hence a study from Poland, which included patients similar to the SMART-MI population, namely postinfarction patients, more specifically, patients surviving their first STEMI[60]. Nevertheless, they found a significant correlation between age and DC similar to Zhao et al. and the results from this dissertation, namely a negative correlation of $r = -0.31$ ($p = 0.011$), meaning patients at increased age (above 65 years) presented considerably lower DC values than younger patients (median DC 4.07 vs. 5.65 ms, $p = 0.030$)[59,60].

As far as PRD is concerned, in the DANISH Study, which included patients with non-ischemic cardiomyopathy, LVEF ≤35%, elevated NT-proBNP (N-terminal probrain natriuretic peptides)

level >200 pg/mL, and optimal stable pharmacologic treatment, the investigators could not identify a significant correlation between PRD and age (r=0.05 [95% CI, –0.02-0.12]; p-value = 0.18)[61], opposed to the results from this thesis analyses. It must be noted that the study collective was also considerably different from the SMART-MI population, the latter including only patients with an LVEF above 35%.

Turning to the first research aim, namely the investigation of the effect of certain risk factors on the function of the ANS and probability of autonomic dysfunction, we found HbA1c (OR 1.19), age (OR 1.06) and LVEF (OR 0.90) to present major predictive qualities. No results on this relationship from other studies were found which are 1:1 comparable, as autonomic dysfunction was usually defined and measured differently than in the studies from our research group[33,50].

First, the predictor HbA1c, where we found no studies outlining the predictive relationship of HbA1c on AD in postinfarction patients specifically. However, a multitude of studies exist examining this relationship in patients suffering from diabetes mellitus. Diabetic cardiomyopathy was first described by Rubler and al. in 1972[62]. Iribarren et al. found then in 2001, in a study population of diabetes patients with no known history of heart failure, that with each 1% increase in HbA1c levels, the risk of heart failure raises simultaneously by 8%[63]. The investigators concluded also that HbA1c levels above or equal to 10% led to a 1.56 times higher risk for heart failure when compared to HbA1c levels lower than 7% (95% CI 1.26 - 1.93)[63]. When looking more specifically at the ANS, already in the years 2000, researchers from Finland highlighted correlations between elevated HbA1c levels and abnormalities in tests on the ANS in diabetes mellitus type 1 patients[64]. Zuern et al., in their study from Tübingen, Germany, which included 97 patients with diabetes mellitus type 2 and coronary artery disease (in sinus rhythm), identified HbA1c levels above 8% to be a significant independent predictor of severe autonomic failure (OR 6.6 [95% CI 1.1 - 40.1]; p-value = 0.043) after multivariable analysis[65]. AD in this study was for instance measured by HRT in combination with DC, calculated from 24-hour Holter recordings[65].

Second, age was also found to be a significant predictor of AD. The detrimental effect of age on the ANS is well known, as already in 1971, Gribbin et al. identified the influence of age on baroreflex sensitivity and demonstrated that with increasing age, baroreflex sensitivity decreases, which they explain by the loss of arterial distensibility at higher age[66]. The baroreflex, being a key mechanism in the cardiovascular system and regulated by both the sympathetic

and parasympathetic nervous system, has thereby served for years as an indicator for neural regulation in the cardiac system[67]. Similarly, Pfeifer et al., who demonstrated in 1983 an increase in sympathetic activity and a decrease in parasympathetic activity in the cardiac ANS with increasing age, and they explained these findings based on a dysfunction in the baroreflex mechanism in elderly people[68]. Even though all the above findings support the results from this thesis, suggesting a predictive relationship of age on AD, it is noteworthy that these studies have been performed in healthy individuals, and not postinfarction patients. However, the predictive relationship of age on AD is supported by the correlations of age and DC and PRD respectively, as identified earlier in these analyses.

Third is LVEF as negative predictor of AD. No studies on this relationship could be identified in the current scientific literature, in healthy nor postinfarction study population. However, low LVEF is known to be associated with cardiac disease. In the same trial as already mentioned above, Zuern et al. from Germany found, in their diabetic study population, next to HbA1c, also LVEF ≤35% to be independently associated with severe autonomic failure, and even to a much higher extent, namely with an OR of 23.1 ([95% CI, 1.8 - 287.0]; p-value = 0.015) after multivariable analyses[65]. They outline LVEF<35% as "marker of structural cardiac damage" and reason that this may be due to the potential microangiopathy caused by both diabetes mellitus and coronary artery disease on the left ventricular pump function[65]. In that sense, as already outlined in the introduction, one must say the criterion of a reduced left ventricular ejection fraction (LVEF ≤ 35%) has already been used as a standard parameter to identify high-risk postinfarction patients in most clinical trials, as recommended by the 2015 ESC Guidelines[37]. This is in concordance with our findings, suggesting lower LVEF associated with cardiac disease and higher LVEF values as negative predictor of cardiac ill-health, including AD.

The analyses on the third and last endpoint, mortality, have also shown several significant predictive relationships. AD and diabetes (both HR 2.68) being the strongest predictor of death, followed by age (HR 1.07) and the negative predictor hemoglobin (HR 0.80).

First, AD as predicting risk factor of death, with respectively weak predictive qualities of both DC and PRD. PRD has already been identified as a strong predictor of 5-year mortality in the post MI patients of the ISAR-Risk Trial, which also included patients undergoing stress-testing[43]. In the multivariable Cox Regression, increased PRD represented a 3-fold risk for all-cause and cardiovascular mortality specifically (HR 3.03; p-value < 0.001 and HR 2.99; p-value = 0.003), representing the single most important independent risk predictor of death in

the trial[43]. The inclusion of PRD in several multivariable risk prediction models for total mortality considerably improved the predictive qualities of those models, highlighting the importance and value of PRD in risk stratification efforts[43]. Rizas et al. thereby conclude that PRD may be used as key parameter in predicting mortality outcomes in postinfarction patients and patients undergoing exercise testing[43]. Also, in a substudy of the MADIT II Trial, including post-MI patients with LVEF <35%, PRD was shown to significantly predict sudden and non-sudden cardiac death[49]. Moreover, in a following prospective validation study, the researchers confirm that PRD has indeed strong and independent predictor qualities for both all-cause and cardiovascular mortality in postinfarction patients with contemporary therapy[69]. These findings go in line with the current scientific literature which highlights the association of increased sympathetic activity in the ANS with increased cardiac vulnerability, including mortality[43].

Next to PRD, the incremental prognostic value of DC has been confirmed previously in literature. Bauer et al. concluded in their original work from 2006, that impaired DC is a strong predictor of fatal outcomes in postinfarction patients, with predictive qualities more powerful than conventional heart rate variability or LVEF as indicative parameters[42]. In three different European cohorts, DC levels were categorised in high, intermediate, or low risk and tested on mortality probability, with low DC levels (high risk) presenting the highest relative risk of dying[42]. But even for short-term mortality, DC has been shown to predict the risk of death significantly and independently in patients admitted to the emergency room[46]. Then, when taking together, impaired DC and/or PRD defining AD in these analyses, the biomarkers are complementing each other in risk prediction, as they capture both facets of the ANS, sympathetic and parasympathetic[50]. This is confirmed in the analyses of Hamm et al., where patients with abnormal DC or PRD have a cumulative 5-year mortality rate of 9.4% and patients with abnormal DC and PRD values present a mortality rate of 25.2%, compared to 2.9% in patients with normal DC and PRD, so no AD[50]. All patients had a LVEF > 35%, so AD highlighted a new risk group in postinfarction patients, which then served as basis and rationale of the SMART-MI Trial[32]. Hence, our findings confirm what has been found in previous literature already.

Second diabetes, whose predictive qualities have already been identified in combination with PRD in a study from 2014, in which diabetic postinfarction patients were at increased risk if they also presented increased PRD levels[43]. Hamm et al. found a HR of 2.2 (95% CI 1.2–3.9, p-value = 0.009) for diabetes on 5-year mortality in postinfarction patients[50]. Outside of the

context of AD, there is a wealth of evidence that diabetic patients experience more cardiovascular morbidity and mortality than nondiabetic patients[70]. Diabetics from the Framingham population in 1974 for instance experienced a mortality rate after 16 years of follow-up that was 3-fold to the one of general population[70]. When looking at the risks for diabetic men and women separately, men are twice as likely to have fatal outcomes from cardiovascular causes when compared to nondiabetic men, and women are even 4 and a half times more likely to die from cardiovascular causes than nondiabetic women[70].

It is also well established that postinfarction patients with diabetes are at enhanced risk of mortality than non-diabetic post-MI patients, as shown by data from the FINMONICA Myocardial Infarction Register[71]. After adjustments for age and area, the mortality rate after one year for diabetics versus non-diabetics was 44.2% vs. 32.6% in men (HR 1.38; 96 % CI 1.18 - 1.61) and 36.9% vs. 20.2% in women (HR 1.86; 95% CI 1.40 - 2.46)[71]. In the Swedish register of coronary care (RIKS-HIA) diabetic patients presented a risk of dying after one year of 1.44 (95% CI 1.36 - 1.52) in 1995–1998 and 1.31 (95% CI 1.24 - 1.38) in 1999–2002, which shows clear improvements in treatment and survival of postinfarction patients with time, but still a significantly higher risk remains for diabetic patients when compared to non-diabetic patients[72]. Furthermore, the ARTEMIS Study in Finland aimed to compare cardiac mortality in prediabetic CAD patients to non-diabetic and diabetes type 2 CAD patients[73]. The researchers concluded that prediabetes is not increasing the morbidity and mortality risk in CAD patients when compared to normal glycemic patients, and the risk of cardiac events is lower when compared to the patients with type 2 diabetes [73]. Data from a large database of 62 036 patients, of whom 10 613 (17.1%) had diabetes, presents a higher unadjusted 1-year mortality risk in diabetics with unstable angina/NSTEMI than with STEMI, suggesting a significant interaction between diabetes and type of ACS on the risk of death (p-value = 0.004)[74]. A Taiwanese cohort of 25,028 diabetic and 56,028 non-diabetic postinfarction patients showed higher mortality rates in diabetics after 1 year of (31.0% vs. 26.8% p-value < 0.01), 3 years (42.4% vs. 34.7%, p-value < 0.01), and 5 years (50.6% vs. 41.1%, p-value < 0.01), and even in patients who underwent PCI, the mortality rates at all time points was significantly higher in diabetics[75]. A systematic review from 2017 claims higher 1-year mortality rates in diabetic postinfarction patients than in nondiabetics, with enhanced risk when the severity of hyperglycemia increases[76]. These findings from the literature and from the dissertation analyses may be explained by the fact that both MI and diabetes mellitus present a characteristic spatially heterogeneous sympathetic innervation, which is in turn associated with a negative prognosis[77,78,79].

Third is mortality which increases with age, a relationship that seems to follow the natural course of life, so we are not going to much into in-depth literature on this association. In that same systematic review from 2017 as mentioned in the paragraph above, age is highlighted as a factor magnifying the risk of dying in the already established increased risk of death in postinfarction patients when compared to the general population[76] . In that sense, in the 1990s McMechan et al. postulate age to be the single most powerful predictor of mortality after acute MI and Herlitz et al. confirm age to be a key factor in long-term survival prognosis[80,81]. In a Danish study that included 4259 patients, researchers analyzed 5-year mortality rates in postinfarction patients according to specific age categories[82]. As suspected, age turned out to be a significant independent risk factor for post MI mortality; and mortality rates in the specific age groups were as follows: <50y (22.3%), 50-59 (29.5%), 60-60 (44.2%), 70-79 (61.5%), 80+ (79%)[82].

Fourth and last, haemoglobin was a negative predictor of death in the present analyses. The current literature mainly confirms our findings. Kalra et al. found in postinfarction patients with stable coronary artery disease that low levels of haemoglobin at baseline significantly predicted total, cardiovascular, and non-cardiovascular mortality and in that sense also identified an association of anaemia at follow-up and all-cause mortality (HR 1.90; 95% CI 1.55-2.33) for anaemic at baseline and follow-up; and HR 1.87; 95% CI 1.54 - 2.28 for normal at baseline and anaemic at follow-up; both p-value < 0.001)[83]. The results from Chinese study confirm the previous findings, as they found an increased risk in 1-year cardiovascular mortality in postinfarction patients with STEMI and anaemia[84]. Moreover, in that same cohort 27.7% of the anaemic post MI patients died as compared to 8.6% of non-anaemic post MI patients (p-value < 0.001), highlighting anaemia as marker for increased mortality risk[84]. As far as 3-year mortality is concerned, researchers found that the comorbidity of diabetes and anemia together significantly increased the risk of dying within 3 years when compared to patients with either diabetes or anemia alone, accumulating to a death rate of 65% in the comorbid group[85]. But even in the absence of comorbidities, the researchers confirmed anemia with its low hemoglobin levels as a risk factor for 3-year mortality[85]. Even in the longer term, in a trial with a median follow-up duration of 4.2 years, all-cause mortality was reaching 11.9%[86]. In patients with mild (HR 1.74; 95% CI 1.23 – 2.45) and moderate to severe anemia (HR 2.05; 95% CI 1.37 – 3.05) the mortality risk was increased when compared to patients without anemia[86]. All this evidence from current literature supports the findings from this study. The results may be explained by different factors, such as the reality that anemic patients are less likely to receive PCIs, more

likely to get blood transfusions or bleeding events and that the heart receives less oxygen which in turn leads to impaired functioning[86]. However, even though the findings are in concordance, it remains unknown whether low hemoglobin alone is responsible for increased mortality or whether anemia is a proxy for overall worse health condition as questioned by Colombo et al.[86].

4.3 Strengths & Limitations

4.3.1 Limitations

Limitations of this dissertation include the fact that the study population does not include patient from all age groups and disproportional number of men and women, which in result means that the cohort does not reflect the general population and leads to reduced generalisability[33]. Hence, women and people below the age of 50 are underrepresented in the study population, which is largely explained by the nature of the underlying disease condition in which age and gender being significant risk factors for cardiovascular disease[5,6].

In addition, as far as the registry (low risk) patients are concerned, no data has been collected over time, and is therefore missing in the analysis. Exclusively baseline data at the beginning of the trial and mortality data at the end of the trial have been collected for these patients. In that sense, no information about potential arrhythmic events, which may or may not have occurred during the trial period, are known of this patient group. Concerning the high-risk group of the SMART-MI Trial, no conclusions about clinical benefits can be drawn, as the study design of SMART-MI was intended to be purely diagnostic and included a correspondingly small sample size[33].

Furthermore, a comprehensive list of modifiable and unmodifiable risk factors has been included in the analyses of this dissertation, but a whole category of risk factors is missing, namely the environmental risk factors, which have been left out of the analyses as no data on those have been collected in the SMART-MI Trial. Advanced echocardiographic parameters other than LVEF or cardiac magnetic resonance imaging data could also not be assessed due to the complicated nature of a multicentric study design[33]. The biomarkers used to define cardiac autonomic dysfunction in this study have been shown to be powerful in predicting poor health outcomes, but the combination of more biomarkers may lead to a better risk prediction[33]. In addition, the optimal time point of the assessment of cardiac autonomic (dys)function remains yet unknown, and in this case the diagnosis was performed shortly after myocardial infarction[33]. It should be noted that not all preventive measures come with an equal amount of

scientific evidence and clinical benefit[33], which restricts the power of the findings on risk factors and corresponding effect of preventive measures.

Finally, a potential intervention bias should be considered, especially in the mortality analyses, due to the nature of the underlying randomized controlled trial.

4.3.2 Strengths

Risk stratification based on patient history, laboratory values, predisposing risk factors, in addition to cardiac autonomic dysfunction, enables a desirable holistic approach in cardiovascular disease prevention efforts. In that sense, this dissertation is the first epidemiological analysis of the SMART-MI study population, giving a valuable insight in the underlying epidemiological aspects and opening the way for more effective and efficient cardiovascular disease prevention efforts.

4.4 Relevance & recommendations for future research

This is the first analysis to give information about the influence of modifiable and unmodifiable risk factors on the function and probability of cardiac autonomic dysfunction and respective mortality, embedded in the innovative field of research on cardiac autonomic dysfunction. The early detection of prognostically relevant risk factors may lead to an optimisation of risk stratification, appropriate preventive measures, and efficient recognition of early warning signals.

For future research it is suggested to attempt a reproduction of the results in a cohort that contains an equal proportion of men and women, as well as younger and older patients, and/or in the general (healthy) population. Furthermore, the list of modifiable and unmodifiable risk factors should be extended by collecting and including data on environmental risk factors, and then to analyse the influence on environmental risk factors on the autonomic nervous system and mortality. The conduction of more studies on the cardiac autonomic nervous system with a focus on preventive medicine and cardiovascular prevention efforts is recommended.

5. Conclusion

In conclusion, this thesis represents the first epidemiological analysis of the SMART-MI study population and investigates essential underlying epidemiological aspects of a postinfarction patient collective with moderately reduced and preserved left ventricular ejection fraction. It is the first time, that the influence of modifiable and unmodifiable risk factors on the function of the ANS and the probability of cardiac AD has been investigated. Also, it is the unprecedented mortality analysis encompassing the complete study population of the SMART-MI trial.

Patients with AD were older, had lower LVEF and higher HbA1c levels. As it has been shown already previously in other studies, AD was significantly associated with increased risk of death. Diabetes mellitus, increased age and low hemoglobin levels were also associated with a higher risk of death. Future studies should test whether primary preventive measures can lead to a reduction in mortality in patients with AD. Furthermore, it should be evaluated whether treatment of modifiable risk factors can lead to a normalization of the cardiac autonomic function in patients with AD.

Contribution by the author

The author participated, together with other members of the research group, in the data collection and curation of the SMART-MI DZHK9 Trial; the data that serves as basis for the analyses in this dissertation. She also co-authored the scientific article that presents the main results from the SMART-MI Trial, published in 2022 in Lancet Digital Health. Under the supervision of Prof. Dr. Konstantinos Rizas, she performed all the statistical analyses independently. Graphs and tables used to display the results were all done by the author. No other person was included in the analyses or writing of this dissertation. No other dissertation, using data of the SMART-MI Trial, has yet been performed.

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Affidavit

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN | Promotionsbüro Medizinische Fakultät | MMRS

Eidesstattliche Versicherung

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Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

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An epidemiological approach

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München, 21.03.2024 — Elodie Eiffener

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List of publications

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